



Submitted by:
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Dear NCCN Acute Myeloid Leukemia Guidelines Panel:

On behalf of Bristol-Myers Squibb Company, we respectfully request that the NCCN Guidelines Panel for Acute Myeloid Leukemia (AML) review the enclosed data regarding the use of CC-486 in patients with AML.

Specific Changes:

We respectfully request the panel's consideration of the enclosed data and inclusion of CC-486 within the AML guidelines for post-remission therapy with a Category 1 recommendation.

FDA Status:

Please note CC-486 is not currently approved by the FDA for any use. The FDA is evaluating CC-486 for the treatment of adult patients with AML who achieved complete remission or complete remission with incomplete blood count recovery following induction therapy with or without consolidation treatment, and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT). The Food and Drug Administration (FDA) has designated a Priority Review and granted a Prescription Drug User Fee Act (PDUFA) target, or action date of September 3, 2020 for the use of CC-486 in AML.

Rationale:

CC-486 is an oral hypomethylating agent (HMA) that contains azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Antileukemic activity of azacitidine was demonstrated by reduction of cell viability and induction of apoptosis in AML cell lines in vitro. In vivo, azacitidine decreased tumor burden and increased survival in leukemic tumor models. Pharmacokinetic and pharmacodynamic profiles of CC-486 are distinct from those of injectable azacitidine. While parenteral azacitidine and CC-486 have the same active ingredient, they are not bioequivalent (Garcia-Manero et al., 2011) (Laille et al., 2015).

CC-486 has been studied in patients with variety of hematologic malignancies such as MDS, CMML and AML, as well as patients with hematologic malignancies who had failed prior HMA treatment (Garcia-Manero et al., 2011) (Garcia-Manero et al., 2016).

The QUAZAR® AML-001 study ([NCT01757535](https://clinicaltrials.gov/ct2/show/study/NCT01757535)) has been submitted to support the regulatory filing. The study assessed the efficacy and safety of CC-486, as maintenance therapy in patients with newly-diagnosed AML in first complete remission (CR) or CR with incomplete blood count recovery (CRi) following induction with intensive chemotherapy, with or without consolidation and demonstrated statistically significant and clinically meaningful improvement in both overall survival (OS) and relapse-free survival (RFS) as compared to placebo.

The QUAZAR® AML-001 study was a randomized, multicenter, double-blind, placebo-controlled, Phase III study in patients aged ≥ 55 years old with first CR or CRi following induction chemotherapy, who were not candidates for HSCT (Wei et al., 2019). All patients received intensive induction chemotherapy, with or without consolidation, before enrollment and were randomized 1:1 to receive CC-486 300 mg or placebo once daily on Days 1-14 of a 28-day cycle within 4 months of achieving their CR/CRi. Patients who developed 5-15% blasts in peripheral blood or bone marrow while on-study could receive an escalated 21-day dosing schedule of their randomized study drug, at the investigator's choice.

The QUAZAR® AML-001 study primary endpoint was overall survival (OS). Key secondary endpoints included: RFS, safety and health-related quality of life (HRQoL). A total of 472 patients were randomized to receive CC-486 (n=238) or placebo (n=234). The median age of patients treated on the CC-486 arm (n=238) was 68 years (range, 55-86); and most patients had *de novo* AML (89%) and intermediate-risk cytogenetics (85%). Participants were not considered candidates for allogeneic HSCT mainly due to advanced age, comorbidities, lack of an available donor, or patient decision. Baseline characteristics were balanced between the treatment and placebo arms.

With a data cutoff date of July 15, 2019, the median follow-up was 41.2 months. The median OS was 24.7 months vs. 14.8 months in patients who received CC-486 vs. placebo, respectively ($P=0.0009$; HR 0.69 [95% CI, 0.55-0.86]). Estimated 1-year and 2-year survival rates in the CC-486 vs. placebo groups were 73% (95% CI, 67-78) vs. 56% (95% CI, 49-62) and 51% (95% CI, 44-57) vs. 37% (95% CI, 31-43), respectively (Wei et al., 2019).

Median RFS was 10.2 months (95% CI, 7.9-12.9) in the CC-486 group and 4.8 months (95% CI, 4.6-6.4) in the placebo group ($P=.0001$; HR, 0.65 [95% CI, 0.52-0.81]). One-year relapse rate in the CC-486 and placebo groups was 53% (95% CI, 46-59) and 72% (95% CI, 65-77). There was no significant difference between the CC-486 and placebo groups in FACIT-Fatigue scores across visits and EQ-5D index scores.

The median treatment duration in CC-486 vs. placebo was 12 cycles (range, 1-80) vs. 6 cycles (range, 1-73). The main reason for treatment discontinuation was AML relapse, which was reported for 60% (n=143) of patients in the CC-486 arm and 77% (n=180) of patients in the placebo arm. Serious adverse events (AEs) in the CC-486 and placebo groups were reported in 33% and 25% patients, respectively. The most frequently reported AEs with CC-486 and placebo were Grade 1 or 2 gastrointestinal (GI) events, including nausea (64% and 23%), vomiting (59% and 10%), and diarrhea (49% and 21%). The most common Grade 3-4 treatment-emergent adverse events (TEAEs) in the CC-486 and placebo arms, were neutropenia (41% and 24%), thrombocytopenia (23% and 22%), and anemia (14% and 13%). Neutropenia was the most common TEAE leading to dose interruptions (CC-486, 20%; placebo, 6%) or dose reductions (6% and 0.4%) in both treatment arms. Treatment discontinuation due to AEs occurred in 13% of patients in the CC-486 group and 4% in the placebo arm. The most common TEAEs leading to discontinuation of CC-486 were GI events (CC-486, 5% vs. placebo, 0.4%).

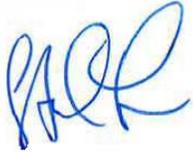
CC-486 is currently being evaluated in an ongoing Phase III, randomized, double-blind, placebo-controlled study ([NCT04173533](#)) as maintenance therapy after allogeneic-SCT in patients with myelodysplasia (MDS) and AML, and has previously been evaluated in a Phase I/II open-label, multicenter study (de Lima et al., 2018) in a similar patient population.

Copies of the recently presented and previously published data using CC-486 in patients with AML are enclosed for your review. Your consideration of this submission is greatly appreciated.

Sincerely,



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Associate Director, US Medical



Chrystal U Louis, MD, MPH
Executive Director, US Medical Affairs, Hematology, Myeloid Disease Lead

Reference List:

1. de Lima M, Oran B, Champlin RE, et al. CC-486 Maintenance After Stem Cell Transplantation in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndromes . *Biol Blood Marrow Transplant*. 2018. <http://www.ncbi.nlm.nih.gov/pubmed/29933073>.
2. Döhner H, Wei AH, Montesinos P, et al. 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 [Poster]. Poster presented at: 25th Congress of the European Hematology Association (EHA); June 11-14, 2020
3. Garcia-Manero G, Savona MR, Gore S, et al. CC-486 (Oral Azacitidine) in Patients with Hematological Malignancies Who Had Received Prior Treatment with Injectable Hypomethylating Agents (HMAs): Results from Phase 1/2 CC-486 Studies [Oral]. Oral presented at: 58th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 3-6, 2016c; San Diego, CA, USA.
4. Garcia-Manero G, Gore SD, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol* 2011;29:2521-7.
5. Laille E, Shi T, Garcia-Manero G, et al. Pharmacokinetics and pharmacodynamics with extended dosing of CC-486 in patients with hematologic malignancies. *PLoS One* 2015;10:e0135520.
6. Ravandi F, Wei AH, Döhner H, et al. CC-486 Maintenance Therapy is Safe and Well Tolerated in Patients Aged ≥ 75 Years With Acute Myeloid Leukemia (AML) in First Remission Following Induction Chemotherapy: Results From QUAZAR AML-001 [Poster]. Poster presented at: 25th Congress of the European Hematology Association (EHA); June 11-14, 2020
7. Roboz GJ, Döhner H, Pocock C, et al. Health-Related Quality of Life with CC-486 in Patients With Acute Myeloid Leukemia (AML) in First Remission Following Induction Chemotherapy (IC): Results from the Phase III QUAZAR-AML-001 Trial [Poster]. Poster presented at: American Society of Clinical Oncology (ASCO); May 29-31, 2020
8. Wei AH, Döhner H, Pocock C, et al. 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. *Blood*. 2019;134(Suppl). [doi:10.1182/blood-2019-132405](https://doi.org/10.1182/blood-2019-132405).