This supplement is sponsored and developed by Bristol-Myers Squibb Company.

A SUPPLEMENT TO FEDERAL PRACTITIONER

ONUREG® (azacitadine) tablets for Continued AML Treatment in Adults in First Remission

ONUREG®, an oral therapy, is the first and only US Food and Drug Administration (FDA)-approved continued acute myeloid leukemia (AML) treatment for adult patients who achieve first complete remission or complete remission (CR) with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.[1] Safety and efficacy was established by the large, multicenter QUAZAR® AML-001 trial.[1]

Introduction

In 2017, an estimated 64,500 Americans were living with AML, and an estimated 19,940 new cases occurred in 2020.[2] Age-adjusted rates for new cases rose approximately 1.5% each year from 2008 to 2017. AML is diagnosed most commonly in the elderly, with a median age at diagnosis of 68.[2] It is a genetically complex disease, with many commonly mutated genes and an even larger number of infrequently mutated genes, leading to active research into the use of genetic data to classify AML and aid in clinical practice.[3]

The 5-year rate of survival for AML is low, with an overall rate of 28.7% for the 5-year period ending in 2016, the most recent data available.[4] There is a significant age disparity in survival; the 5-year relative survival rate for those younger than 65 is 47.5%, while the corresponding figure for those 65 and over is much lower, 8.2%.[2]

Following an AML diagnosis, patients may receive intensive induction therapy to induce remission, but this is given most often in younger, fit patients.[5] For those who achieve remission, relapse is common.[6,7] This is especially true for older patients, with approximately 85% relapsing within 2 to 3 years.[6,8] Adverse-risk cytogenetics and *FLT3* mutation status have been linked to poorer outcome in patients treated with induction chemotherapy.[7] Also, disparities in outcomes between older and younger populations were seen across prognostic groups defined by cytogenetics and *NPMI*/*FLT3* mutations.[9]

Limited role of HSCT particularly in the older patient with AML

An important goal for continued treatment for patients with AML is to extend overall survival (OS) in those who have achieved remission.[10] Options at that point may include hematopoietic stem cell transplantation (HSCT), continued treatment, and watchful waiting (Figure 1).[11]

Many adult patients with AML, especially the elderly, do not go on to receive HSCT, according to an analysis of the SEER-Medicare 2013-2015 database by Medeiros and Satram, who classified 11,142 newly diagnosed adult patients with AML into 2 groups: those who received chemotherapy (n=4772) and those who did not (n=6370).[5] That is, about 40% (4772/11,142)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

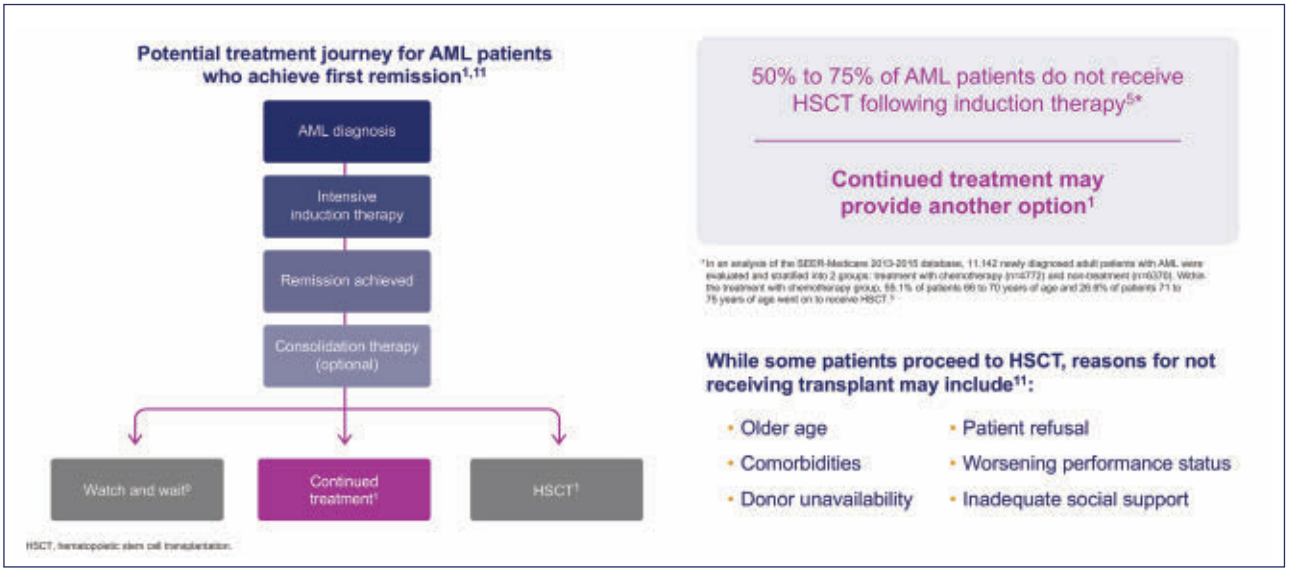
ONUREG® is contraindicated in patients with known severe hypersensitivity to azacitidine or its components.

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.

FIGURE 1 A goal of continued treatment for AML is extending overall survival in patients who have achieved remission[10]



received chemotherapy that can lead to remission and HSCT.[5] Within this group, 55.1% of patients 66 to 70 years of age and 26.6% of patients 71 to 75 years of age went on to receive HSCT.[5]

A physician's decision whether or not to recommend transplantation is complex and depends on several clinical factors, including age, performance status, and comorbidities.[12] A workup for a transplantation includes evidence of remission and the availability of an allogeneic transplant candidate, and also may include the results of a number of clinical tests, including a complete metabolic profile with a dietary consult if indicated; left ventricular ejection fraction; electrocardiogram; chest X-ray; pulmonary function testing; serology testing for cytomegalovirus, herpes simplex virus, Epstein-Barr virus, varicella-zoster virus, HIV, hepatitis B and C, and human T-lymphotropic virus; and a dental evaluation.[12] The 2017 European LeukemiaNet (ELN) recommendations also include use of cytogenetic and molecular genetic features of the patient's AML to inform the risk/benefit assessment of HSCT.[3] In addition to clinical and genetic factors, social and personal issues must be considered as well, including whether family support is available, socioeconomic issues, and the individual's motivation to fully participate in the self-care required for a successful outcome.[12] Several considerations can contribute to HSCT being an appropriate option for patients with AML.

A significant unmet need for continued therapy options exists for patients with AML in remission.[13]

ONUREG® indication

ONUREG® is indicated for continued treatment of adult patients with AML 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.[1] ONUREG® is contraindicated in patients with known severe hypersensitivity to azacitidine or its components.[1]

Mechanism of action and pharmacodynamic profile

ONUREG® (azacitidine) is a pyrimidine nucleoside analog of cytidine that inhibits DNA and RNA methyltransferases. After being taken up by the cells and converted to azacitidine nucleotide triphosphates by endogenous enzymes, azacitidine is incorporated into both DNA and RNA.[1] Once incorporated into cancer cells *in vitro*, including into AML cells, azacitidine

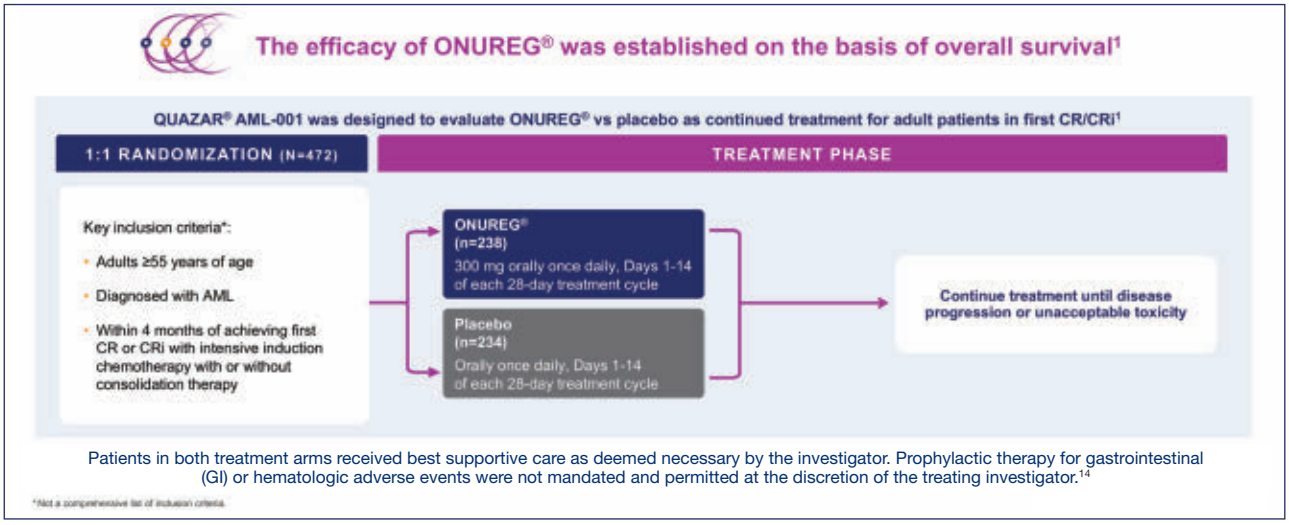
IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

FIGURE 2 The large, multicenter QUAZAR® AML-001 trial established the efficacy and safety of the first and only FDA-approved continued AML treatment for patients in first remission[1,13]



inhibited DNA methyltransferases, reduced DNA methylation, and altered gene expression, including reexpression of genes regulating tumor suppression and cell differentiation. Incorporation of azacitidine into the RNA of cancer cells, including leukemic cells, inhibited RNA methyltransferases, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.[1] Antileukemic activity of azacitidine was demonstrated by reduction of cell viability and induction of apoptosis in AML cell lines *in vitro*.[1]

A greater reduction in global DNA methylation was observed with higher azacitidine plasma exposure in patients with AML administered ONUREG® for 14 days of a 28-day treatment cycle.[1]

The QUAZAR® AML-100 clinical trial

The QUAZAR® AML-100 clinical trial evaluated ONUREG® vs placebo as a continued treatment for adult patients with AML who had achieved a CR or CRi with intensive induction chemotherapy. Patients were eligible if they were 55 years or older, had AML, and were within 4 months of achieving first CR or CRi with intensive induction chemotherapy (Figure 2). Patients may have received consolidation therapy prior to enrollment. Patients who were candidates for HSCT at the time of screening were excluded.[1]

A total of 472 patients completed induction with or without consolidation therapy and were randomized 1:1 to receive ONUREG® 300 mg (n=238) or placebo (n=234) orally on days 1 through 14 of each 28-day cycle. Randomization was stratified by age at time of induction therapy (55 to 64 vs ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs poor risk), prior history of myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) (yes vs no), and whether patients had received consolidation therapy following induction therapy (yes vs no).[1]

Baseline demographic and disease characteristics are shown in Table 1. Median age in each arm was 68 years (ONUREG® range, 55-86 vs 55-82),[1] and 50% (ONUREG®) and 54% (placebo) were men.[1] Ninety-one percent had *de novo* AML.[15] Most patients were ECOG performance status 0 or 1.[1] Approximately 76% (ONUREG®) and 77% (placebo) of patients had received 1 or 2 cycles of consolidation following induction therapy.[1] At study baseline, most were in CR (ONUREG®, 78% vs placebo, 77%) or CRi (18% vs 16%).[1]

Treatment with ONUREG® or placebo was continued until disease progression or unacceptable toxicity.[16] The median duration of exposure to ONUREG® was 11.6 months (range, 0.5 to 74.3 months) and the median number of cycles was 12 (range, 1 to 82 cycles).[1]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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.

TABLE 1 Baseline demographics

The QUAZAR® AML-001 trial enrolled a broad AML population[1]

Baseline demographics and disease-related characteristics in the QUAZAR® AML-001 trial[1]

Parameter	ONUREG® (n=238)	Placebo (n=234)
Age (years)		
Median (min, max)	68.0 (55, 86)	68.0 (55, 82)
Age category, n (%)		
<65 years	66 (28)	68 (29)
65 years to <75 years	144 (61)	142 (61)
≥75 years	28 (12)	24 (10)
Sex, n (%)		
Male	118 (50)	127 (54)
Female	120 (50)	107 (46)
Race, n (%)		
White	216 (91)	197 (84)
Black or African American	2 (1)	6 (3)
Asian	6 (3)	20 (9)
Other	12 (5)	11 (5)
Not collected or reported	2 (1)	0 (0)
ECOG performance status, n (%)		
0	116 (49)	111 (47)
1	101 (42)	106 (45)
2	21 (9)	15 (6)
3	0 (0)	2 (1)
Cytogenetic risk status at diagnosis, n (%)		
Intermediate risk[1]	203 (85)	203 (87)
Poor risk[13]	35 (15)	31 (13)
Initial AML classification, n (%)		
AML with recurrent genetic abnormalities	39 (16)	46 (20)
AML with myelodysplasia-related changes	49 (21)	42 (18)
Therapy-related myeloid neoplasms	2 (1)	0 (0)
AML not otherwise specified	148 (62)	145 (62)
Missing	0 (0)	1 (<1)
Type of AML, n (%)		
Primary (de novo)	213 (89)	216 (92)
Secondary	25 (11)	18 (8)
Induction response		
CR	187 (79)	197 (84)
CRi	51 (21)	37 (16)
Received consolidation following induction therapy		
None	52 (22)	42 (18)
1 cycle	110 (46)	102 (44)
2 cycles	70 (29)	77 (33)
3 cycles	6 (3)	13 (6)
Disease status at study baseline		
CR	185 (78)	181 (77)
CRi	44 (18)	38 (16)
Not in CR or CRi	9 (4)	13 (6)
Not reported	0	2 (1)

72% of patients were 65 years or older

Most patients had an ECOG performance status of 0 or 1

76% of patients received 1 or 2 cycles of consolidation

ECOG, Eastern Cooperative Oncology Group.
[a]Intermediate risk was defined as normal cytogenetics +8, t(9;11), or other undefined.
[b]Poor risk was defined as complex (≥3 abnormalities): -5; 5q-; -7; 7q-; 11q23 - non t(9;11); inv(3); t(3;3); t(6;9); or t(9;22).
Source for Intermediate and Poor Risk: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia. National Comprehensive Cancer Network® (NCCN®) website. Available at http://www.nccn.org/professionals/physician_gls/PDF/aml.pdf. Accessed March 1, 2011.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

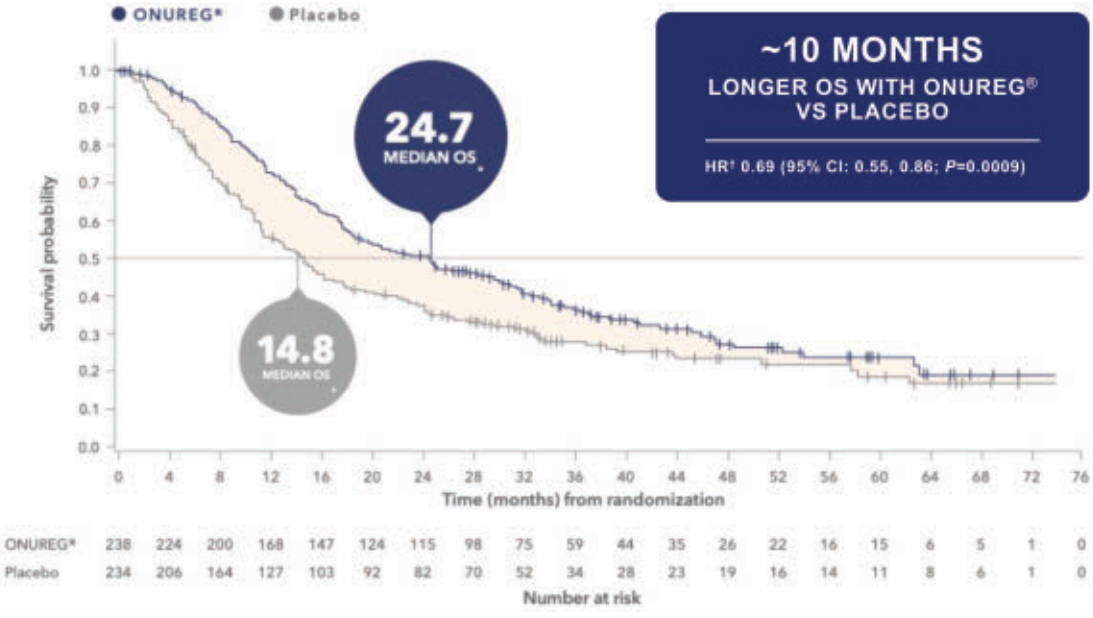
Embryo-Fetal Toxicity

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/m^2 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®.

FIGURE 3 ONUREG® demonstrated >2 years median overall OS for AML patients in first remission[1]



CI, confidence interval; ITT, intention-to-treat.
*ONUREG® (95% CI: 18.7, 30.5); placebo (95% CI: 11.7, 17.6).
†The HR is from a Cox proportional hazards model stratified by age (55 to 64 vs ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs poor risk), and received consolidation therapy (yes vs no).

Results: efficacy

The efficacy of ONUREG® was established on the basis of the primary endpoint, OS. Median follow-up was 41.2 months.[15] The trial demonstrated a statistically significant improvement in OS for patients randomized to ONUREG® compared to placebo, with a median OS of 24.7 months in the treated arm vs 14.8 months in the placebo arm (Figure 3).[1] That is an increase of approximately 10 months for ONUREG® vs placebo (hazard ratio [HR] 0.69; 95% confidence interval [CI]: 0.55-0.86; *P*=0.0009).[1] Survival estimates were 73% for ONUREG® (n=168; 95% CI: 67, 78) and 56% for placebo (n=127; 95% CI: 49, 62) at 1 year, and 51% for ONUREG® (n=115; 95% CI: 44, 57) and 37% for placebo (n=82; 95% CI: 31, 43) at 2 years.[14]

Additional analyses show the influence of ONUREG® across subgroups vs placebo for median OS (Table 2).[15]

Results: safety

Patients received a median of 12 cycles (median length, 28 days per cycle) of ONUREG®; 71% of patients were exposed for 6 months or longer and 49% of patients were exposed for more than 1 year.[1]

The majority of adverse reactions (ARs) with ONUREG® and placebo were Grade 1 or 2 gastrointestinal events, including nausea (65% and 24%, respectively), vomiting (60% and 10%), and diarrhea (50% and 21%).[1] The most common Grade 3-4 hematological ARs were neutropenia (ONUREG®, 49%; placebo, 23%), thrombocytopenia (21% and 10%), and anemia (4% and 3%) (Figure 4).[1]

Permanent discontinuation of ONUREG® due to an AR occurred in 8% of patients (Figure 5). ARs that resulted in permanent discontinuation of ONUREG® in more than 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%). Interruptions of

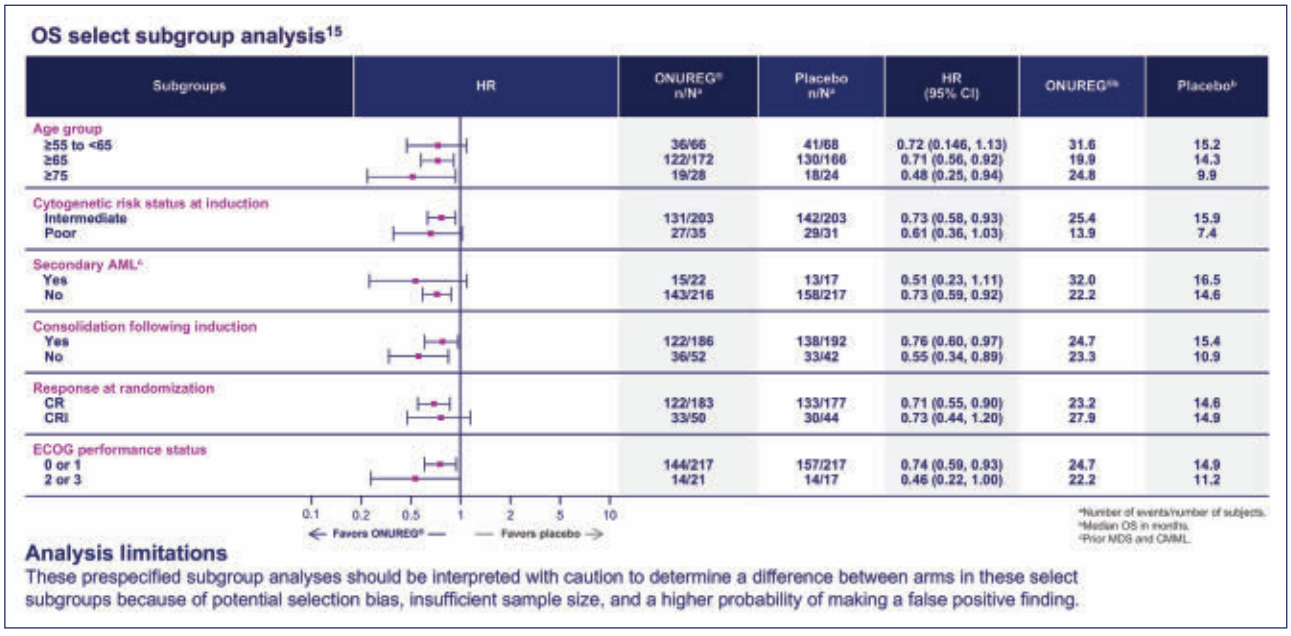
Patients in both treatment arms received best supportive care as deemed necessary by the investigator. Prophylactic therapy for gastrointestinal (GI) or hematologic adverse events were not mandated and permitted at the discretion of the treating investigator.[14]

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

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%).

TABLE 2 Primary endpoint subgroup analysis: treatment with ONUREG® across subgroups vs placebo for median OS[15]



OS select subgroup analysis[15]

Subgroups	ONUREG® n/N[a]	Placebo n/N[a]	HR (95% CI)	ONUREG® [b]	Placebo [b]
Age group					
≥55 to <65	36/66	41/68	0.72 (0.146, 1.13)	31.6	15.2
≥65	122/172	130/166	0.71 (0.56, 0.92)	19.9	14.3
≥75	19/28	18/24	0.48 (0.25, 0.94)	24.8	9.9
Cytogenetic risk status at induction					
Intermediate	131/203	142/203	0.73 (0.58, 0.93)	25.4	15.9
Poor	27/35	29/31	0.61 (0.36, 1.03)	13.9	7.4
Secondary AML[c]					
Yes	15/22	13/17	0.51 (0.23, 1.11)	32.0	16.5
No	143/216	158/217	0.73 (0.59, 0.92)	22.2	14.6
Consolidation following induction					
Yes	122/186	138/192	0.76 (0.60, 0.97)	24.7	15.4
No	36/52	33/42	0.55 (0.34, 0.89)	23.3	10.9
Response at randomization					
CR	122/183	133/177	0.71 (0.55, 0.90)	23.2	14.6
CRi	33/50	30/44	0.73 (0.44, 1.20)	27.9	14.9
ECOG performance status					
0 or 1	144/217	157/217	0.74 (0.59, 0.93)	24.7	14.9
2 or 3	14/21	14/17	0.46 (0.22, 1.00)	22.2	11.2

[a]Number of events/number of subjects.
[b]Median OS in months.
[c]Prior MDS and CMML.

Analysis limitations

These prespecified subgroup analyses should be interpreted with caution to determine a difference between arms in these select subgroups because of potential selection bias, insufficient sample size, and a higher probability of making a false positive finding.

ONUREG® due to an AR occurred in 35% of patients. ARs that required an interruption of ONUREG® in more than 5% of patients included neutropenia (20%), thrombocytopenia (8%), and nausea (6%).[1]

Warnings and precautions

Risks of substitution with other azacitidine products include:

- 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[1]
- Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG® may result in a fatal AR[1]
- Treatment of patients using ONUREG® at the doses recommended for intravenous or subcutaneous azacitidine may not be effective[1]
- Do not substitute ONUREG® for intravenous or subcutaneous azacitidine[1]

Myelosuppression

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG®, respectively.[1] Febrile neutropenia occurred in 12%.[1] A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia, respectively.[1] Less than 1% of patients discontinued ONUREG® due to either neutropenia or thrombocytopenia.[1] Recommendations regarding myelosuppression in the ONUREG® prescribing information include:

- Monitor complete blood counts and modify the dosage as recommended[1]
- Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs[1]

Increased early mortality in patients with MDS

In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion–dependent anemia and thrombocytopenia due to MDS were randomized to ONUREG® or placebo.[1] A total of 107 patients received a median of 5 cycles of ONUREG® 300 mg daily for 21 days of a 28-day cycle.[1] Enrollment was discontinued early due to a higher incidence of early fatal and/or serious ARs in patients who received ONUREG® compared with placebo; the most frequent fatal AR was sepsis.[1] The ONUREG® prescribing information states that safety and effectiveness of ONUREG® for treatment of MDS have not been established, and treatment of patients with MDS with ONUREG® is not recommended outside of controlled trials.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

LACTATION

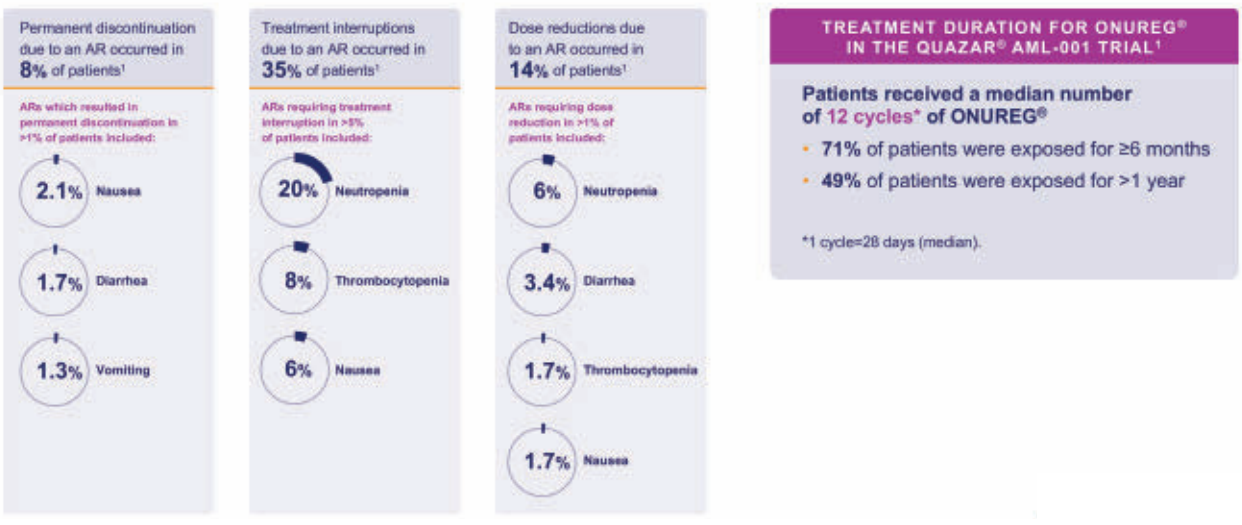
There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG® and for 1 week after the last dose.

FIGURE 4 ONUREG® safety was assessed in the QUAZAR® AML-001 trial[1]

Selected hematological laboratory abnormalities that worsened from baseline in patients who received ONUREG® in the QUAZAR® AML-001 trial[1]

Laboratory abnormality	ONUREG®		Placebo	
	Baseline Grade 0-2 N	Post-baseline Grade 3 or 4 n (%)	Baseline Grade 0-2 N	Post-baseline Grade 3 or 4 n (%)
Neutropenia	223	109 (49)	217	50 (23)
Thrombocytopenia	222	46 (21)	212	22 (10)
Anemia	229	10 (4)	223	7 (3)

FIGURE 5 Discontinuations and dose modifications in the QUAZAR® AML-001 trial with ONUREG®



Embryo-fetal toxicity

ONUREG® can cause fetal harm when administered to a pregnant woman, based on the mechanism of action and findings in animals.[1] The ONUREG® prescribing information recommends[1]:

- 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

Dosing

ONUREG® offers convenient, once-daily, oral dosing and can be taken at home. The recommended dosage of ONUREG® is one 300-mg tablet orally, once daily, taken with or without food on days 1-14 of each 28-day treatment cycle (Figure 6).[1] The patient should continue ONUREG® until disease progression or unacceptable toxicity.[1] The prescribing information recommends administering an antiemetic 30 minutes prior to each dose of ONUREG® for the first 2 cycles and states that antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.[1]

If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on day 1 of a cycle, ONUREG® should not be administered. The prescribing information states to delay the start of the cycle until the ANC is 0.5 Gi/L or more.[1] In addition, the tablets should not be split, crushed, or chewed, and the dose should be taken at approximately the same time each day.[1] If a dose is missed or not taken at the usual time, then the dose should be taken as soon as possible on the same day and the normal schedule resumed the following day, but 2 doses should not be taken on the same day.[1] If a dose is vomited, the patient should not take another dose that same day but should

FIGURE 6 ONUREG® offers convenient, once-daily, oral dosing that patients can take at home.[1] The recommended dosage of ONUREG® is one 300-mg tablet orally, once daily, with or without food on days 1-14 of each 28-day treatment cycle[1]

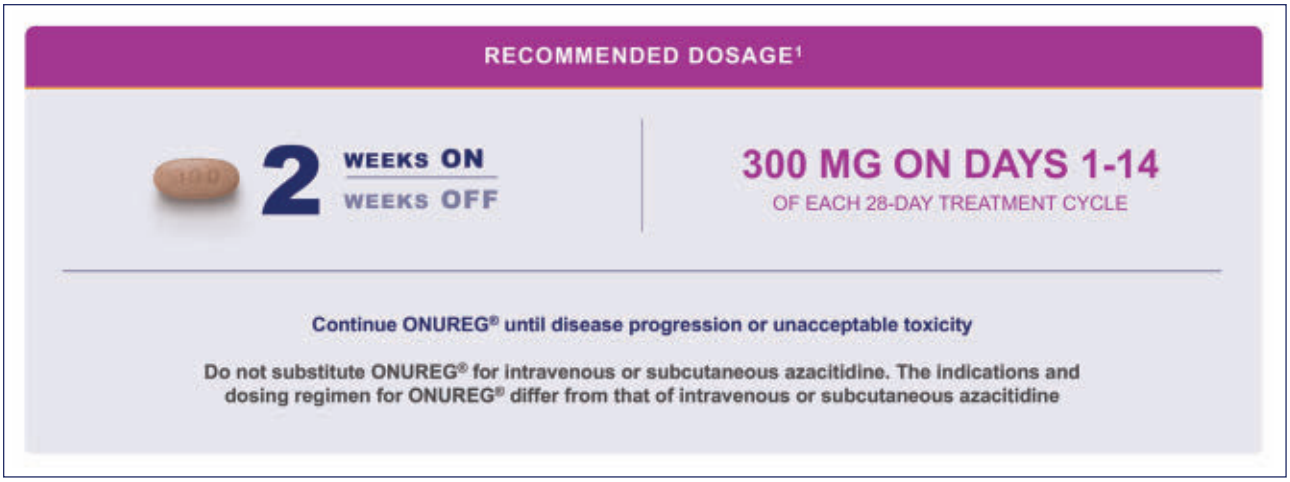
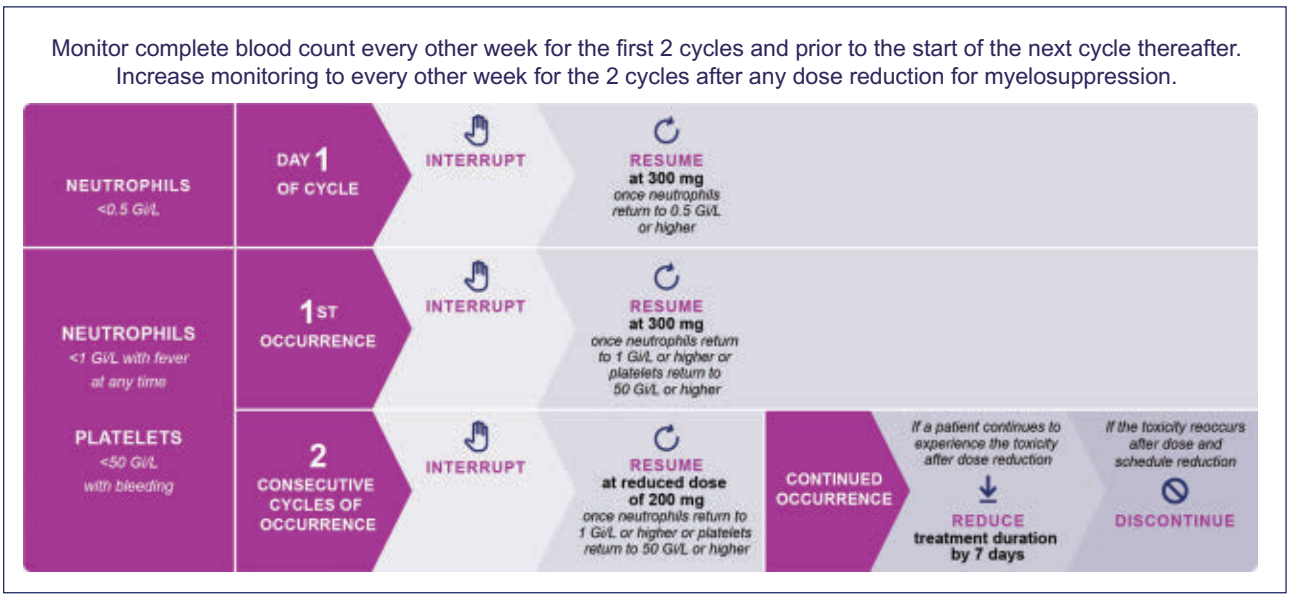


FIGURE 7 Recommended dosage modifications for ARs: myelosuppression[1]



resume the normal schedule the following day.[1]

Doses should be modified for ARs such as myelosuppression and gastrointestinal toxicity. Detailed directions on recommended dosing modifications for adverse reactions are available in the ONUREG® prescribing information.

Summary

AML is a genetically complex disease with a low overall rate of survival, particularly in the elderly, in whom the disease is most frequently diagnosed. Options for those who have achieved remission may include HSCT, continued treatment, and watchful waiting, but many patients, especially the elderly, do not proceed to HSCT for reasons including clinical, social, and personal factors as well as the cytogenetic and molecular characteristics of the individual patient's disease.

ONUREG®, an oral therapy, is the first and only FDA-approved continued AML treatment for adult patients in first remission. ONUREG® is indicated for continued treatment of adult patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy. ONUREG® is a pyrimidine nucleoside analog of cytidine that inhibits DNA and RNA methyltransferases. The QUAZAR® AML-100 clinical trial evaluated ONUREG® vs placebo as a continued treatment for adult patients with AML who had achieved a first remission (CR or

CRi). The trial demonstrated a statistically significant improvement in OS for patients randomized to ONUREG® compared to placebo, with a median OS of 24.7 months in the treated arm vs 14.8 months in the placebo arm (HR 0.69 [95% CI: 0.55, 0.86; *P*=0.0009]). The majority of ARs with ONUREG® and placebo were Grade 1 or 2 gastrointestinal events. The most common hematological Grade 3-4 ARs were neutropenia, thrombocytopenia, and anemia.

ONUREG® is given as a once-daily oral dose (one 300-mg tablet orally, with or without food, on days 1-14 of each 28-day treatment cycle).

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ONUREG® (azacitidine) tablets, for oral use Rx ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

ONUREG (azacitidine) 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.

DOSAGE AND ADMINISTRATION

Important Administration Information

Do not substitute ONUREG for intravenous or subcutaneous azacitidine. The indications and dosing regimen for ONUREG differ from that of intravenous or subcutaneous azacitidine *[see Warnings and Precautions]*.

Recommended Dosage

The recommended dosage of ONUREG is 300 mg orally once daily with or without food on Days 1 through 14 of each 28-day cycle. Continue ONUREG until disease progression or unacceptable toxicity.

Administer an antiemetic 30 minutes prior to each dose of ONUREG for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.

If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on Day 1 of a cycle, do not administer ONUREG. Delay the start of the cycle until the ANC is 0.5 Gi/L or more.

Instruct patients on the following:

- Do not split, crush, or chew ONUREG tablets.
- Take a dose about the same time each day.
- If a dose of ONUREG is missed, or not taken at the usual time, take the dose as soon as possible on the same day, and resume the normal schedule the following day. Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day. Resume the normal schedule the following day.

ONUREG is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Monitoring and Dosage Modifications for Adverse Reactions

Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression.

The recommended dosage modifications for adverse reactions are provided in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Recommended Dosage Modification
Myelosuppression *[see Warnings and Precautions]*	Neutrophils less than 0.5 Gi/L on Cycle Day 1	• Interrupt treatment. Resume at the same dose once neutrophils return to 0.5 Gi/L or higher.
	Neutrophils less than 1 Gi/L with fever at anytime	First Occurrence • Interrupt treatment. Resume at the same dose once neutrophils return to 1 Gi/L or higher. Occurrence in 2 Consecutive Cycles • Interrupt treatment. After neutrophils return to 1 Gi/L or higher, resume at reduced dose of 200 mg. • If a patient continues to experience febrile neutropenia after dose reduction, reduce the treatment duration by 7 days. • If febrile neutropenia reoccurs after dose and schedule reduction, discontinue ONUREG.
	Platelets less than 50 Gi/L with bleeding	First Occurrence • Interrupt dose. Resume at the same dose once platelets return to 50 Gi/L or higher. Occurrence in 2 Consecutive Cycles • Interrupt dose. After platelets return to 50 Gi/L or higher, resume at reduced dose of 200 mg. • If a patient continues to experience thrombocytopenia with bleeding after dose reduction, reduce the treatment duration by 7 days. • If thrombocytopenia with bleeding reoccurs after dose and schedule reduction, discontinue ONUREG.

(Continued)

Table 1: Recommended Dosage Modifications for Adverse Reactions *(Continued)*

Adverse Reaction	Severity	Recommended Dosage Modification
Gastrointestinal Toxicity *[see Adverse Reactions]*	Grade 3 or 4 Nausea or Vomiting	• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG (azacitidine).
	Grade 3 or 4 Diarrhea	• Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.
Other Adverse Reactions *[see Adverse Reactions]*	Grade 3 or 4	• Interrupt dose and provide medical support. Resume at the same dose once toxicity has resolved to Grade 1 or lower. • If toxicity re-occurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.

CONTRAINDICATIONS

ONUREG is contraindicated in patients with known severe hypersensitivity to azacitidine or its components *[see Adverse Reactions and Description (11) in full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters *[see Clinical Pharmacology (12.3) in full Prescribing Information]*, 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 of patients using ONUREG at the doses recommended for intravenous or subcutaneous azacitidine may not be effective.

Do not substitute ONUREG for intravenous or subcutaneous azacitidine *[see Dosage and Administration]*.

Myelosuppression

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%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia, respectively. Less than 1% of patients discontinued ONUREG due to either neutropenia or thrombocytopenia.

Monitor complete blood counts and modify the dosage as recommended *[see Dosage and Administration]*. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes

In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodysplastic syndromes were randomized to ONUREG or placebo. One-hundred and seven patients 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 patients who received ONUREG compared with placebo. The most frequent fatal adverse reaction was sepsis. The safety and effectiveness of ONUREG for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG is not recommended outside of controlled trials.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis caused fetal death and anomalies.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG (azacitidine) 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 *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Acute Myeloid Leukemia

The safety of ONUREG was evaluated in QUAZAR *[see Clinical Studies (14) in full Prescribing Information]*. Patients received ONUREG 300 mg (N=236) or placebo (N=233) orally once daily on Days 1 through 14 of each 28-day cycle. Among patients who received ONUREG, 71% were exposed for 6 months or longer, and 49% were exposed for greater than one year. The median duration of exposure to ONUREG was 11.6 months (range: 0.5 to 74.3 months) and the median number of cycles was 12 (range: 1 to 82 cycles).

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

Permanent discontinuation of ONUREG due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ONUREG in > 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%). Interruptions of ONUREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required an interruption of ONUREG in > 5% of patients included neutropenia (20%), thrombocytopenia (8%), and nausea (6%).

Dose reductions of ONUREG due to an adverse reaction occurred in 14% of patients. Adverse reactions which required a dose reduction in > 1% of patients included neutropenia (6%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

The most common (≥ 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.

Table 2 summarizes the adverse reactions in QUAZAR.

Table 2: Adverse Reactions (≥ 5%) in Patients with AML Who Received ONUREG with a Difference Between Arms of > 2% Compared to Placebo in QUAZAR

Adverse Reaction	ONUREG (N=236)		Placebo (N=233)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	65	3	24	< 1
Vomiting	60	3	10	0
Diarrhea	50	5	21	1
Constipation	39	1	24	0
Abdominal pain[a]	22	2	13	< 1
General disorders and administration site conditions				
Fatigue/asthenia[b]	44	4	25	1
Infections				
Pneumonia[c]	27	9	17	5
Musculoskeletal and connective tissue disorders				
Arthralgia	14	1	10	< 1
Pain in extremity	11	< 1	5	0
Metabolism and nutrition disorders				
Decreased appetite	13	1	6	1
Blood and lymphatic disorders				
Febrile neutropenia	12	11	8	8
Nervous system disorders				
Dizziness	11	0	9	0

[a] Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain.
[b] Grouped term includes fatigue and asthenia.
[c] Broad scope term includes influenza, pneumonia, respiratory tract infection, respiratory tract infection viral, bronchopulmonary aspergillosis, lung infection, Staphylococcal infection, atypical pneumonia, lower respiratory tract infection, lung abscess, Pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia fungal, Pseudomonas infection, hemoptysis, productive cough, pleural effusion, atelectasis, pleuritic pain, rales, Enterobacter test positive, and Hemophilus test positive.

Clinically relevant adverse reactions that did not meet criteria for inclusion in Table 2 were weight decreased (4%) in patients who received ONUREG (azacitidine).

Neutropenia, thrombocytopenia, and anemia of any grade occurred in 74%, 65%, and 25% of patients treated with ONUREG. Table 3 summarizes select Grades 3 or 4 hematological laboratory abnormalities in QUAZAR.

Table 3: Selected Hematological Laboratory Abnormalities That Worsened from Baseline in Patients Who Received ONUREG in QUAZAR

Laboratory Abnormality	ONUREG		Placebo	
	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)
Neutropenia	223	109 (49)	217	50 (23)
Thrombocytopenia	222	46 (21)	212	22 (10)
Anemia	229	10 (4)	223	7 (3)

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of intravenous or subcutaneous azacitidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reaction
- Interstitial lung disease
- Tumor lysis syndrome
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1) in full Prescribing Information]* and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. There are no available data on ONUREG use in pregnant women to evaluate for a drug-associated risk. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis *(see Data)*. Advise pregnant women of the potential risk to the fetus.

The estimated background of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No reproductive or developmental toxicity studies have been conducted with oral azacitidine.

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of 6 mg/m^2 azacitidine (at doses less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis) on gestation Day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation Day 15 at doses of approximately 3 to 12 mg/m^2 (at doses less than the recommended human daily dose of oral azacitidine on a mg/m^2 basis).

In rats, azacitidine was clearly embryotoxic when given an intraperitoneal injection on gestation Days 4 to 8 (postimplantation) at a dose of 6 mg/m^2 (at doses less than the recommended human daily dose on a mg/m^2 basis), although treatment in the preimplantation period (on gestation Days 1 to 3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single intraperitoneal dose of 3 to 12 mg/m^2 (at doses less than the recommended human daily dose on a mg/m^2 basis) given on gestation Days 9, 10, 11, or 12. In this study, azacitidine caused fetal death when administered at 3 to 12 mg/m^2 on gestation Days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation Day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

Lactation

Risk Summary

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.

Females and Males of Reproductive Potential

ONUREG can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting ONUREG (azacitidine).

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose.

Males

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.

Infertility

Based on animal data, ONUREG may impair male or female fertility *[see Nonclinical Toxicology (13.1) in full Prescribing Information]*.

Pediatric Use

The safety and effectiveness of ONUREG in pediatric patients have not been established.

Geriatric Use

Of the 238 patients in QUAZAR who received ONUREG, 72% were 65 years of age or older, while 12% were 75 years of age or older. No overall differences in safety or effectiveness of ONUREG were observed between these patients and younger patients.

Renal Impairment

Monitor patients with severe renal impairment (creatinine clearance [CLcr] 15 to 29 mL/min calculated by Cockcroft-Gault formula) more frequently for adverse reactions and modify the ONUREG dosage for adverse reactions *[see Dosage and Administration]*.

No dose adjustment of ONUREG is recommended for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min) *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

ONUREG has not been studied in patients with pre-existing severe hepatic impairment (total bilirubin > 3 × ULN).

A recommended dosage of ONUREG has not been established for patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN).

No dose adjustment of ONUREG is recommended for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Advise patients of the risk of myelosuppression with ONUREG and of the need to monitor complete blood counts before and during treatment *[see Warnings and Precautions]*.

Gastrointestinal Toxicity

Advise patients of the risk of gastrointestinal toxicity with ONUREG (azacitidine) and of the potential need to use anti-emetic or anti-diarrheal medications during treatment *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose *[see Use in Specific Populations]*.

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 *[see Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose *[see Use in Specific Populations]*.

Administration

Advise patients to take ONUREG with or without food at about the same time each day and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to cut, split, crush, or chew the tablets *[see Dosage and Administration]*.

Storage Instructions

Advise patients to keep ONUREG in the original container (bottles or blisters). If bottles are dispensed, advise patients to keep the container tightly closed with both desiccant canisters inside and to not eat the desiccant canisters *[see How Supplied/Storage and Handling (16) in full Prescribing Information]*.

REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

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