Research Review™ STUDY REVIEW

Oral azacitidine (Onureg®) in the QUAZAR AML-001 trial

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This publication summarises data from QUAZAR AML-001, a phase 3 randomised controlled trial evaluating the efficacy and safety of oral azacitidine (Onureg®) as maintenance therapy for older patients with acute myeloid leukaemia (AML) who were in first remission after intensive chemotherapy.[1] QUAZAR AML-001 met its primary endpoint, showing a significant overall survival benefit with oral azacitidine compared with placebo.[1] Relapse-free survival was also significantly prolonged with oral azacitidine compared with placebo.[1]

Introduction

Oral azacitidine is a hypomethylating agent with pharmacokinetic and pharmacodynamic profiles distinct from those of injectable azacitidine.[2,3] It can be administered in extended dosing cycles to sustain therapeutic activity.[2] Early studies found a response to oral azacitidine in patients with clinical resistance to injectable hypomethylating agents.[4]

The recently published QUAZAR AML-001 trial demonstrated the efficacy of oral azacitidine for prolonging both overall survival and relapse-free survival in older patients with acute myeloid leukaemia (AML) who were in first remission after induction chemotherapy.[1] Based on results of this trial, oral azacitidine (Onureg®) was approved by the Therapeutic Goods Administration in April 2022 for the continued treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are not able to complete intensive curative therapy.[5] Oral azacitidine was listed on the Pharmaceutical Benefits Scheme for this indication on 1 September 2023.

Methods

Participants

QUAZAR AML-001 was a phase 3 trial, conducted at 148 sites in 23 countries.[1] Eligible patients were aged ≥55 years and had newly diagnosed de novo AML, or secondary AML and intermediate- or poor-risk cytogenetic characteristics at diagnosis.[1] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 3, and had recovered from induction chemotherapy (with or without consolidation therapy) with an absolute neutrophil count ≥0.5 x 10^9/L and platelet count ≥20 x 10^9/L.[1] Patients had to be in first complete remission or complete remission with incomplete blood recovery in the 4 months prior to trial entry.[1] Patients were not candidates for haematopoietic stem cell transplantation.[1]

Treatment and assessment

Patients were randomised (1:1) in a double-blind fashion to receive oral azacitidine 300 mg or placebo once daily on days 1 to 14 of repeated 28-day cycles.[1]

Remission status was determined via examination of bone marrow and peripheral blood every 3 cycles for the first 24 cycles, at cycles 30 and 36, and as clinically indicated.[1]

Patients identified as having AML relapse with 5-15% blasts in blood or bone marrow during treatment could have their dosing regimen increased to 21 days per cycle at the discretion of the treating investigator.[1] Treatment was continued until >15% blasts were present or unacceptable toxicity occurred.[1]

Patients were able to receive best supportive care measures according to local practice, including blood product transfusions, erythropoiesis-stimulating agents, granulocyte colony-stimulating factors, nutritional support, and antibiotic, antiviral, antifungal, antiemetic or antidiarrheal therapies.[1,6]

Study endpoints

The primary study endpoint was overall survival, defined as the time from randomisation to death from any cause. All patients were followed until death, withdrawal of consent, or loss to follow-up.[1] The key secondary endpoint was relapse-free survival, defined as the time from randomisation to relapse or death, whichever occurred first.[1]

Additional secondary endpoints included health-related quality of life (HRQoL), assessed as changes from baseline in scores on the patient-reported Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale and three-level version of the European Quality of Life-5 Dimensions (EQ-5D-3L) questionnaires, and safety.[1]

Data cut-off for the primary analysis occurred in July 2019, with unblinding of treatment groups in August 2019.[7] In an optional open-label extension phase, patients who had been randomised to oral azacitidine could continue to receive treatment, while those randomised to placebo had treatment discontinued and were followed for overall survival.[7] Further analysis of overall survival was performed after a second data cut-off in September 2020.[7]

Expert comment

An ideal maintenance therapy should improve overall survival, delay or prevent relapse and be easily administered with a manageable safety profile, conducive for long-term use. QUAZAR AML-001 was an international, multicentre, phase 3, randomised double-blind trial of oral azacitidine versus placebo as maintenance therapy after first remission in older AML patients with intermediate- and high-risk cytogenetics deemed ineligible for allogeneic stem cell transplant. The study focused on a group of patients constituting an area of unmet need. Patients could be included in the trial irrespective of whether they had received consolidation chemotherapy after achieving remission. Randomisation was stratified based on age, cytogenetics, number of consolidation cycles and prior history of myelodysplastic syndrome or chronic myelomonocytic leukaemia. The primary and secondary endpoints of overall survival and relapse-free survival were measured from randomisation. The inclusion of HRQoL assessment ensured the trial was patient-focused and able to identify any significant negative impact of maintenance therapy, while incorporation of central measurable residual disease (MRD) testing provided additional vital information. Historically, maintenance therapy in AML has failed to demonstrate survival benefit (except with the immune modulator histamine dihydrochloride), and no such treatments are approved in the Australian context for patients who may require but are not eligible for allogeneic stem cell transplant. The QUAZAR-AML-001 trial thus aimed to address the treatment gap for such AML patients.

Results

Patient characteristics

A total of 472 patients were randomised to treatment with oral azacitidine (n=238) or placebo (n=234).[1] Baseline characteristics were generally balanced between treatment groups (see **Table 1**).[1,6] Median age was 68 years, and most patients had de novo AML (91%) and intermediate-risk cytogenetic characteristics (86%).[1]

All patients received induction with cytarabine-based regimens, in combination with an anthracycline or similar agent, before trial entry.[1] In addition, 80% of patients received at least one course of consolidation chemotherapy.[1]

The median time from complete remission to randomisation was 85.0 days.[1] At randomisation, 2% of patients in the oral azacitidine group and 5% of patients in the placebo group were no longer in remission.[1]

Table 1. Baseline characteristics in the QUAZAR AML-001 trial[1,6]

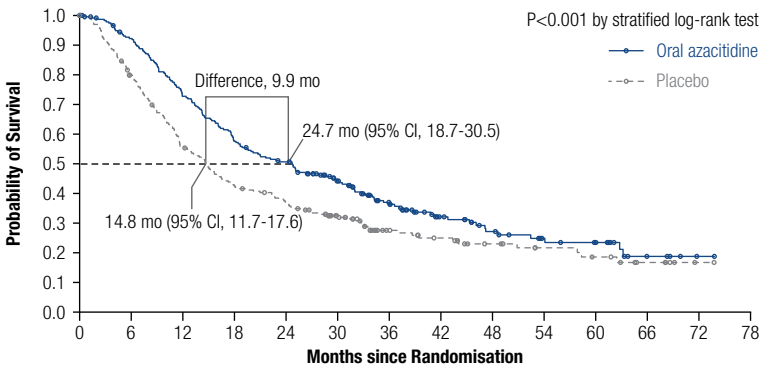
Characteristic	Placebo (n = 234)	Oral azacitidine (n = 238)
Median age, years (range)	68 (55-82)	68 (55-86)
Male, patients	54%	50%
AML WHO classification, patients		
AML with recurrent genetic abnormalities*	20%	16%
AML with myelodysplasia-related changes	18%	21%
AML not otherwise specified	62%	62%
AML type, patients		
De novo	92%	89%
Secondary	8%	11%
Prior history of MDS/CMML, patients		
ECOG PS at screening, patients		
0	47%	49%
1	45%	42%
2 or 3	7%	9%
Cytogenetic risk at diagnosis, patients		
Intermediate	87%	85%
Poor	13%	15%
Receipt of ≥2 courses of induction therapy, patients	18%	21%
Response after induction, patients		
Complete remission	84%	79%
Complete remission with incomplete blood recovery	16%	21%
Receipt of consolidation therapy, patients	82%	78%
Median time from induction to randomisation, months (range)	4.0 (1.3-15.1)	4.0 (1.4-8.8)
Median time from complete remission to randomisation, months (range)	86.0 (7-263)	84.5 (7-154)
Median bone marrow blasts, % (range)	2.0 (0.0-6.5)	2.0 (0.0-5.0)
MRD positive, patients	50%	43%
Median platelet count, x 10^9/L (range)	179 (16-636)	154 (22-801)
Median absolute neutrophil count, x 10^9/L (range)	2.8 (0.5-9.6)	3.0 (0.3-15.9)

*Includes AML with mutated *NMP1*.
AML = acute myeloid leukaemia; **CMML** = chronic myelomonocytic leukaemia; **ECOG PS** = Eastern Cooperative Oncology Group performance status; **MDS** = myelodysplastic syndrome; **MRD** = measurable residual disease; **WHO** = World Health Organization.

Efficacy

Overall survival in the primary analysis

At a median follow-up duration of 41.2 months, median overall survival was significantly longer in the oral azacitidine group compared with the placebo group (24.7 months vs 14.8 months, p<0.001; see **Figure 1**).[1]



No. at Risk

Oral azacitidine	238	213	168	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	127	96	82	58	34	27	19	14	11	6	1	0

Figure 1. Overall survival from the time of randomisation in the QUAZAR-001 trial.[1]
CI = confidence interval; **mo** = months.

The estimated proportion of patients surviving at 1 year was 72.8% in the oral azacitidine group and 55.8% in the placebo group (difference 17.0%; 95% CI 8.4%-25.6%).[1] Corresponding proportions at 2 years were 50.6% and 37.1%, respectively (difference 13.5%; 95% CI 4.5%-22.5%).[1] An overall survival benefit at 2 years was apparent with oral azacitidine in most subgroups when patients were assessed according to baseline characteristics, including use of consolidation therapy, remission status after induction and MRD status at randomisation (see **Table 2**).[1]

Table 2. Univariate analyses of overall survival at 2 years according to baseline characteristics[1]

Characteristic	Overall survival at 2 years		
	Placebo	Oral azacitidine	Difference (95% CI)
Overall	37.1%	50.6%	13.5% (4.5%, 22.5%)
Age			
≥55 to <65 years	45.1%	61.3%	16.2% (-0.9%, 33.4%)
≥65 years	33.9%	46.7%	12.8% (2.3%, 23.3%)
≥75 years	24.8%	51.9%	27.1% (0.7%, 53.4%)
Sex			
Male	39.0%	47.8%	8.8% (-3.7%, 21.4%)
Female	34.8%	53.4%	18.6% (5.7%, 31.5%)
WHO AML classification			
AML with recurrent genetic abnormalities	47.0%	50.0%	3.0% (-18.6%, 24.5%)
AML with myelodysplasia-related changes	29.8%	43.5%	13.8 (-6.3%, 33.8%)
AML not otherwise specified	35.6%	53.8%	18.1% (6.8%, 29.5%)
ECOG PS score			
0 or 1	38.0%	50.9%	13.0% (3.5%, 22.4%)
2 or 3	25.5%	47.6%	22.1% (-8.2%, 52.4%)
History of MDS or CMML			
Yes	31.4%	66.7%	35.3% (4.9%, 65.7%)
No	37.5%	49.0%	11.5% (2.1%, 20.9%)
Cytogenetic risk at induction			
Intermediate	40.4%	54.1%	13.6% (3.9%, 23.4%)
Poor	15.5%	30.03%	14.8% (-5.6%, 35.2%)
Consolidation after induction			
Yes	39.2%	50.8%	11.6% (1.4%, 21.7%)
No	27.4%	50.0%	22.6% (3.2%, 42.0%)
Consolidation cycles			
1 or 2	37.6%	50.8%	13.3% (2.9%, 23.7%)
3	61.5%	50.0%	-11.5% (-59.5%, 36.4%)
Response at randomisation			
Complete remission	36.7%	49.7%	13.0% (2.7%, 23.3%)
Complete remission with incomplete blood recovery	38.6%	55.1%	16.5% (-3.8%, 36.8%)
MRD status at randomisation			
Positive	22.0%	39.5%	17.5% (5.3%, 29.8%)
Negative	51.7%	58.6%	6.9% (-5.8%, 19.5%)

AML = acute myeloid leukaemia; **CI** = confidence interval;
CMML = chronic myelomonocytic leukaemia;
ECOG PS = Eastern Cooperative Oncology Group performance status;
MDS = myelodysplastic syndrome; **MRD** = minimal residual disease;
WHO = World Health Organization.

Overall survival in updated analysis

At extended follow-up (median 51.7 months), median overall survival remained unchanged in both treatment arms, but Kaplan-Meier curves showed greater separation at later time points than in the primary analysis (see **Figure 2**).[7] The estimated proportion of patients surviving at 3 years was 37.4% in the oral azacitidine group and 27.9% in the placebo group.[7] Corresponding proportions at 5 years were 26.2% and 19.2%, respectively.[7]

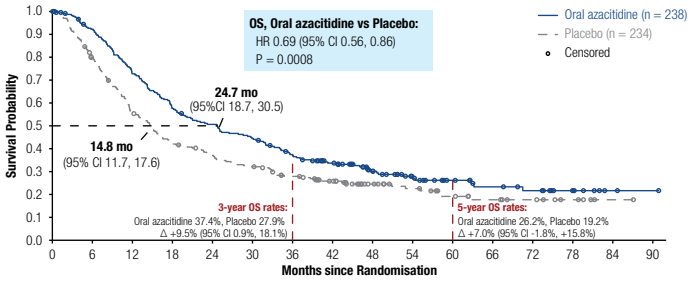


Figure 2. Long-term overall survival from the time of randomisation in the QUAZAR-001 trial.[7]
CI = confidence interval; **HR** = hazard ratio; **mo** = months; **OS** = overall survival.

When baseline characteristics of long-term survivors (alive at ≥3 years after randomisation) were compared with those of non-long-term survivors (died or were censored for overall survival <3 years after randomisation), the long-term survivors were more likely to have intermediate-risk cytogenetics and mutated *NPM1* at AML diagnosis, and to be MRD-negative at randomisation (see **Table 3**).[7]

Table 3. Baseline characteristics of long-term vs non-long term survivors[7]

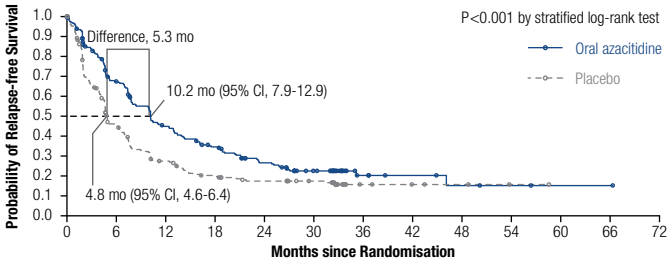
Characteristic	Placebo		Oral azacitidine	
	Long-term survivors* (n = 57)	Non-long-term survivors† (n = 177)	Long-term survivors* (n = 83)	Non-long-term survivors† (n = 155)
Median age, years (range)	67 (55-79)	69 (55-82)	67 (55-80)	69 (55-86)
Cytogenetic risk at diagnosis, patients				
Intermediate	96%	84%	94%	81%
Poor	5%	16%	6%	19%
Mutated *NPM1* at diagnosis, patients	46%	26%	45%	19%
Response after induction, patients				
Complete remission	84%	84%	80%	78%
Complete remission with incomplete blood recovery	16%	16%	20%	22%
Consolidation after induction, patients				
Yes	88%	80%	77%	79%
No	12%	20%	23%	21%
Consolidation cycles, patients				
1	39%	45%	42%	48%
2	42%	30%	33%	28%
3	7%	5%	2%	3%
MRD-positive at randomisation, patients	30%	56%	35%	48%
Conversion to negative status on-study	71%	10%	76%	22%

*Alive at ≥3 years after randomisation; †Died or were censored for overall survival <3 years after randomisation.
MRD = minimal residual disease.

Conversion from MRD-positive status at baseline to MRD-negative status during the study was significantly more frequent in long-term survivors compared with non-long-term survivors (p<0.001).[7] Conversion to MRD-negative status was approximately 2 times more frequent in the oral azacitidine vs placebo group (37% vs 19%, respectively).[7]

Relapse-free survival

At a median follow-up of 41.2 months, median relapse-free survival was significantly longer in the oral azacitidine group compared with the placebo group (10.2 months vs 4.8 months, p<0.001; see **Figure 3**).[1] The estimated proportion of patients with relapse-free survival at 6 months was 67.4% in the oral azacitidine group and 45.2% in the placebo group.[1] Corresponding proportions at 1 year were 44.9% and 27.4%, respectively.[1] A relapse-free survival benefit at 1 year was apparent with oral azacitidine at 1 year in most subgroups when patients were assessed according to baseline characteristics, including use of consolidation therapy, remission status after induction and MRD status at randomisation.[1]



No. at Risk

Oral azacitidine	238	143	92	68	47	30	8	5	3	2	1	1	0
Placebo	234	96	55	37	29	23	6	4	3	1	0		

Figure 3. Relapse-free survival from the time of randomisation in the QUAZAR-001 trial.[1]
CI = confidence interval; **mo** = months.

Expert comment

The study population of QUAZAR AML-001 represented a cohort of older AML patients (median age 68 years), the majority of whom were diagnosed with de novo AML and had intermediate-risk cytogenetics. Baseline patient characteristics, disease biology, treatment received and disease status at randomisation were well matched in the oral azacitidine and placebo groups. The study met the primary and secondary endpoints of overall survival and relapse-free survival. At a median follow-up of 41 months, median overall survival in the oral azacitidine group was 24.7 months compared with 14.8 months in the placebo group. The overall survival benefit with oral azacitidine was maintained across various subgroups of baseline patient and disease characteristics. The survival benefit was observed regardless of the number of consolidation chemotherapy cycles received. An extended follow-up showed ongoing survival benefit, reinforcing the sustained benefit from maintenance therapy after treatment completion. There was a higher rate of MRD conversion (positivity to negativity) with oral azacitidine maintenance, and a quarter of MRD responders achieved a response more than 6 months after commencing oral azacitidine maintenance.[8] Oral azacitidine maintenance improved survival independent of the *NPM1* or *FLT3* mutation status, cytogenetics or MRD status at randomisation.[9] Long-term survivors were more likely to have intermediate-risk cytogenetics, mutated *NPM1* or be MRD-negative at randomisation.

Health-related quality of life

At baseline, patients reported relatively low levels of fatigue and physical impairment, and FACIT-Fatigue and EQ-5D-3L scores were similar between the oral azacitidine and placebo groups.[1] There were no meaningful differences between groups in FACIT-Fatigue scores at any time point during the treatment period.[1] EQ-5D-3L health utility index scores were also similar in the oral azacitidine and placebo groups at all time points except cycles 22 and 23, when they were numerically higher in the placebo vs oral azacitidine group.[1] However, after controlling for baseline HRQoL scores and other preselected covariates, there were no clinically meaningful differences in least-squares mean changes from baseline between treatment groups at any time point.[1]

Safety

The median duration of oral azacitidine treatment was 12 cycles (range 1-80), and the median duration of placebo treatment was 6 cycles (range 1-73).[1] In the period between the first dose and 28 days after the last dose, the most common adverse events were nausea, vomiting and diarrhoea, which all occurred more frequently in the oral azacitidine vs placebo group (see **Table 4**).[1] The most common haematologic adverse events were neutropenia, thrombocytopenia and anaemia.[1]

Oral azacitidine-induced nausea and vomiting occurred mainly during the first 2 treatment cycles, and was less common during subsequent cycles after incorporation of antiemetic agents.[1] The frequency of haematologic adverse events was relatively constant over the first 12 treatment cycles.[1]

Table 4. Adverse events occurring in ≥10% of patients in either group in the QUAZAR AML-001 trial[1]

	Placebo (n = 233)		Oral azacitidine (n = 236)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any event	97%	63%	98%	72%
Nausea	24%	<1%	65%	3%
Vomiting	10%	0	60%	3%
Diarrhoea	21%	1%	50%	5%
Neutropenia	26%	24%	44%	41%
Constipation	24%	0	39%	1%
Thrombocytopenia	27%	21%	33%	22%
Fatigue	19%	1%	30%	3%
Anaemia	18%	13%	20%	14%
Asthenia	6%	<1%	19%	1%
Pyrexia	19%	<1%	15%	2%
Arthralgia	10%	<1%	14%	1%
Abdominal pain	7%	0	13%	1%
Upper respiratory tract infection	14%	0	13%	<1%
Decreased appetite	6%	1%	13%	1%
Cough	17%	0	12%	0
Febrile neutropenia	8%	8%	12%	11%
Back pain	10%	1%	12%	1%
Leukopenia	8%	6%	11%	8%
Pain in extremity	5%	0	11%	<1%
Dizziness	9%	0	11%	0
Headache	11%	<1%	10%	0
Peripheral oedema	10%	<1%	9%	0

Infections were the most common serious adverse event, occurring in 17% of patients in the oral azacitidine group and 8% of patients in the placebo group.[1]

Adverse events led to dose interruptions in 43% of patients in the oral azacitidine group and 8% of patients in the placebo group, and led to dose reductions in 16% and 3% of patients, respectively.[1] The most common adverse event leading to dose modification in both groups was neutropenia.[1]

Adverse events leading to treatment discontinuation occurred in 13% of patients in the oral azacitidine group and 4% of patients in the placebo group.[1] The most common events leading to discontinuation were gastrointestinal events; ≤1% of patients in each group discontinued treatment because of a haematologic adverse event (thrombocytopenia).[1,6]

Adverse events leading to death occurred in 4% of patients in the oral azacitidine group (causes included aspiration pneumonia, cardiogenic shock, cerebral/intracranial haemorrhage, multiorgan failure, sepsis and suicide) and 2% of patients in the placebo group (cerebral hemorrhage, general health deterioration and multiorgan failure).[1]

Expert comment

HRQoL was a secondary endpoint of the QUAZAR AML-001 trial. Overall HRQoL at study entry was preserved during oral azacitidine treatment, with no clinically meaningful differences in patient-reported HRQoL scores from baseline, or in scores in the placebo arm at any post-baseline visit.

Oral azacitidine maintenance had a manageable toxicity and safety profile. Median duration of treatment with oral azacitidine was 12 cycles. The most common non-haematological adverse events were nausea, vomiting and diarrhoea. These were largely low grade, occurred most frequently in the first two treatment cycles and could be managed by prophylactic use of antiemetic agents in the first 2 cycles.[10] The most common haematologic adverse events were neutropenia, thrombocytopenia and anaemia. These were also the most frequent Grade 3-4 adverse events with oral azacitidine. The frequency of haematologic adverse events during initial treatment cycles was relatively consistent in the oral azacitidine arm, with a downward trend in later cycles. Blood count monitoring every other week, for at least the first 2 cycles of oral azacitidine treatment and before the start of each cycle, is recommended.[10] More frequent monitoring is also recommended for the 2 treatment cycles following any dose reduction for myelosuppression. Haematologic adverse events secondary to oral azacitidine rarely required treatment cessation and could be managed with treatment delays, interruptions, or oral azacitidine dosing modifications.

Oral azacitidine significantly improves overall survival and relapse-free survival without diminishing HRQoL, has a manageable toxicity and safety profile and is convenient for use in the outpatient setting.

Escalated dosing

The dosing regimen was increased to 21 days per cycle in 21% of patients in the oral azacitidine group and 17% of patients in the placebo group, following identification of AML relapse with 5-15% blasts.[1] Median overall survival from the time of randomisation among these patients was 22.8 months in the oral azacitidine group and 14.6 months in the placebo group.[1] Among the patients who had central confirmation of ≥5% blasts in their bone marrow immediately before 21-day dosing, 23% of those in the oral azacitidine group and 11% of those in the placebo group had restoration of complete remission status while receiving escalated dosing.[1]

Study interpretation

Oral azacitidine is not bioequivalent to injectable azacitidine and cannot be used interchangeably.[3] In the UK National Cancer Research Institute AML16 trial involving patients with AML or high-risk myelodysplastic syndromes, maintenance therapy with injectable azacitidine did not improve overall survival compared with no maintenance therapy in patients who had received one previous consolidation cycle or in those who were MRD-positive after induction chemotherapy.[11] In comparison, the QUAZAR AML-001 trial showed a survival benefit with oral azacitidine regardless of receipt of consolidation therapy or MRD status at randomisation. Differences may reflect the pharmacodynamic effect of extending drug exposure and sustaining epigenetic regulation over the course of the treatment cycle.[2] Furthermore, the convenience of oral dosing may improve adherence and facilitate longer-term treatment than is practical with injectable agents.

Take-home messages

- In the QUAZAR AML-001 trial, oral azacitidine prolonged overall survival and relapse-free survival in older patients with AML in first remission after induction chemotherapy, without impacting on health-related quality of life[1]
- The benefits of oral azacitidine were evident in most subgroups when patients were assessed according to age, sex, cytogenetic risk, response to induction chemotherapy, receipt of consolidation therapy and MRD status at randomisation[1]
- Gastrointestinal events were the most common adverse events overall, but decreased in frequency after the incorporation of antiemetic agents[1]
- Neutropenia was the most common haematologic adverse event; this could be managed via dose modification[1]

Expert's concluding remarks

The QUAZAR AML-001 trial established the role of oral azacitidine maintenance in older AML patients with intermediate- and high-risk cytogenetics in first remission. A survival benefit was achieved with an oral maintenance therapy in the outpatient setting, with a manageable safety profile and no adverse impact on HRQoL. In the absence of similar options, oral azacitidine maintenance therapy is the treatment standard for older AML patients with intermediate- and high-risk cytogenetics who are in remission after intensive chemotherapy but are ineligible for allogeneic transplant.

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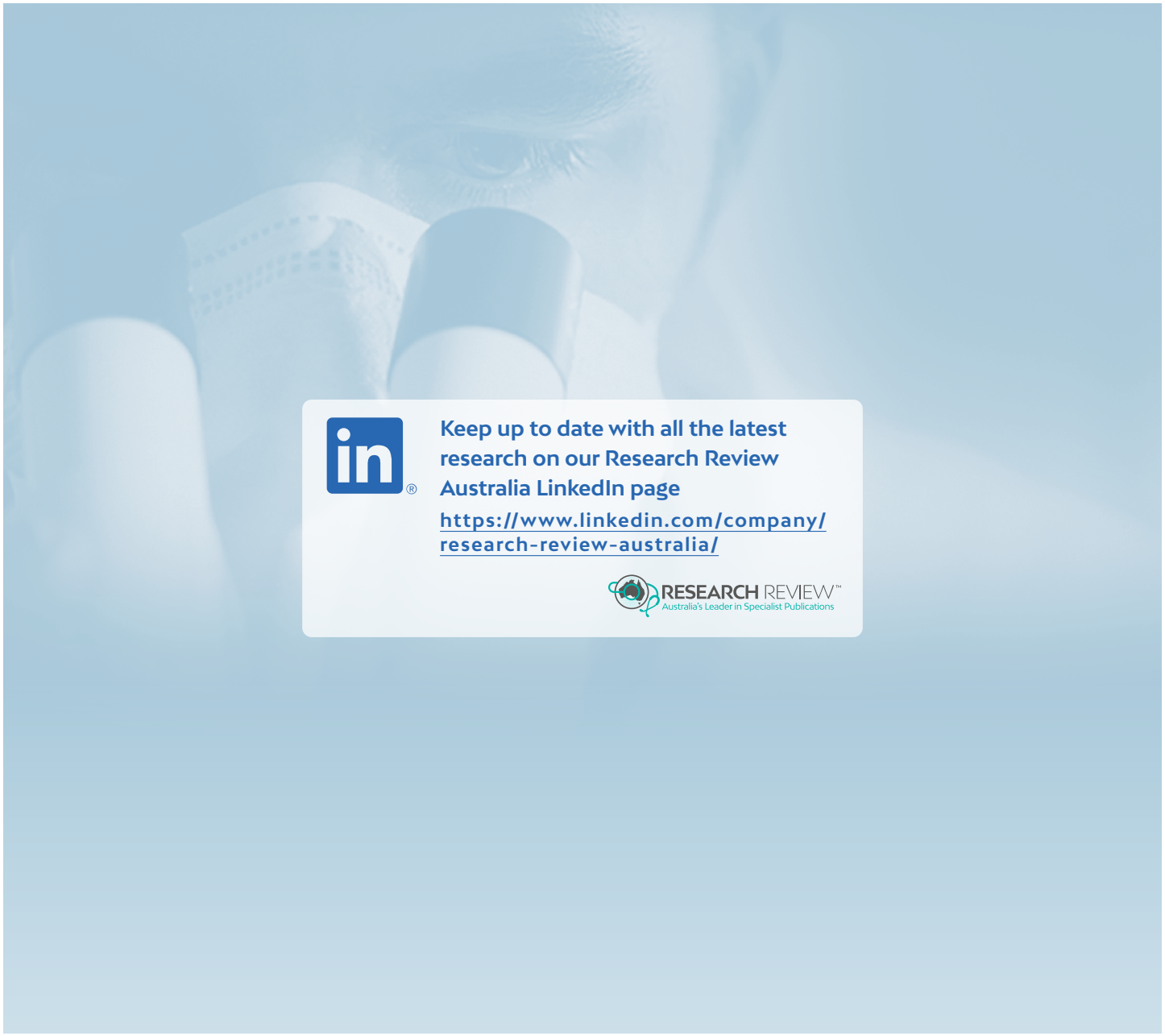

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