SPECIAL SUPPLEMENT
January 2024

CANADIAN HEMATOLOGY TODAY

MAINTENANCE THERAPY IN ACUTE MYELOID LEUKEMIA: A NEW STANDARD OF CARE

Andre Schuh, MD

ABOUT THE AUTHOR

Andre Schuh, MD

Dr. Andre Schuh is a staff hematologist at the Princess Margaret Cancer Centre, and a Professor of Medicine at the University of Toronto, Toronto, Ontario, Canada. He has been at Princess Margaret since 1992, where he has focused on acute leukemia and MDS, and has managed an extensive clinical trial portfolio. In addition to a variety of other administrative roles, he was the head of the leukemia program at Princess Margaret from 2010–2014, and from 2012–2018, was Medical Director, Malignant Hematology. His current interests include acute leukemia management and clinical trials (especially in the older patient), and the development of Canadian province- and country-wide leukemia management strategies. He is the founding Chair of the Canadian Leukemia Study Group (CLSG)/Groupe Canadien d'Étude Sur La Leucémie (GCEL), a country-wide cooperative of leukemia-treaters who share the goal of improving acute leukemia diagnosis and management across Canada, by identifying and defining diagnostic and management best practices, promoting Canada-wide standards-of-care, fostering clinical and basic leukemia research, and improving new drug access.

Affiliations: Princess Margaret Cancer Centre, Toronto, ON
University of Toronto, Toronto, ON

MAINTENANCE THERAPY IN ACUTE MYELOID LEUKEMIA: A NEW STANDARD OF CARE

Introduction and History

Initial adult acute myeloid leukemia (AML) treatment is generally divided into two intensity-based approaches based on patient (age, comorbidities, patient preference, among others) and disease (genetic risk, natural history [de novo vs. secondary AML (sAML) vs. therapy-related AML (tAML)], among others) factors.[1] For those patients deemed appropriate for intensive treatment, current approaches result in the achievement of a complete remission (CR) in a majority of cases. In such patients, remissions are generally consolidated by further cycles of chemotherapy, or by additional chemotherapy followed by an allogenic hematopoietic stem cell transplant (alloHSCT), as appropriate, depending on patient and disease factors as above.[1]

Nevertheless, a significant proportion (>50% overall) of patients consolidated with chemotherapy or alloHSCT still experience disease relapse.[2,3] Transplant-requiring patients who are transplant ineligible, or who are ultimately unable to proceed to transplant because of patient or donor factors, are at a particularly high risk of relapse.

Relapsed AML is difficult to treat, and outcomes are extremely poor.[4] Relapsed AML is also associated with profound patient and caregiver suffering, along with considerable overall societal costs. An ongoing question in leukemia treatment is thus how AML relapse can be prevented in patients who are not proceeding to transplant, as well as in high-risk patients after transplant.

The Concept of Maintenance Therapy

An obvious solution to this question would be ongoing chemotherapy, with a view toward preventing (or at least delaying) disease relapse. Indeed, such an approach has been used successfully for decades in acute lymphoblastic leukemia (ALL),[5] and until recently in acute promyelocytic leukemia (APL).[6] For example, in the pediatric-inspired adult ALL protocol used at Princess Margaret Cancer Centre, patients ultimately complete 24 cycles of maintenance therapy, each lasting 3 weeks, each of which includes dexamethasone, vincristine/vinblastine, methotrexate (MTX), and 6-mercaptopurine (6-MP).[7,8] In the case of APL, maintenance (now largely eliminated in the age of arsenic trioxide) consisted of cyclic all-trans retinoic acid (ATRA), 6-MP, and MTX, given for 1–2 years.[6]

Considering the established maintenance traditions for adult ALL and APL, the question of why there are no similar maintenance approaches in AML has remained an ongoing issue. Surely, there must be a way to recreate the ALL and APL maintenance experience in AML. Consistent with this notion, there have been numerous AML maintenance trials over the last several decades trying to replicate the ALL/APL maintenance experience.

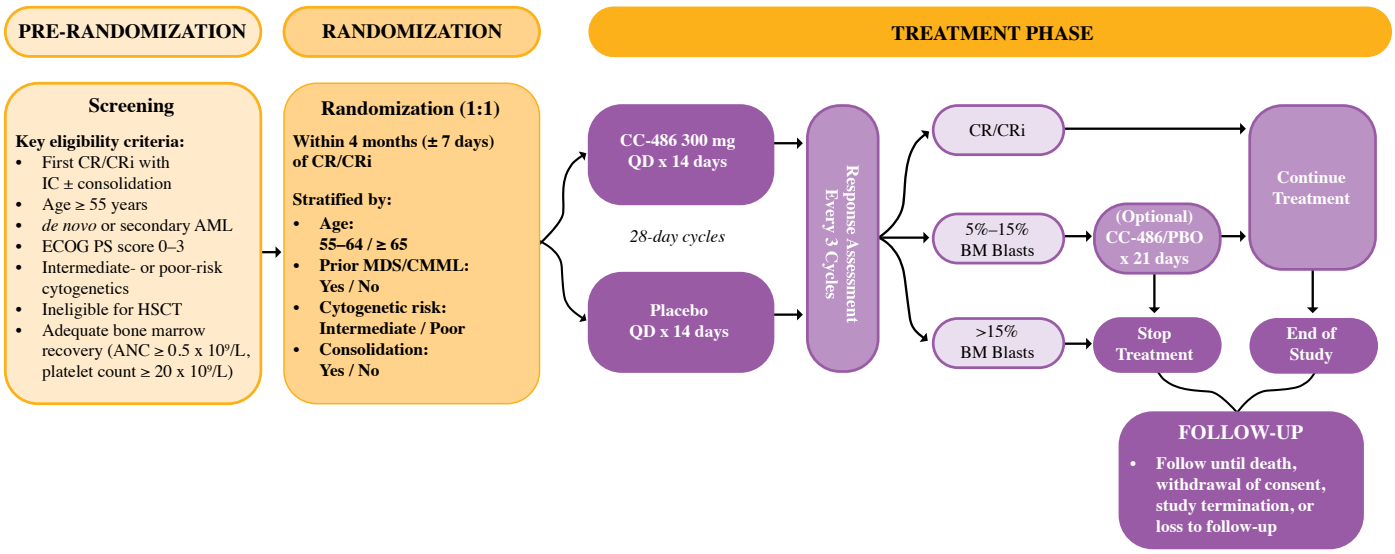


Figure 1. Quazar AML-001 - Study Deisgn; *adapted from Wei and Dohner, 2020.*

These trials have included studies in 4 main categories: post-induction cytotoxic chemotherapy, immunotherapy, hypomethylating agents (HMAs), and targeted small molecule therapy, (reviewed overall in[9,10]) with the latter focusing predominantly on post-alloHSCT TKI maintenance in patients with internal tandem duplications (ITDs) in the *fms like tyrosine kinase 3 (FLT3)* gene.[11-13] This review will focus on post-induction maintenance therapy in AML.

While numerous maintenance studies have been conducted in AML over the last few decades, practice-changing results have remained elusive. A subset of studies did demonstrate modestly improved disease-free survival (DFS), but this effect did not translate into improved overall survival (OS), which is a metric generally considered essential for maintenance drug approval. Recently, the most exciting and accessible studies have focused on maintenance therapy with HMAs - both decitabine and azacitidine. Coming from a Canadian perspective, this review will focus on azacitidine.

Adult Acute Myeloid Leukemia Maintenance With Azacitidine: HOVON97

The phase 3 HOVON97 study[14] included 116 patients (≥ 60 years of age) with AML or with high-risk myelodysplastic syndrome (MDS) (Refractory Anemia With Excess Blasts) in CR/CRi (CR with incomplete hematologic recovery) after at least 2 cycles of intensive chemotherapy (IC). These patients were randomized to observation (N=60), or subcutaneous (SC) azacitidine maintenance (N=56; 50 mg/m^2, subcutaneously, days 1–5, every 4 weeks until relapse, for a maximum of 12 cycles). Fifty-five patients received at least 1 cycle of azacitidine, 46 patients received at least 4 cycles, and 35 patients received at least 12 cycles. DFS was significantly better for the azacitidine treatment group (P = 0.04), including after adjustment for poor-risk cytogenetic abnormalities at diagnosis and platelet count at randomization (as a surrogate for CR vs CRi), with an estimated 12-month DFS of 64% for the azacitidine group and 42% for the control group. Consistent with this finding, rescue treatment was used more often in the observation group (n=32) than in the azacitidine maintenance group (n=9). However, as in prior maintenance studies, OS did not differ between treatment groups, both with and without censoring for alloHSCT.

Quazar AML-001:

The phase 3, double-blind, placebo-controlled, randomized Quazar AML-001 trial[15] assessed an oral formulation of azacitidine (CC-486, Oral-AZA; not bioequivalent to injectable azacitidine) as maintenance therapy in patients in first CR after IC.

The Quazar AML-001 study design is shown in **Figure 1**. Patients were eligible for the study if they were in first CR/CRi after IC +/- consolidation chemotherapy, were ≥ 55 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤3, had *de novo* or secondary AML with intermediate- or poor-risk cytogenetics, and were deemed ineligible for alloHSCT. A total of 427 patients met these criteria and were randomized 1:1 within 120 (+/-) 7 days of CR/CRi to oral azacitidine (CC-486, Oral-AZA, 300 mg) or placebo once daily for 14 days in 28-day cycles. The primary end point was OS. Secondary end points included relapse-free survival (RFS) and health-related quality of life outcomes.

Patients in the oral azacitidine and placebo arms were well balanced for baseline demographics and disease characteristics including age (median 68 years; range 55–86 years), sex, type of AML, ECOG PS score at screening, cytogenetic risk at diagnosis, induction response (CR vs. CRi), number of induction courses received (1 vs. ≥2), receipt of consolidation chemotherapy (yes/no), median times from receipt of IC and from CR/CRi to randomization, and marrow blasts (%) and measurable residual disease (MRD) positivity (%) at randomization.

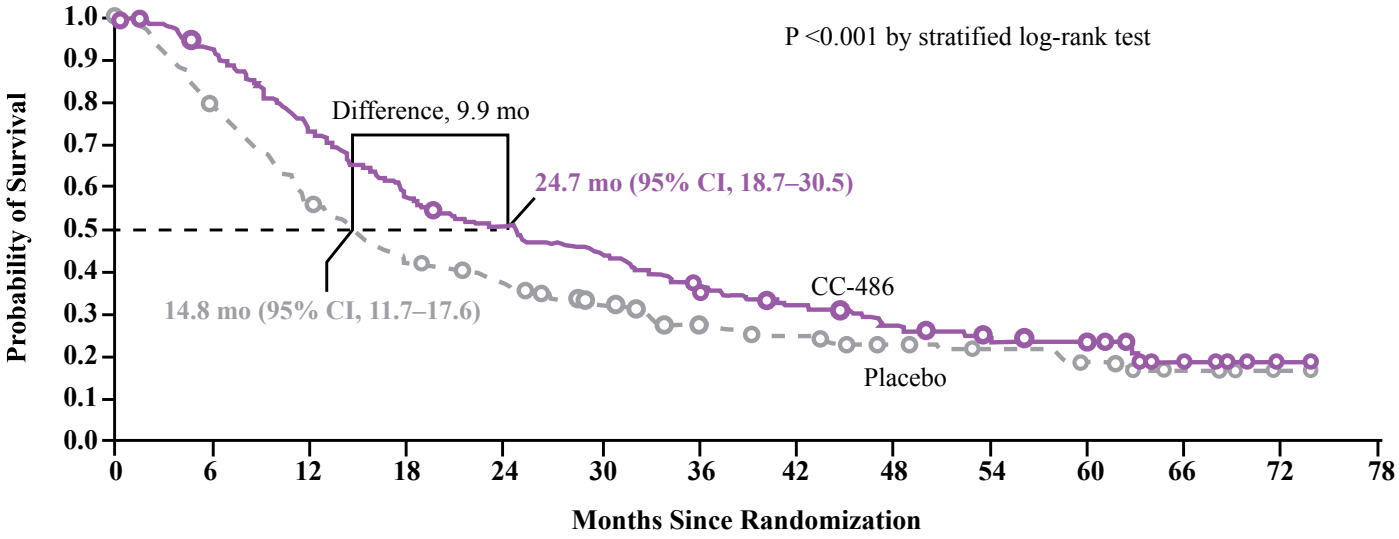


Figure 2. Overall Survival - Quazar AML-001; *adapted from Wei and Dohner, 2020.*

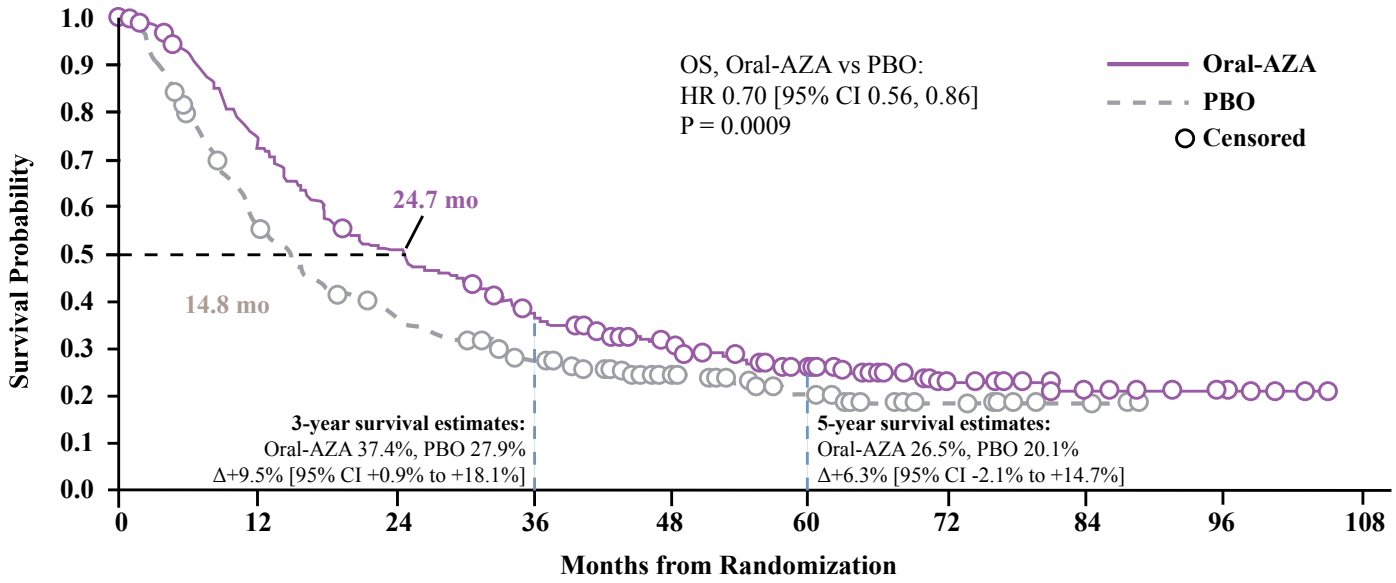


Figure 3. Overall Survival - Quazar AML-001 - 55.5 month median follow-up; *adapted from Wei and Dohner, 2023.*

As shown in **Figure 2**, with a median follow-up of 41.2 months, median OS from the time of randomization was significantly longer with Oral-AZA (CC-486) than with placebo (24.7 months and 14.8 months, respectively; P<0.001). Median RFS was also significantly longer with Oral-AZA than with placebo (10.2 months and 4.8 months, respectively; P<0.001). At both 12 and 24 months, the proportion of patients still alive was significantly greater with Oral-AZA than with placebo (12 months, 73% vs. 56%; 24 months, 51% vs. 37%, respectively). Consistent with these findings, univariate subgroup analysis looking at survival at two years demonstrated that Oral-AZA was favoured over placebo in virtually all demographic- and disease characteristic-defined subgroups. A notable exception was the small subgroup of patients (n=6) who had received 3 consolidations.

Importantly, although other AML maintenance studies have demonstrated an RFS benefit, *this trial was the first (and to date, only) to demonstrate an OS benefit as well*. Longer follow-up (**Figure 3**) has confirmed the OS benefit of oral azacitidine.[16] Indeed, with 55.5 months of follow-up, estimated 3-year survival rates in the Oral-AZA and placebo arms were 37.4% and 27.9%, respectively, while 5-year survival rates were 26.5% versus 20.1%.[16]

Quazar AML-001: Adverse Events

Overall, oral azacitidine was well-tolerated. The most common adverse events in the CC-486 (Oral-AZA) and placebo groups were grade 1 or 2 gastrointestinal (GI) events.[15] Notably, however, the frequency of GI toxicities in the Oral-AZA arm resembled that of the placebo arm after one to two cycles of therapy (anti-nausea prophylaxis had not been included up-front in the study, and thus was introduced during the study only as required).[17]

Other common grade 3 or 4 adverse events were neutropenia (in 41% of patients in the CC-486 group and 24% of patients in the placebo group) and thrombocytopenia (22% in the CC-486 group and 21% in the placebo group).[15,17] These hematologic events were managed easily, and also were less commonly observed with subsequent cycles. Overall, drug discontinuation due to toxicity was extremely rare.

Quazar AML-001: Health-Related Quality of Life Measures

An obvious theoretical concern in the Quazar AML-001 study was that ongoing chemotherapy to maintain remission might achieve this goal, but at the cost of impaired quality of life. Patients in the Quazar AML-001 study were thus followed using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, as well as by the EQ-5D-3L wellness tool. Notably, the OS and RFS benefits of Oral-AZA for patients with AML in remission were not associated with increased fatigue or with inferior Health-Related Quality of Life.[18]

Quazar AML-001: Alternative Explanations for Study Results?

Following the first dissemination of the initial Quazar AML-001 data, questions regarding potential alternative explanations for the study results were raised. Alternative explanations included the following: Could the Quazar results be attributed not to oral azacitidine, but rather to patient status at randomization with respect to 1.) **differences in induction and consolidation chemotherapy received**, 2.) **MRD status at baseline**, and 3.) **mutational status of the *nucleophosmin1* (*NPM1*) and *FLT3* genes at diagnosis?**

1.) Differences in Induction and Consolidation Chemotherapy Received

The most common agents used for induction and consolidation were cytarabine (induction, 99%, consolidation, 80%), idarubicin (induction, 55%, consolidation, 20%), and daunorubicin (induction, 33%, consolidation, 8%). The use of these agents was similar between the Oral-AZA and placebo arms. Overall, 79% of patients (n=375) received a single induction course before achieving remission, while 21% (n=97) received ≥2 inductions.[19]

The majority of patients (~80%) received consolidation after induction, and use of consolidation was similar

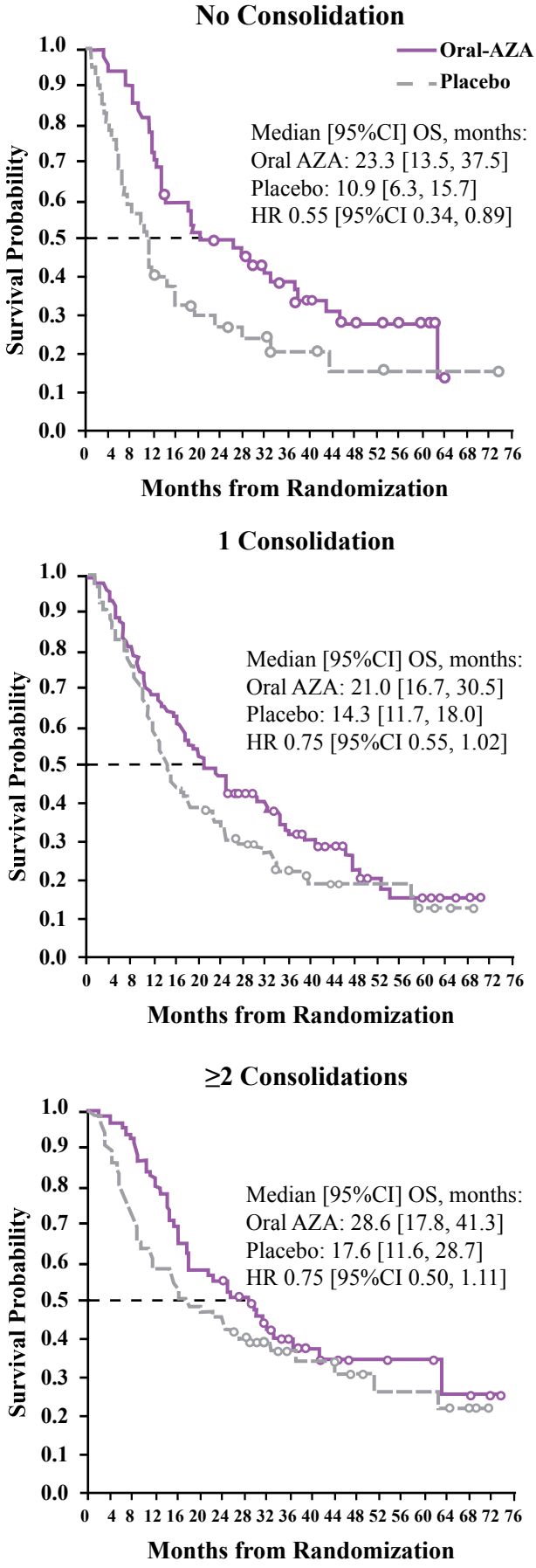


Figure 4. Overall survival by number of consolidations received; *adapted from Wei and Roboz, 2023.*

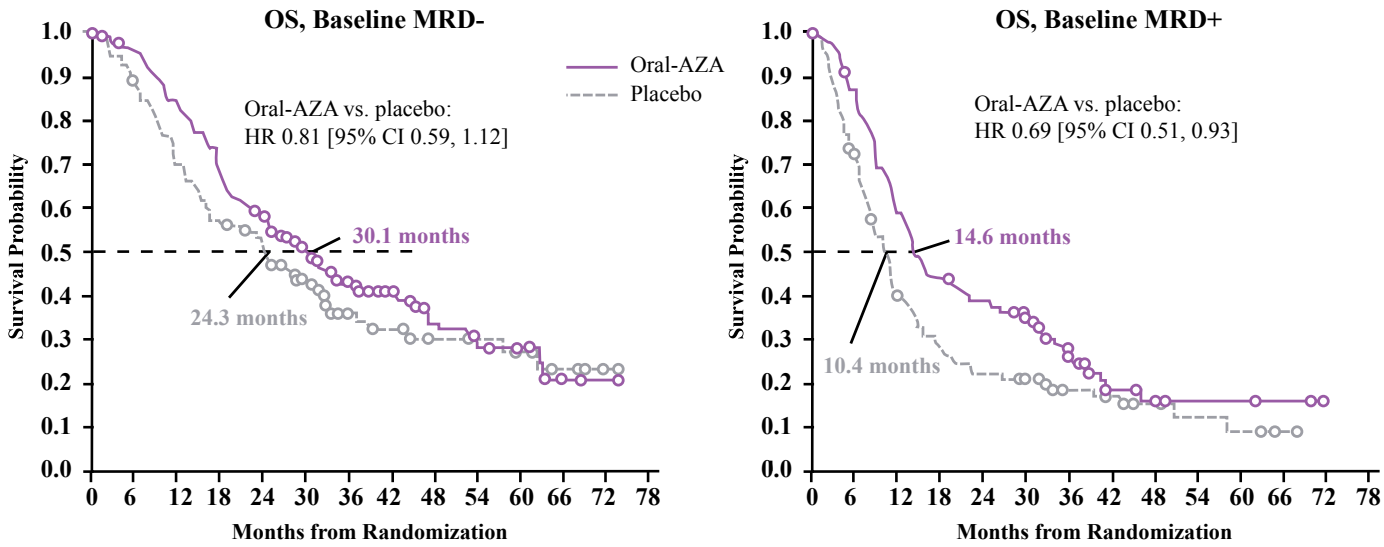


Figure 5. Overall Survival by baseline MRD status; *adapted from Roboz and Ravandi, 2022.*

between treatment arms (Oral-AZA, 78% [186/238]; and placebo, 82% [192/234]). Specifically, approximately half of the patients in the Oral-AZA (n=110 [46%]) and placebo (n=102 [44%]) arms received one prior consolidation, while 32% (n=76) in the Oral-AZA arm and 38% (n=90) in the placebo arm received ≥2 prior consolidation cycles. The remaining ~20% of patients (n=94) did not receive consolidation, including 52 patients (22%) in the Oral-AZA arm and 42 (18%) in the placebo arm. Notably, baseline characteristics were similar among consolidation-defined subgroups both within and between treatment arms.[19]

Most importantly, as shown in **Figure 4**, Oral-AZA maintenance significantly prolonged OS compared with placebo, regardless of whether patients received consolidation (or the number of cycles of consolidation received) after initial induction. RFS was also prolonged in a similar fashion.[19]

2.) Measurable Residual Disease Status at Baseline

Bone marrow MRD analysis was performed centrally by multiparameter flow cytometry in all patients at baseline, and with a plan for ongoing analyses every 3 months while in the study. MRD positivity (MRD+) was defined as a value of ≥ 0.1% based on the European LeukemiaNet (ELN) 2017 recommendations.[20] At baseline, MRD negativity (MRD-) was observed in 56% of patients in the Oral-AZA arm and in 49% of patients receiving placebo. Patient demographics and disease characteristics were well balanced among MRD- and randomization-defined subgroups.[21]

The effect of MRD on treatment was evaluated in patients with a baseline MRD assessment and ≥ 1 subsequent assessment. As shown in **Figure 5**, baseline MRD+ status was associated with inferior OS in both treatment arms (a similar effect on RFS was also observed). Notably, Oral-AZA improved survival regardless of baseline MRD status.[21] In addition, Oral-AZA was also associated with a higher proportion of MRD responders, with 37% of patients MRD+ at baseline converting to MRD- status at a later study timepoint compared with 19% of patients receiving placebo. This finding indicates that Oral-AZA has MRD-erasing activity. Consistent with this finding, Oral-AZA was also associated with a longer duration of MRD- status (~11.0 months compared with ~5.0 months in the placebo arm). The effect of Oral-AZA on MRD status was unrelated to the number of consolidations received.[21]

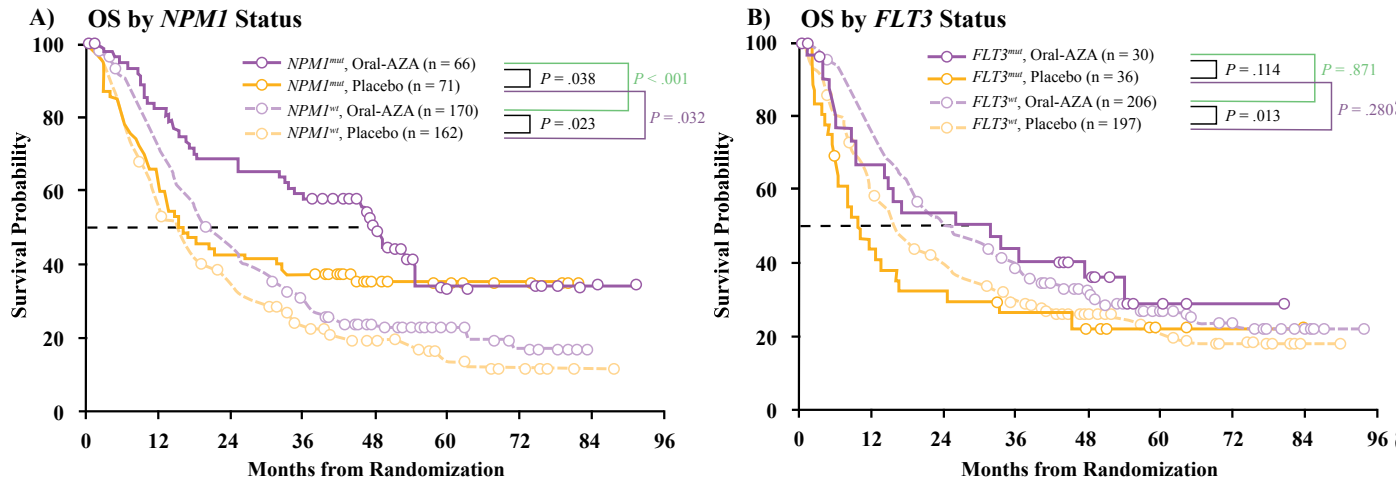
3.) Mutational Status at Diagnosis

Considering that patients were enrolled into the Quazar AML-001 study not at diagnosis, but after the achievement of CR/CRi, mutational status at disease diagnosis was obtained from patient case report forms. Molecular data were available at diagnosis for 99.4% of enrolled patients. *NPM1* mutations (*NPM1*^{mut}) were found in 29.2% of patients, *FLT3* mutations (*FLT3*^{mut}; *FLT3*-ITD or *FLT3*-TKD, or both) were found in 14.1% of patients, and 6.4% of patients had both an *NPM1* and a *FLT3*-ITD mutation.[22]

As shown in **Figure 6**, among patients with *NPM1*^{mut}, OS was improved with Oral-AZA by 37% (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.41-0.98), while RFS was improved by 45% (HR, 0.55; 95% CI, 0.35-0.84, vs. placebo.) This improvement in median OS was observed in patients both MRD- (48.6 months vs. 31.4 months with placebo) and MRD+ (46.1 months vs. 10.0 months with placebo) at randomization.[22]

Among patients with *FLT3*^{mut}, Oral-AZA improved OS by 37% (HR, 0.63; 95% CI, 0.35–1.12) and RFS by 49% (HR, 0.51; 95% CI, 0.27-0.95), vs. placebo. This improvement in median OS was observed in patients both MRD- (28.2 months vs. 16.2 months with placebo) and MRD+ (24.0 months vs 8.0 months with placebo) at randomization.[22]

The sample size of patients bearing both *NPM1*^{mut} and a *FLT3*-ITD mutation was too small to draw firm

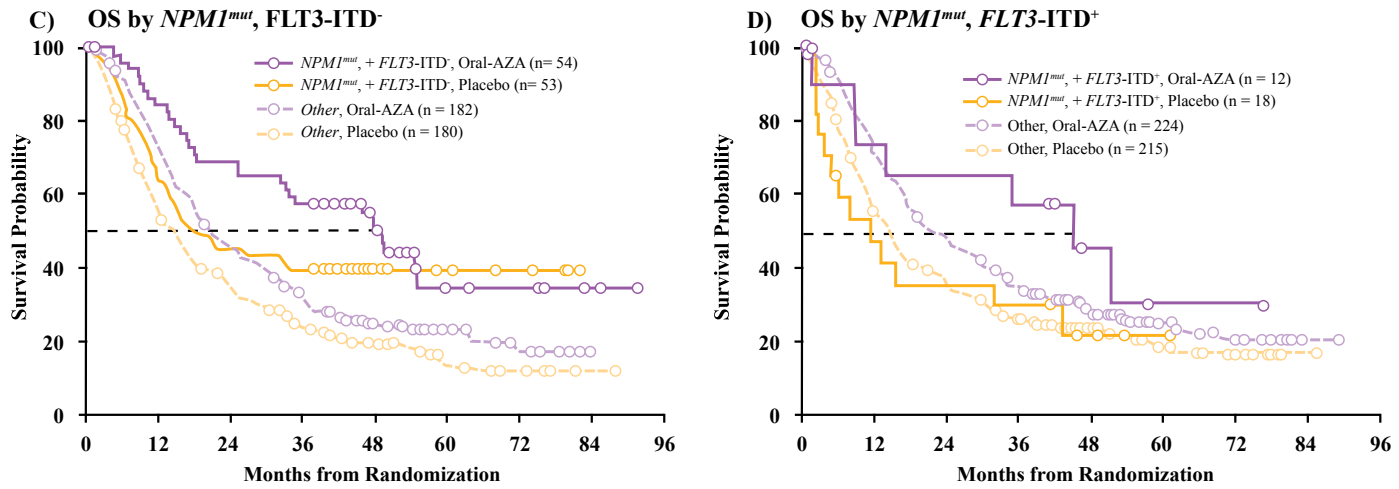


Median OS, months

NPM1^{mut}, Oral-AZA	**47.2**	*NPM1*^{wt}, Oral-AZA	**19.6**
NPM1^{mut}, Placebo	**15.9**	*NPM1*^{wt}, Placebo	**14.6**

Median OS, months

FLT3-ITD/TKD, Oral-AZA	**28.2**	*FLT3*^{wt}, Oral-AZA	**24.7**
FLT3-ITD/TKD, Placebo	**9.7**	*FLT3*^{wt}, Placebo	**15.2**



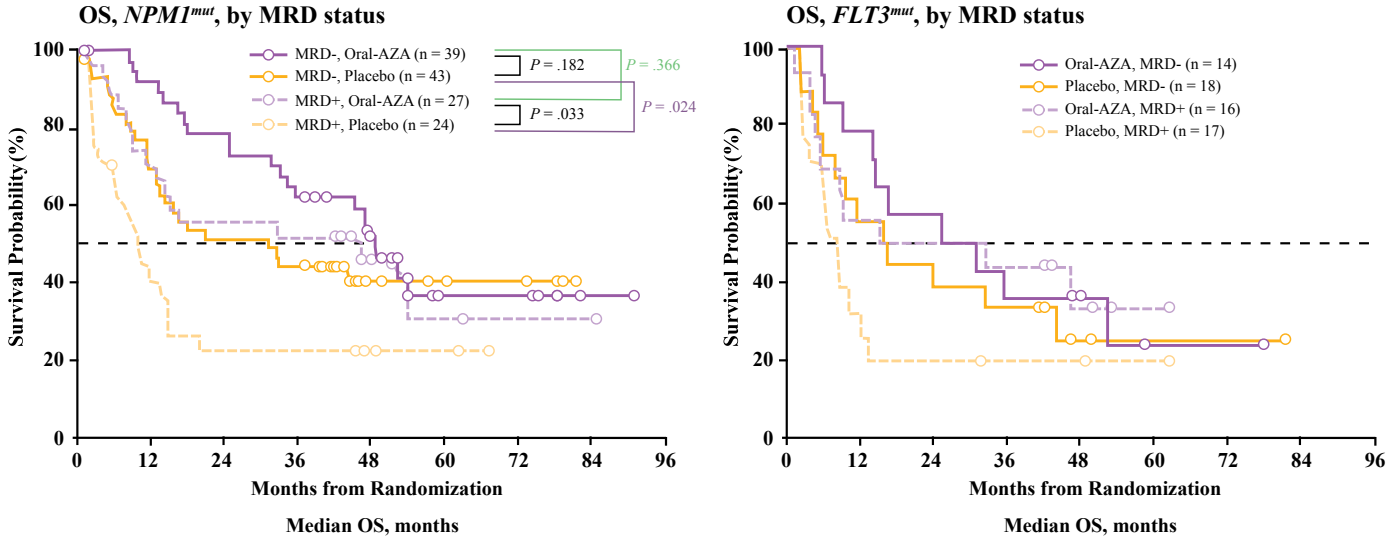
Median OS, months

NPM1^{mut}, *FLT3*-ITD^{neg}, Oral-AZA	**48.6**	Other, Oral-AZA	**20.2**
NPM1^{mut}, *FLT3*-ITD^{neg}, Placebo	**18.0**	Other, Placebo	**14.6**

Median OS, months

NPM1^{mut}, *FLT3*-ITD, Oral-AZA	**46.1**	Other, Oral-AZA	**24.7**
NPM1^{mut}, *FLT3*-ITD, Placebo	**11.5**	Other Placebo	**14.9**

Figure 6. Overall Survival by mutational status at diagnosis; *adapted from Dohner and Wei, 2022 and Dohner, 2020.*



Median OS, months

MRD-, Oral-AZA	**48.6**	MRD+, Oral-AZA	**46.1**
MRD-, Placebo	**31.4**	MRD+, Placebo	**10.0**

Median OS, months

MRD-, Oral-AZA	**28.2**	MRD+, Oral-AZA	**24.0**
MRD-, Placebo	**16.2**	MRD+, Placebo	**8.0**

Figure 7. Overall survival by *NPM1*, *FLT3*-ITD, and MRD status; *adapted from Dohner and Wei, 2022 and Dohner, 2020.*

conclusions. However, as shown in **Figure 6C**, in the placebo arm median OS was 18.0 months for *NPM1*^{mut} patients without a *FLT3*-ITD mutation vs. 11.5 months in patients with both mutations. In contrast, within the Oral-AZA arm the co-occurrence of *FLT3*-ITD mutations in patients with *NPM1*^{mut} did not significantly affect survival: median OS was 46.1 months for patients with co-occurring *FLT3*-ITD and 48.6 months for those without *FLT3*-ITD. Oral-AZA nominally prolonged OS vs placebo in patients with *NPM1*^{mut} with or without a co-occurring *FLT3*-ITD mutation.[1]

Taken together, the data summarized in sections **1., 2.,** and **3.** above indicate that the effect of Oral-AZA on survival is independent of prior chemotherapy received (and in particular, of the number of consolidations received), MRD status at baseline, and *NPM1* and *FLT3* mutational status at diagnosis. In addition, these data demonstrate that Oral-AZA has MRD-erasing ability and suggest that Oral-AZA may improve outcomes in at least some patients with *FLT3*^{mut}.

Oral-AZA: Canadian Perspective

The Quazar AML-001 study of Oral-AZA maintenance is the first study to demonstrate a benefit in both RFS and OS. Consequently, Oral-AZA has rapidly received approval for use in multiple jurisdictions and has defined a new standard-of-care in AML treatment.

Quazar AML-001 had specific eligibility criteria for patients to receive Oral-AZA. The criteria included the following: patients had to be in first CR/CRi after IC +/- consolidation chemotherapy, aged ≥ 55 years, with an ECOG PS ≤3, with *de novo* or secondary AML with intermediate- or poor-risk cytogenetics, and deemed ineligible for alloHSCT.

The Canadian Agency for Drugs and Technologies in Health (CADTH) pan-Canadian Oncology Drug Review (pCODR) Oral-AZA reimbursement recommendations have retained most of these study criteria (except for patients needing to be aged ≥ 55 years):

- Newly diagnosed AML (*de novo* or secondary to prior MDS or chronic myelomonocytic leukemia)
- Intermediate- or poor-risk cytogenetics
- In first remission (CR or CRi) following induction chemotherapy with or without consolidation chemotherapy
- Not eligible for alloHSCT
- Must be adult (≥ 18 years of age)

Oral-AZA: Canadian Perspective: Common Questions

1.) Eligibility Issues

While the above reimbursement criteria appear relatively straightforward, ongoing questions regarding eligibility remain:

- *'Therapy-related AML'.*

This remains excluded.

- *'Intermediate- or poor-risk cytogenetics'.*

Cytogenetic risk stratification in Quazar AML-001 was based on NCCN 2011 criteria which did not include molecular diagnostics.[23]

The CADTH recommendations retain this cytogenetic definition, but their wording has caused confusion, as they specify 'intermediate- or poor-risk cytogenetics defined according to the ELN 2017 recommendations for risk stratification in AML.[20] ELN 2017 actually defines 'risk stratification by *genetics*' which is a synthesis of defined *cytogenetic* and *molecular abnormalities*. 'Cytogenetic risk' excludes molecular diagnostics. AML patients with intermediate-risk cytogenetics who are also *NPM1*^{mut} were included in the Quazar AML-001 study, and they remain eligible today for Oral-AZA, assuming that the other criteria are met.

Therefore, by extension, the only patients with AML excluded from access to Oral-AZA are those with 'good-risk' cytogenetics (i.e., the core binding factor (CBF) leukemias [t(8;21), inv(16), and t(16;16)], APL [t(15;17]), and intermediate- and high-risk patients proceeding to alloHSCT.

The term 'not eligible for transplant' has also caused confusion. First, transplant eligibility is dynamic, with 'eligible' patients often becoming 'ineligible', and vice versa. Second, transplant ineligibility can incorporate a number of potential factors including transplant deemed not appropriate or needed, no suitable donor found (to date), patient declines transplant, transplant delayed due to recipient or donor issues, among others. Oral-AZA could be considered for patients in these clinical scenarios.

2.) Management Issues

How long should a patient remain on Oral-AZA?

- The duration of treatment with Oral-AZA remains controversial. In the Quazar AML-001 study the median duration of treatment was 12 cycles (range 1-80) for Oral-AZA, and 6 cycles (range 1–73) for placebo.[15] **Figure 2** shows that the Oral-AZA and placebo OS curves remain separated at 36 and 48 months. A reasonable suggestion might therefore be to continue maintenance therapy for ~4 years. With longer follow-up, (**Figure 3**)[16] the two curves remain separated at 60 months, although at the 60-month time point the difference is small, as are patient numbers.

Do the GI and other toxicities associated with Oral-AZA preclude long-term use?

- The Quazar AML-001 safety data illustrate that Oral-AZA is generally well-tolerated, and adverse events are usually easily treated. Moreover, adverse events decreased significantly after 1 to 2 cycles (the study did not include up-front prophylactic antinausea medications).[17] In addition, only ~3.5% of patients discontinued Oral-AZA due to nausea/vomiting.[15]

Will treatment with Oral-AZA select for treatment-resistant cells, thereby jeopardizing salvage therapy following relapse?

- In a post-hoc analysis of outcomes in Quazar AML-001 patients receiving subsequent therapy for relapse, salvage outcomes in Oral-AZA-treated patients were identical to those of placebo-treated patients. Thus, Oral-AZA maintenance can prolong AML remission duration without negatively impacting survival outcomes after salvage therapies.[24]

When should I first introduce the topic of post-intensive chemotherapy maintenance therapy to my patients with AML?

- Maintenance therapy has been used routinely for decades in patients with ALL, and is usually discussed with the patient up-front, at the initial treatment discussion. Ideally, the same early discussion of maintenance therapy should now occur in newly diagnosed AML, to avoid surprising the patient later during their treatment course. The possibility of post-IC alloHSCT is often discussed routinely at the time of AML diagnosis. However, in the absence of an alloHSCT, post-IC maintenance therapy is a new approach where previously there was none. The possibility of maintenance therapy for AML should also be discussed up-front.

Conclusions

The Quazar AML-001study of Oral-AZA maintenance in AML is the first to demonstrate a benefit in both RFS and OS. Consequently, Oral-AZA has received approval for use in multiple jurisdictions. After many years, maintenance therapy has finally emerged as a new standard-of-care in AML treatment. Oral-AZA provides an OS benefit that is independent of the number of consolidations received, baseline MRD, or mutational status at diagnosis. Furthermore, Oral-AZA is well-tolerated, with easily-managed toxicities. Moreover, the oral formulation lends itself to easy delivery closer to home.

A wide range of patients are eligible for maintenance therapy with Oral-AZA. By current eligibility criteria, the only patients with AML excluded from Oral-AZA are those with 'good-risk' cytogenetics (i.e., the CBF leukemias, and APL), and intermediate- and high-risk patients proceeding to alloHSCT. While indicated for patients 'not eligible' for alloHSCT, transplant ineligibility includes a variety of clinical scenarios, and in addition, transplant eligibility can be dynamic.

The advent of effective maintenance therapy for AML, defines a new, and long-awaited, era in AML treatment. We can anticipate that the indications for maintenance therapy will widen going forward, and that other maintenance approaches will follow in the footsteps of Oral-AZA.

Correspondence

Dr. Andre Schuh
Email: andre.schuh@uhn.ca

Financial Disclosures

None declared.

References

1. *Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867*
2. *Yanada M, Garcia-Manero G, Borthakur G, Ravandi F, Kantarjian H, Estey E. Potential cure of acute myeloid leukemia : analysis of 1069 consecutive patients in first complete remission. Cancer. 2007;110(12):2756-2760. doi:10.1002/cncr.23112*
3. *Röllig C, Bornhäuser M, Thiede C, Taube F, Kramer M, Mohr B, et al. Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system. J Clin Oncol. 2011;29(20):2758-2765. doi:10.1200/jco.2010.32.8500*
4. *DeWolf S, Tallman MS. How I treat relapsed or refractory AML. Blood. 2020;136(9):1023-1032. doi:10.1182/blood.2019001982*
5. *Toksvang LN, Lee SHR, Yang JJ, Schmiegelow K. Maintenance therapy for acute lymphoblastic leukemia: basic science and clinical translations. Leukemia. 2022;36(7):1749-1758. doi:10.1038/s41375-022-01591-4*
6. *Kilic Gunes E, Ozkurt ZN, Yildiz S, Ozet G, Ceran F, Albayrak M, et al. Comparison of maintenance regimens in acute promyelocytic leukemia patients. Leuk Res. 2023;128:107055. doi:10.1016/j.leukres.2023.107055*
7. *Storring JM, Minden MD, Kao S, Gupta V, Schuh AC, Schimmer AD, et al. Treatment of adults with BCR-ABL negative acute lymphoblastic leukaemia with a modified paediatric regimen. Br J Haematol. 2009;146(1):76-85. doi:10.1111/j.1365-2141.2009.07712.x*
8. *Sibai H, Chen R, Liu X, Falcone U, Schimmer A, Schuh A, et al. Anticoagulation prophylaxis reduces venous thromboembolism rate in adult acute lymphoblastic leukaemia treated with asparaginase-based therapy. Br J Haematol. 2020;191(5):748-754. doi:10.1111/bjh.16695*
9. *Rashidi A, Walter RB, Tallman MS, Appelbaum FR, DiPersio JF. Maintenance therapy in acute myeloid leukemia: an evidence-based review of randomized trials. Blood. 2016;128(6):763-773. doi:10.1182/blood-2016-03-674127*
10. *Reville PK, Kadia TM. Maintenance therapy in AML. Front Oncol. 2020;10:619085. doi:10.3389/fonc.2020.619085*
11. *Gagelmann N, Wolschke C, Klyuchnikov E, Christopeit M, Ayuk F, Kröger N. TKI maintenance after stem-cell transplantation for FLT3-ITD positive acute myeloid leukemia: a systematic review and meta-analysis. Front Immunol. 2021;12:630429. doi:10.3389/fimmu.2021.630429*
12. *Blackmon A, Aldoss I, Ball BJ. FLT3 Inhibitors as maintenance therapy after allogeneic stem-cell transplantation. Blood Lymphat Cancer. 2022;12:137-147. doi:10.2147/blctt.S281252*
13. *Perl AE, Larson RA, Podoltsev NA, Strickland S, Wang ES, Atallah E, et al. Outcomes in patients with FLT3-mutated relapsed/ refractory acute myelogenous leukemia who underwent transplantation in the phase 3 ADMIRAL trial of gilteritinib versus salvage chemotherapy. Transplant Cell Ther. 2023;29(4):265.e261-265.e210. doi:10.1016/j.jtct.2022.12.006*
14. *Huls G, Chitu DA, Havelange V, Jongen-Lavrencic M, van de Loosdrecht AA, Biemond BJ, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. Blood. 2019;133(13):1457-1464. doi:10.1182/blood-2018-10-879866*
15. *Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med. 2020;383(26):2526-2537. doi:10.1056/NEJMoa2004444*
16. *Wei AH, Döhner H, Sayar H, Ravandi F, Montesinos P, Dombret H, et al. Long-term survival with oral azacitidine for patients with acute myeloid leukemia in first remission after chemotherapy: Updated results from the randomized, placebo-controlled, phase 3 QUAZAR AML-001 trial. Am J Hematol. 2023;98(4):E84-e87. doi:10.1002/ajh.26847*
17. *Ravandi F, Roboz GJ, Wei AH, Döhner H, Pocock C, Selleslag D, et al. Management of adverse events in patients with acute myeloid leukemia in remission receiving oral azacitidine: experience from the phase 3 randomized QUAZAR AML-001 trial. J Hematol Oncol. 2021;14(1):133. doi:10.1186/s13045-021-01142-x*
18. *Roboz GJ, Döhner H, Pocock C, Dombret H, Ravandi F, Jang JH, et al. Oral azacitidine preserves favorable level of fatigue and health-related quality of life for patients with acute myeloid leukemia in remission: results from the phase 3, placebo-controlled QUAZAR AML-001 trial. Haematologica. 2021;106(12):3240-3244. doi:10.3324/haematol.2021.279174*
19. *Wei AH, Roboz GJ, Dombret H, Dohner H, Schuh AC, Montesinos P, et al. Survival outcomes with oral azacitidine maintenance in patients with acute myeloid leukemia in remission by receipt of initial chemotherapy: subgroup analyses from the phase III QUAZAR AML-001 trial. Haematologica. 2023;108(10):2820-2825. doi:10.3324/haematol.2022.282296*
20. *Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196*
21. *Roboz GJ, Ravandi F, Wei AH, Dombret H, Thol F, Voso MT, et al. Oral azacitidine prolongs survival of patients with AML in remission independently of measurable residual disease status. Blood. 2022;139(14):2145-2155. doi:10.1182/blood.2021013404*
22. *Döhner H, Wei AH, Roboz GJ, Montesinos P, Thol FR, Ravandi F, et al. Prognostic impact of NPM1 and FLT3 mutations in patients with AML in first remission treated with oral azacitidine. Blood. 2022;140(15):1674-1685. doi:10.1182/blood.2022016293*
23. *O'Donnell MR, Abboud CN, Altman J, Appelbaum FR, Coutre SE, Damon LE, et al. Acute myeloid leukemia. J Natl Compr Canc Netw. 2011;9(3):280-317. doi:10.6004/jnccn.2011.0027*
24. *Ravandi F, Döhner H, Wei AH, Montesinos P, Pfeilstöcker M, Papayannidis C, et al. Survival outcomes in patients with acute myeloid leukaemia who received subsequent therapy for relapse in QUAZAR AML-001. Br J Haematol. 2023. doi:10.1111/bjh.19202*

Canadian Hematology Today
Science for the Real World

The content published in this supplement to *Canadian Hematology Today* qualifies for Section 2 (self-learning) credits towards the maintenance of certification.

For information on how this activity fits in the Royal College Maintenance of Certification (MOC) Program, please visit the Royal College's website (royalcollege.ca/moc). For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, canadianhematologytoday.com.

To subscribe to Canadian Hematology Today and more open access scientific specialty journals published by Catalytic Health, please visit catalytichealth.com/cht.

SPECIAL SUPPLEMENT

January 2024

CANADIAN HEMATOLOGY TODAY

SHARE OUR WEBLINK ON YOUR SOCIAL MEDIA PLATFORM:

REGISTER FOR FUTURE DIGITAL AND PRINT ISSUES BY VISITING US AT CANADIANHEMATOLOGYTODAY.COM

CALLING ALL AUTHORS! DO YOU HAVE A TOPIC THAT YOU WOULD LIKE TO SEE COVERED IN 2024?

DROP US A LINE AND TELL US ABOUT IT OR SEND US A SHORT ABSTRACT

INTERESTED IN RECORDING A PODCAST? WE WANT TO EXPLORE TOPICS WITH YOU!

EMAIL US: INFO@CATALYTICHEALTH.COM