Azacitidine (Onureg®) for the maintenance treatment of patients with acute myeloid leukaemia (AML)

General information

Drug description [1]	Indication [2]
Azacitidine (CC-486), a hypomethylating agent that is not bioequivalent to injectable azacitidine.	Azacitidine is intended for the maintenance treatment of patients with AML who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) 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).

Current treatment [3]

- Midostaurin is recommended, within its marketing authorisation, as an option in adults for treating newly diagnosed acute FLT3mutation-positive myeloid leukaemia
  - with standard daunorubicin and cytarabine as induction therapy,
  - with high-dose cytarabine as consolidation therapy,
  - and alone after complete response as maintenance therapy.

Regulatory status

EMA [2]	FDA [4]
Approval status for this indication: On 22 April 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Onureg®, intended for the maintenance treatment of patients with AML. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 17/06/2021 The full indication is: ❖ Onureg® is indicated as maintenance therapy in adult patients with AML who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, HSCT. **Other indications**: none	**Approval status for this indication**: On 1 September 2020, the FDA approved azacitidine tablets (Onureg®), for continued treatment of patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive curative therapy. ✓ Priority review ✓ Orphan drug designation **Other indications**: none

Costs

14 Onureg® tablets 300 mg = € 12,896.00 (ex-factory price) [5]

QUAZAR AML-001 trial patients received CC-486 (300 mg) once daily on days 1 through 14 of repeated 28-day cycles; the median duration of receipt of CC-486 was 12 cycles (range, 1 to 80) [1].

Warnings and precautions [6]

- **Risks of substitution with other azacitidine products**: Do not substitute Onureg® for intravenous or subcutaneous azacitidine.
- **Myelosuppression**: Monitor complete blood counts 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. Withhold and then resume at same or reduced dose or discontinue Onureg® based on severity.
- **Embryo-foetal toxicity**: Can cause foetal harm. Advise patients of the potential risk to a foetus and use of effective contraception.

Study characteristics [1, 7-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
QUAZAR AML-001, CC-486-AML-001 NCT01757535	472	CC-486 (300 mg) administered once daily on days 1 through 14 of repeated 28-day cycles	placebo	OS	international, double-blind, placebo-controlled, phase 3 trial	-	Celgene	[1]

Efficacy (I vs. C) | **Safety** (I vs. C)

Median OS (at a median follow-up of 41.2 months): 24.7 months vs. 14.8 months; p<0.001
Estimated percentages of patients surviving at **1 year**: 72.8% vs. 55.8%
Estimated percentages of patients surviving at **2 years**: 50.6% vs. 37.1%
Median relapse-free survival: 10.2 months vs. 4.8 months; p<0.001
Median time to relapse: 10.2 months vs. 4.9 months
Median time to treatment discontinuation: 11.4 months vs. 6.1 months

HRQoL:

- At baseline, patients reported relatively low levels of fatigue and physical impairment, and the FACIT Fatigue Scale and EQ-5D-3L scores were similar in the two treatment groups.
- No meaningful differences in FACIT Fatigue scores were noted between the groups across post-baseline visits.
- Similarly, EQ-5D-3L health utility index scores were similar in the two treatment groups at all visits except at cycles 22 and 23, when scores were numerically higher in C than in I.
- Mixed-effects models with repeated measures, which controlled for baseline health-related QoL scores and other preselected covariates, showed no clinically meaningful differences in least-squares mean changes from baseline between the treatment groups at any visit.

Escalated Dosing

On identification of AML relapse with 5 to 15% blasts, 21% of patients in I group and 17% of patients in C group were assigned by their treating investigator to receive an escalated 21-day dosing schedule.
Median time to escalated dosing was 9.2 months vs. 6.0 months.
Patients received a median of two escalated dosing cycles in both the I group and the C group. 43% of the patients in the I group received more than 3 escalated dosing cycles, as compared with 18% of the patients in the C group.
Median OS among these 91 patients was 22.8 months vs. 14.6 months.

Subsequent therapy

65% of patients received at least one course of **subsequent treatment after discontinuation** of the trial regimen (including 58% in the I group and 73% in the C group). Among the patients who had AML relapse during the trial, 96% of those in the I group and 94% of those in the C group received **subsequent therapy**. 33% of patients received an **intensive chemotherapy** regimen as salvage therapy. 6% of patients in the I group proceeded to **HSCT**: 6 remained in the first remission at the time of HSCT, and 9 had had a relapse. In the C group, 14% of patients underwent HSCT, all of whom had had a relapse.

Grade ≥3 AEs: n=169/236 (72%) vs. n=147/233 (63%)

Serious TEAEs reported in ≥1% of patients: n=79/236 (33%) vs. n=59/233 (25%)

TEAEs leading to study drug discontinuation in >1 patient: n=31/236 (13%) vs. n=10/233 (4%)

AEs leading to death: n=9/236 (4%)[1] vs. n=4/233 (2%)[2]

Risk of bias (study level) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete remission, Cri=complete remission with incomplete blood count recovery, EMA=European Medicines Agency, EQ-5D-3L= three-level version of the European Quality of Life–5 Dimensions, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACIT=Functional Assessment of Chronic Illness Therapy, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRQoL=health-related quality

[1] 2 patients died from sepsis, 2 from cerebral haemorrhage, 1 from both sepsis and multiorgan failure, and 1 each from intracranial haemorrhage, cardiogenic shock, aspiration pneumonia, and suicide.
[2] 2 patients died from multiorgan failure, 1 from cerebral haemorrhage, and 1 from general health deterioration.
[3] QUAZAR AML-001 trial is currently ongoing; estimated study completion date is 12/2021.
[4] The sponsor provided the drug and placebo and designed the trial in collaboration with the authors and an independent steering committee and with advice from regulatory agencies, in accordance with principles of the Declaration of Helsinki. The sponsor collected and analysed the data and participated with the authors in its interpretation. A professional writer paid by the sponsor assisted with preparation of the submitted manuscript.

of life, HSCT=hematopoietic stem cell transplantation, I=intervention, Int.=intention, n=number, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

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