U.S. Food and Drug Administration Approves Onureg® (azacitidine tablets), a New Oral Therapy, as Continued Treatment for Adults in First Remission with Acute Myeloid Leukemia

**Release Date:**
Tuesday, September 1, 2020 12:50 pm EDT

**Terms:**
Corporate/Financial News  #BMS  $BMY  AML  Caregivers  doctors  FDA  Nurses  Onureg  patients  QUAZAR

**Dateline City:**
PRINCETON, N.J.

*In the QUAZAR® AML-001 study, Onureg significantly improved overall survival by nearly 10 months compared to placebo (24.7 months [95% CI: 18.7 to 30.5] vs. 14.8 months [95% CI: 11.7 to 17.6]) in patients with acute myeloid leukemia in first remission*

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol Myers Squibb (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved Onureg® (azacitidine 300 mg tablets, CC-486) for the continued treatment of adult patients with acute myeloid leukemia (AML) who achieved first complete remission (CR) or CR with incomplete blood count recovery (CRi) following intensive induction chemotherapy and who are not able to complete intensive curative therapy.

AML is one of the most common acute leukemias in adults. The approval is based on results from the pivotal Phase 3 QUAZAR® AML-001 study in which treatment with Onureg resulted in a statistically significant and clinically meaningful improvement in overall survival (OS), the study's primary endpoint, of nearly 10 months compared to placebo. Median OS from time of randomization was greater than two years (24.7 months; 95% Confidence Interval [CI]: 18.7 to 30.5) among patients who received Onureg compared to 14.8 months (95% CI: 11.7 to 17.6) among patients receiving placebo (Hazard Ratio [HR]: 0.69, 95% CI: 0.55 to 0.86; p=0.0009). Onureg was continued until disease progression or unacceptable toxicity. Onureg has warnings and precautions for risks of substitution with other azacitidine products, myelosuppression, increased early mortality in patients with myelodysplastic syndromes (MDS) and embryo-fetal toxicity. Due to substantial differences in the pharmacokinetic parameters, Onureg should not be substituted for intravenous or subcutaneous azacitidine as it may result in a fatal adverse reaction. New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received Onureg, respectively. Febrile neutropenia occurred in 12% of patients. Complete blood counts should be monitored, dosing should be modified as recommended and standard supportive care should be provided if myelosuppression occurs. Enrollment was discontinued early in the study AZA-MDS-003 due to a higher incidence of early fatal and/or serious adverse reactions in the Onureg arm compared with the placebo arm. Treatment of MDS with Onureg is not recommended outside of controlled trials. Onureg can cause fetal harm when administered to a pregnant woman.

"Continued treatment with Onureg demonstrated an overall survival benefit in adults with AML who had achieved first complete remission in the QUAZAR® AML-001 study and, notably, it has the potential to do this in a convenient manner, given its once daily oral formulation," said Andrew Wei, MBBS, Ph.D., QUAZAR® AML-001 lead investigator, Alfred Hospital and Monash University, Melbourne, Australia. "This approval should help establish continued treatment with Onureg as a standard component of AML therapy for adults who achieved first complete remission following chemotherapy and who cannot proceed to intensive curative therapy, like hematopoietic stem cell transplant."

"The FDA approval of Onureg is the culmination of over a decade of research and 13 pre-clinical and clinical trials. We are grateful to the patients, families and caregivers who participated in and supported these trials, and who ultimately made today’s advancement possible,” said Giovanni Caforio, M.D., chairman and chief executive officer, Bristol Myers Squibb. “This milestone is representative of our commitment to helping patients with hard-to-treat cancers live longer, and the approval of Onureg as an oral therapy option for patients is more relevant now than ever as the world continues to navigate the COVID-19 pandemic.”

The New Drug Application was granted Priority Review Designation by the FDA, and a Marketing Authorization Application (MAA) for this indication was validated by the European Medicines Agency in May 2020.

**QUAZAR® AML-001 Pivotal Trial Results**

The FDA approval of Onureg is based on data from QUAZAR® AML-001, a Phase 3, international, randomized, double-blind study. Eligible patients were ages 55 years or older, had AML, were within four months of achieving first CR or CRi following...
intensive induction chemotherapy with or without consolidation treatment (per investigator preference prior to study entry), and were not candidates for hematopoietic stem cell transplant (HSCT) at the time of screening. The study enrolled 472 patients, randomized 1:1 to receive either Onureg 300 mg (n=238) or placebo (n=234) orally, once daily, for 14 days of a 28-day cycle, plus best supportive care.

Results showed continued treatment with Onureg significantly improved OS in patients with AML in remission compared to placebo, establishing Onureg as a new continued therapy option for patients who are not able to complete intensive curative therapy, including HSCT. Median OS, the primary endpoint, from time of randomization was greater than two years (24.7 months; 95% CI: 18.7 to 30.5) in the Onureg arm compared to 14.8 months for placebo (HR: 0.69, 95% CI: 0.55 to 0.86; p=0.0009). A subgroup analysis showed consistency in the OS benefit for patients in either CR or CRi. The median duration of treatment was 12 cycles (1 to 82) for Onureg and 6 cycles with placebo (1 to 76).

Serious adverse reactions occurred in 15% of patients who received Onureg. Serious adverse reactions in ≥2% of patients who received Onureg included pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received Onureg. The most common adverse reactions with Onureg versus placebo were nausea (65%, 24%), vomiting (60%, 10%), diarrhea (50%, 21%), fatigue/asthenia (44%, 25%), constipation (39%, 24%), pneumonia (27%, 17%), abdominal pain (22%, 13%) arthralgia (14%, 10%), decreased appetite (13%, 6%), febrile neutropenia (12%, 8%), dizziness (11%, 9%) and pain in extremity (11%, 5%). Of patients who received Onureg, permanent discontinuation due to an adverse reaction occurred in 8% of patients.

Results from the QUAZAR® AML-001 trial were first presented at the American Society of Hematology (ASH) Annual Meeting in December 2019.

About AML

There will be nearly 20,000 new cases of acute myeloid leukemia (AML) in the United States this year, accounting for 1.1% of all cancer cases, with an estimated 11,180 deaths resulting from the disease. There were an estimated 64,500 people living with AML in the United States in 2017. AML is one of the most common acute leukemias in adults. AML is characterized by the rapid growth of abnormal cells in the bone marrow and as such interferes with normal blood cell production and function. Because of the impaired production of red blood cells, platelets and white blood cells, it can present with signs of anemia, bleeding and infections. AML is a heterogeneous disease associated with diverse genetic mutations, and can rapidly progress and lead to death if not promptly treated. AML response to treatment may be of short duration, meaning following patients' initial response to chemotherapy, there is still a very high risk of relapse, thus representing a significant unmet need for continued therapy options that prolong overall survival.

About Onureg

Onureg, the first and only FDA-approved continued AML therapy for patients in remission, is an oral hypomethylating agent that incorporates into DNA and RNA. The main mechanism of action is thought to be hypomethylation of DNA, as well as direct cytotoxicity to abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes that are critical for cell differentiation and proliferation.

INDICATION

- ONUREG is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- ONUREG is contraindicated in patients with known severe hypersensitivity to azacitidine or its components.

WARNINGS AND PRECAUTIONS

- **Risks of Substitution with Other Azacitidine Products:** Due to substantial differences in the pharmacokinetic parameters, the recommended dose and schedule for ONUREG are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG may result in a fatal adverse reaction. Treatment with ONUREG at the doses recommended for intravenous or subcutaneous azacitidine may not be effective. Do not substitute ONUREG for intravenous or subcutaneous azacitidine.

- **Myelosuppression:** New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia. Less than 1% of patients discontinued ONUREG due to either neutropenia or thrombocytopenia. Monitor complete blood counts and modify the dosage as recommended. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

- **Increased Early Mortality in Patients with Myelodysplastic Syndromes (MDS):** In AZA-MDS-003, 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to MDS were randomized to ONUREG or placebo. 107 received a median of 5 cycles of ONUREG 300 mg daily for 21 days of a 28-day cycle. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in the ONUREG arm compared with placebo. The most frequent fatal adverse reaction was sepsis. Safety and effectiveness of ONUREG for MDS have not been established. Treatment of MDS with ONUREG is not recommended outside of controlled trials.

- **Embryo-Fetal Toxicity:** ONUREG can cause fetal harm when administered to a pregnant woman. Azacitidine caused fetal death and anomalies in pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mg/m2 basis. Advise pregnant women of the potential risk to a fetus. Advise females of
reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose.

**ADVERSE REACTIONS**

- Serious adverse reactions occurred in 15% of patients who received ONUREG. Serious adverse reactions in ≥2% included pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG.

- Most common (≥10%) adverse reactions with ONUREG vs placebo were nausea (65%, 24%), vomiting (60%, 10%), diarrhea (50%, 21%), fatigue/asthenia (44%, 25%), constipation (39%, 24%), pneumonia (27%, 17%), abdominal pain (22%, 13%), arthralgia (14%, 10%), decreased appetite (13%, 6%), febrile neutropenia (12%, 8%), dizziness (11%, 9%), pain in extremity (11%, 5%).

**LACTATION**

- There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose.

Please see full **Prescribing Information** for ONUREG.

**Bristol Myers Squibb: Advancing Cancer Research**

At Bristol Myers Squibb, patients are at the center of everything we do. The goal of our cancer research is to increase patients’ quality of life, long-term survival and make cure a possibility. We harness our deep scientific experience, cutting-edge technologies and discovery platforms to discover, develop and deliver novel treatments for patients.

Building upon our transformative work and legacy in hematology and Immuno-Oncology that has changed survival expectations for many cancers, our researchers are advancing a deep and diverse pipeline across multiple modalities. In the field of immune cell therapy, this includes registralional CAR T cell agents for numerous diseases, and a growing early-stage pipeline that expands cell and gene therapy targets, and technologies. We are developing cancer treatments directed at key biological pathways using our protein homeostasis platform, a research capability that has been the basis of our approved therapies for multiple myeloma and several promising compounds in early- to mid-stage development. Our scientists are targeting different immune system pathways to address interactions between tumors, the microenvironment and the immune system to further expand upon the progress we have made and help more patients respond to treatment. Combining these approaches is key to delivering potential new options for the treatment of cancer and addressing the growing issue of resistance to immunotherapy. We source innovation internally, and in collaboration with academia, government, advocacy groups and biotechnology companies, to help make the promise of transformational medicines a reality for patients.

**About Bristol Myers Squibb**

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, Facebook and Instagram.

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**Cautionary Statement Regarding Forward-Looking Statements**

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, whether Onureg for the indication described in this release will be commercially successful and that continued approval of such product candidate for such indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials. No forward-looking statement can be guaranteed: Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb’s business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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Ticker Slug:
Ticker: BMY
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$BMY announces #FDA approval of a new therapy for people with acute myeloid #leukemia