The ASCO Post

Oral CC-486 Maintenance Therapy Extends Survival in Older Patients With AML

By Alice Goodman
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Use of CC-486—an investigational oral form of azacitidine—as maintenance therapy significantly improved overall survival and relapse-free survival in older patients with newly diagnosed acute myeloid leukemia (AML) who were in remission following induction chemotherapy with or without consolidation therapy, according to results of the phase III QUAZAR AML-001 study. Results of the trial were reported at a late-breaking session of the 2019 American Society of Hematology (ASH) Annual Meeting & Exposition.[1]

CC-486 improved survival by 31% and improved relapse-free survival by 35% compared with placebo. These findings represent statistically significant and clinically significant - improvements.

"This pivotal maintenance study demonstrates significant improvement in overall survival and relapse-free survival in a broad range of patients with AML in remission following induction chemotherapy with or without consolidation," stated lead author **Andrew H. Wei, MBBS, PhD**, of Alfred Hospital and Monash University, Melbourne.

Screen Capture completed by J L Mullins from "The ASCO Post" on October 10, 2023, from URL: https://ascopost.com/issues/january-25-2020/oral-cc-486-maintenance-therapy-extends-survival-in-older-patients-with-aml/

"The safety and tolerability of CC-486 were manageable, and CC-486 preserved health-related quality of life. Maintenance therapy therefore represents a potential new standard of care for patients aged 55 and older in first remission who are not candidates for hematopoietic stem cell transplantation following induction chemotherapy," he said.

Study Background

> "Maintenance therapy represents a new standard of care for patients aged 55 and older in first remission following induction chemotherapy."
>
> — *Andrew H. Wei, MBBS, PhD*
>
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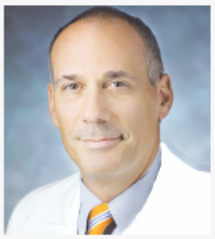
"This is a transformative trial and will change practice once CC-486 is available," said ASH Secretary **Robert A. Brodsky, MD**, of Johns Hopkins University Medical Center, Baltimore, who moderated a press conference where these data were discussed.

"Five-year survival in AML is dismal—around 30%. Standard induction chemotherapy achieves complete remission in 60% to 80% of patients aged 60 or younger and in 40% to 60% of older patients. The majority of patients will relapse even if they achieve complete remission, and relapse is the primary obstacle to long-term survival," Dr. Wei told listeners.



Several agents have been studied in the maintenance setting for AML over the past 30 years, and some have extended relapse-free survival, but until this study, no therapy has shown an overall survival benefit. CC-486 may have the potential to delay the need for further AML therapy, which is currently either observation or stem cell transplant, the latter being complex and not feasible for older patients due to associated morbidity.

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CC-486 is an investigational oral hypomethylating agent, with a pharmacokinetic profile distinct from that of injectable azacitidine, which has shown activity in AML. Dr. Wei noted that the oral dosing schema enables extended drug exposure with greater patient convenience, compared to injectable azacitidine.

"CC-486 is molecularly identical to azacitidine, but it is an oral drug. This study is the first step toward regulatory approval. An oral form of azacitidine also gives us future potential to investigate the role of this drug in older patients with AML in the front-line setting. One can envision this oral drug as a building block for novel AML regimens where azacitidine is used; for example, in combination with BCL2, FLT3, and IDH inhibitors," Dr. Wei explained.

Methodology and Outcomes

QUAZAR AML-001 is an international multicenter, placebo-controlled, double-blind, randomized phase III study conducted at 148 sites in 23 countries. The study enrolled 472 patients aged 55 and older (range = 55–86 years) with de novo or secondary AML in first remission who were ineligible for hematopoietic stem cell transplant (HSCT). After induction chemotherapy, 81% had complete remission and 19% had complete remission with incomplete hematologic recovery. Approximately 85% had received at least two cycles of prior intensive chemotherapy.

Within 4 months of achieving first remission, patients were randomly assigned 1:1 to receive CC-486 at 300 mg/d for the first 14 days of each 28-day cycle vs placebo given on the same schedule. Bone marrow assessments were performed every 3 months. Patients remaining in remission could continue treatment. If bone marrow assessment showed relapse (5%–15% blasts), CC-486 could be given for 21 days of each 28-day cycle. If the bone marrow blasts were > 15%, patients ceased therapy and went into follow-up.

At baseline, the median age was 68 years, and more than two-thirds of patients were over age 65. Most patients had a performance status of 0 or 1. About 85% had intermediate risk and 15% poor-risk cytogenetics. Patients who were minimal residual disease (MRD)-positive by flow cytometry at study screening accounted for 43% of the experimental arm and 50% of the placebo arm.

KEY POINTS

- CC-486, an investigational oral formulation of azacitidine, extended relapse-free survival and overall survival in older patients with AML as maintenance therapy after first remission.
- This is the first study showing that maintenance therapy has a survival benefit in this setting.
- This may be a practice-changing study, once the oral formulation is approved.

After a median follow-up of 41.2 months, a 9.9-month improvement in overall survival was observed with CC-486 vs placebo: 14.8 months for placebo and 24.7 months in the CC-486 arm. This difference was highly significant, representing a 31% improvement in median survival for the investigational agent compared with placebo ($P = .0009$). Median relapse-free survival improved by nearly 5.3 months vs placebo in the CC-486 arm: 4.8 months in the placebo arm and 10.2 months in the CC-486 arm—a 35% improvement with CC-486 compared with placebo ($P = .0001$).

Safety Profile

Patients in the CC-486 arm were able to tolerate a median of 12 cycles of therapy, compared with 6 cycles in the placebo group.

"One measure of safety is the number of cycles of therapy a patient can tolerate. Some patients in the CC-486 arm received up to 80 cycles of therapy," Dr. Wei noted. "Some patients still remain on therapy."

The safety profile of CC-486 is similar to that of azacitidine. "As this was a placebo-controlled trial, there were initially more adverse events in the active arm than in the placebo arm, which was ameliorated by supportive care approaches in subsequent cycles," he noted.

The most common side effects in the CC-486 arm were gastrointestinal (nausea in 65%, vomiting in 60%, diarrhea in 50%, and constipation in 39%), and these side effects were reduced after prophylaxis was initiated after cycle 2. The most common grade 3 and higher adverse events in the CC-486 arm vs the placebo arm, respectively, were neutropenia (41% vs 24%), thrombocytopenia (23% vs 22%), anemia (14% vs 13%), diarrhea (5% vs 1%), vomiting (3% vs 0%), fatigue (3% vs 1%), and nausea (3% vs 0.4%). Treatment discontinuation due to adverse events was infrequent in the CC-486 arm, and no treatment-related deaths occurred.

Comments on QUAZAR AML-001

Dr. Brodsky said, "Treating AML in older patients is a very difficult problem.... It is easy to get older patients with poor- and intermediate-risk AML into remission, but remissions are short-lived. For the first time, we have seen an oral drug that can lead to improved relapse-free survival and overall survival in this setting. This is a practice-changing trial," Dr. Brodsky stated.

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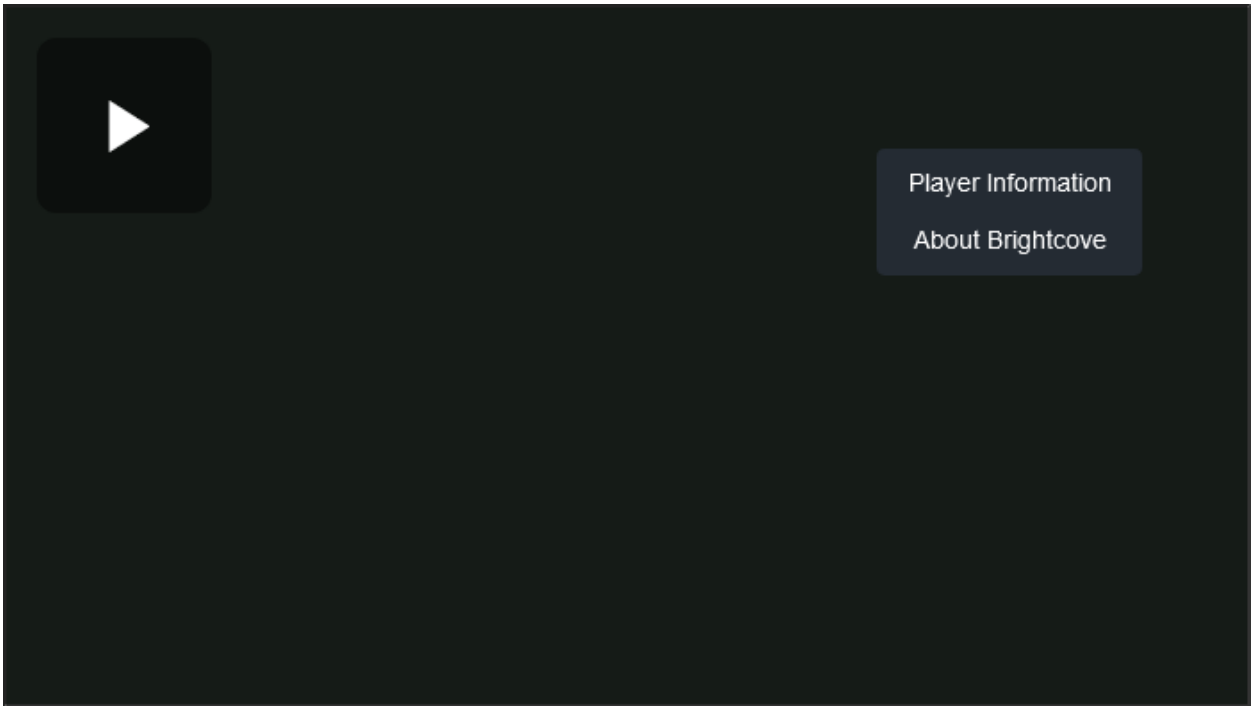
Amir T. Fathi, MD

Amir T. Fathi, MD, Program Director of the Center for Leukemia, Massachusetts General Cancer Hospital, Boston, commented, "This is an impressive survival advantage and one of the first studies to show a benefit of maintenance therapy in AML. The hope now is to better define which patients may benefit from maintenance therapy, based on specific molecular subtypes and MRD status. It is very exciting news."

He also added: "In the United States, consolidation chemotherapy is typically reserved for favorable-risk patients, while the remainder of patients are frequently candidates for stem cell transplantation as consolidative therapy. Therefore, in certain settings, it may be challenging to identify patients who are similar to the patient population in this study; those who would not be traditionally offered stem cell transplant and consolidation, and who would instead be treated with consolidation chemotherapy followed by maintenance. Subsequent studies may be necessary to compare consolidation followed by maintenance therapy with CC-468 vs the route of consolidative transplant for some patients. Nevertheless, the study is likely practice changing, given then survival advantage demonstrated in this traditionally higher-risk, older patient population."



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