Author/s:
Chua, CC;Loo, S;Fong, CY;Ting, SB;Tiong, IS;Fleming, S;Anstee, NS;Ivey, A;Ashby, M;Teh, TC;Reynolds, J;Roberts, AW;Wei, AH

Title:
Final analysis of the phase 1b Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT)

Date:
2025-04-22

Citation:
Chua, C. C., Loo, S., Fong, C. Y., Ting, S. B., Tiong, I. S., Fleming, S., Anstee, N. S., Ivey, A., Ashby, M., Teh, T. C., Reynolds, J., Roberts, A. W. & Wei, A. H. (2025). Final analysis of the phase 1b Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT). Blood Advances, 9 (8), pp.1827-1835. https://doi.org/10.1182/bloodadvances.2024014900.

Persistent Link:
https://hdl.handle.net/11343/359637

REGULAR ARTICLE

blood advances

Final analysis of the phase 1b Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT)

Chong Chyn Chua,[1-4] Sun Loo,[2,3,5] Chun Yew Fong,[6,7] Stephen B. Ting,[8] Ing Soo Tiong,[5,9] Shaun Fleming,[4] Natasha S. Anstee,[2,10] Adam Ivey,[4] Michael Ashby,[4] Tse-Chieh Teh,[4,8] John Reynolds,[4] Andrew W. Roberts,[2,5,11] and Andrew H. Wei[2,5,10]

[1]Department of Haematology, Monash Hospital and Monash University, Melbourne, Australia; [2]Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; [3]Department of Clinical Haematology, Northern Hospital, Melbourne, Australia; [4]Malignant Haematology and Stem Cell Transplant Service, Alfred Hospital and Australian Centre for Blood Diseases, Monash University, Melbourne, Australia; [5]Department of Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia; [6]Department of Haematology, Austin Health, Melbourne, Australia; [7]Olivia Newton John Cancer Research Institute, Melbourne Australia; [8]Department of Haematology, Eastern Health and Monash University, Melbourne, Australia; and [9]Sir Peter MacCallum Department of Oncology, [10]Department of Medical Biology, and [11]Centre for Cancer Research, The University of Melbourne, Parkville, Australia

Key Points

- Venetoclax plus modified intensive chemotherapy (CAVEAT) is well tolerated and effective (75% remission) in fit, older patients with AML.
- Patients aged ≥65 years with de novo *NPM1* or *IDH2* mutant AML experience durable treatment-free remissions with this time-limited regimen.

Venetoclax plus azacitidine represents a key advance for older, unfit patients with acute myeloid leukemia (AML). The Chemotherapy and Venetoclax in Elderly AML Trial (CAVEAT) was first to combine venetoclax with intensive chemotherapy in newly diagnosed patients aged ≥65 years. In this final analysis, 85 patients (median age, 71 years) were followed up for a median of 41.8 months. The CAVEAT induction combined cytarabine and idarubicin with 5 dose levels of venetoclax (50-600 mg) for up to 14 days. Two additional cohorts explored adjusted-dose venetoclax (50 mg and 100 mg) with posaconazole. CAVEAT induction was well tolerated, with low mortality (4%) and limited high-grade gastrointestinal toxicity (4%). Delayed hematologic recovery after consolidation was ameliorated by omitting idarubicin from postremission therapy. The overall response rate (ORR; complete response [CR] + CR with partial hematologic recovery + CR with incomplete count recovery) was 75%, with a median overall survival (OS) of 19.3 months (95% confidence interval [CI], 11.1-31.3). Among de novo AML, ORR was 88% and median OS was 33.1 months (95% CI, 19.3-54.3). Almost one-third have not relapsed, many benefiting from prolonged treatment-free remission (median, 17.9 months). CAVEAT induction was well tolerated and associated with high ORR that was durable, particularly for de novo AML. CAVEAT represents an effective time-limited treatment option for fit, older patients with AML. This trial was registered at https://www.anzctr.org.au as #ACTRN12616000445471.

Introduction

Although azacitidine or low-dose cytarabine (LDAC) combined with venetoclax is standard for patients aged ≥75 years or unfit for intensive chemotherapy (IC), the optimal treatment for fit, older adults aged ≥65 years with newly diagnosed acute myeloid leukemia (AML) remains uncertain.[1,2] Intensive 7+3 induction is associated with higher treatment-related complications and inferior survival in older, compared with younger AML populations. We previously reported the results of the Chemotherapy and Venetoclax in the Elderly AML Trial (CAVEAT), to our knowledge, the first study to explore feasibility of

Submitted 23 September 2024; accepted 5 January 2025; prepublished online on *Blood Advances* First Edition 18 January 2025. https://doi.org/10.1182/bloodadvances.2024014900.

Original data and deidentified individual participant data that underlie the reported results are available on request from the corresponding author, Andrew H. Wei (andrew.wei@petermac.org).

The full-text version of this article contains a data supplement.

venetoclax in combination with modified (5+2) IC as frontline induction in 51 patients (median age, 72 years) with AML.[3] The maximum tolerated dose of venetoclax with IC was not reached at 600 mg/d. Complete remission (CR)/CR with incomplete count recovery (CRi) was observed in 72% (97% in de novo AML). Although induction was well tolerated, prolonged post-consolidation thrombocytopenia was observed, hampering deliverability. The original report had a median follow-up time of 22.9 months.[3] With a data lock on 31 July 2023, we now present the final analysis of the CAVEAT study, totaling 85 patients with a median survival follow-up of 41.8 months (range, 7.8-78.1). The objectives of this final report are to determine the optimal dose of venetoclax when combined with posaconazole, assess the best approach to reduce the risk of prolonged postconsolidation thrombocytopenia, and analyze the long-term durability of remission within defined molecular subgroups.

Methods

CAVEAT was an investigator-sponsored phase 1b study enrolling patients aged ≥65 years with newly diagnosed AML considered suitable for IC. A full list of eligibility criteria are published.[3] CAVEAT was designed with the aim of minimizing the risk of marrow and gastrointestinal toxicity in this elderly population by truncating the induction chemotherapy backbone of "7+3" to 5 days of cytarabine and 2 days of idarubicin (5+2). For patients responding to induction, up to 4 consolidation cycles were permitted, comprising 14 days of venetoclax at the cohort-specified dose, with bolus cytarabine 100 mg/m^2 per day IV on days 1 to 2 and idarubicin 12 mg/m^2 IV on day 1 (2+1). This postremission strategy was adapted from the randomized Acute Leukemia French Association 9803 study that confirmed favorable outcomes in an elderly AML population using an ambulatory postremission strategy of idarubicin 9 mg/m^2 or daunorubicin 45 mg/m^2 for day 1 combined with 60 mg/m^2 cytarabine, 12 hourly subcutaneously on days 1 to 5, compared with a second cycle of IC.[4] To minimize marrow toxicity with concurrent venetoclax in an elderly AML population, subsequent cycles of therapy only commenced after hematologic recovery of neutrophils to ≥0.5 × 10^9/L and platelets to ≥25 × 10^9/L. After completing induction and consolidation therapy, patients could receive up to 7 cycles of venetoclax maintenance (days 1-14 in each 28-day cycle).

Five venetoclax dose-escalation cohorts (50, 100, 200, 400, and 600 mg) were explored initially with initial results published and the treatment schedule detailed in the supplemental Appendix of the current manuscript.[1] For this updated analysis, 2 additional cohorts (cohorts F and G) are included to examine the safety of dose-adjusted venetoclax when combined with posaconazole antifungal prophylaxis during induction. In addition, cohort H was introduced to alleviate delayed platelet recovery after consolidation. Delayed hematopoietic recovery was defined as failure to recover neutrophils (≥0.5 × 10^9/L) and/or platelets (≥50 × 10^9/L) by day 42 of any treatment cycle. Patients with prior myelofibrosis or prior hypomethylating agents exposure were excluded from cohorts F, G, and H because of poor efficacy and hematologic toxicities observed in prior dosing cohorts.[3] Patients with prior exposure to venetoclax or other B-cell lymphoma 2 inhibitors were excluded from this study.

Cohort F and G treatment schedule

Cohort F (n = 9) was designed to examine the safety of venetoclax 50 mg as the target dose with concurrent administration of the CYP3A4 antagonist posaconazole during induction. Cohort G (n = 9) was almost identical but with venetoclax 100 mg as the target dose in combination with posaconazole. Posaconazole commenced at a dose of 300 mg daily, with dose adjustments based on posaconazole trough levels permitted as per investigators' discretion.

Induction comprised 14 days of venetoclax, commencing with a 7-day prephase (day −6 to 0) inclusive of a venetoclax dose ramp-up (10, 20, 50 [peak dose for cohort F], 100 mg [peak dose for cohort G]), followed by a 7-day overlap with 5+2 chemotherapy (cytarabine 100 mg/m^2 per day IV infusion, days 1-5; idarubicin 12 mg/m^2 IV on days 2-3). Consolidation comprised up to 4 cycles of venetoclax with 2+1 chemotherapy (venetoclax days −6 to 7, with an IV push of cytarabine 100 mg/m^2 on days 1-2 and idarubicin 12 mg/m^2 on day 1). Consolidation was followed by up to 7 cycles of venetoclax monotherapy maintenance (venetoclax days 1-14, of each 28-day cycle). During consolidation and maintenance, venetoclax 400 mg daily was generally administered without posaconazole coadministration.

Cohort H treatment schedule

Cohort H (n = 16) was designed to alleviate delayed platelet recovery observed after consolidation therapy in cohorts A through G. Consolidation with 2+1 (bolus cytarabine and idarubicin) was replaced with LDAC 20 mg/m^2 per day subcutaneously on days 1 to 10 combined with venetoclax at 400 mg daily on days 1 to 7, given in an ambulatory setting, for up to 4 cycles (supplemental Figure 1). Up to 7 cycles of venetoclax monotherapy maintenance (400 mg daily) were administered on days 1 to 14 of each 28-day cycle. Azole antifungals during induction were permitted after completion of venetoclax dosing. In cohort H, the venetoclax prephase during induction was shortened to 2 days (200 mg on day −1 and 400 mg on day 0), followed by 600 mg on days 1 to 7. This shortened the total venetoclax duration during induction to 9 days (instead of 14 days). For cohorts E, F, G, and H, if the planned number of consolidation cycles were not deliverable, patients could proceed directly to maintenance venetoclax monotherapy with approval from the chief investigator.

Statistical analysis

Efficacy end points. Clinical response, relapse-free survival (RFS), and overall survival (OS) were reported in accordance with the European LeukemiaNet (ELN) 2022 definitions.[5] Descriptive statistics were expressed as counts, percentage frequencies, median, and range, as appropriate. Comparisons between 2 groups were evaluated using χ^2 test or Fishers exact test for categorical data, and Mann-Whitney *U* test for continuous variables. The Kaplan-Meier method was used to calculate OS and RFS distribution curves, with log-rank test used to compare patient groups with 95% confidence intervals provided as applicable. Pairwise comparisons were performed using the Bonferroni method. A 2-tailed *P* value of $< .05$ was considered statistically significant. All statistical analysis used procedures in R statistical software version 4.2.3 and GraphPad Prism version 10.1.1 (GraphPad Software, La Jolla, CA).

Please see supplemental Appendix for additional methods.

Results

A total of 85 patients were enrolled, with a median age of 71 years (range, 63-80). Poor-risk disease features included 39% secondary AML, 60% ELN 2022 adverse risk, and 18% with *TP53* mutations (Table 1).

Hematologic impact of posaconazole added to venetoclax-based intensive induction

Previous pharmacokinetic studies indicate that the CYP3A4 inhibitor posaconazole is associated with an approximate eightfold increase in venetoclax exposure.[6] Having confirmed the safety of venetoclax 600 mg combined with cytarabine/idarubicin (cohort E),[3] the clinical impact of posaconazole combined with either venetoclax 50 mg (cohort F) or 100 mg (cohort G) in induction after venetoclax dose ramp-up was examined (supplemental Figure 1).[6] During induction, 30-day mortality was 0% (0/18) in cohorts F and G, compared with 6% (3/51) in prior cohorts (A-E). Rates of delayed hematopoietic recovery were low: 1 of 9 (11%) patients in each of cohorts F and G, with latest recovery by day 81 in a patient with prior myelodysplastic syndrome (Figure 1A-B). Rates of invasive fungal infection were 5.6% (1/18, suspected) in the posaconazole-supported cohorts (F-G), compared with 4.6% (3/65, 2 proven, 1 suspected) in the non-posaconazole arms (A-E, prophylaxis liposomal amphotericin B was permitted as per investigator discretion; supplemental Tables 1 and 2).

However, after consolidation cycle 1, poor hematopoietic recovery in the posaconazole cohorts limited deliverability, with none receiving >1 consolidation cycle. Failure to recover neutrophils by day 42 was observed in 75% (3/4) in cohort F and 83% (5/6) in cohort G (Figure 1A). This compared with delayed neutrophil recovery in only 7% in cohorts A through D (venetoclax 50-400 mg, without posaconazole) and 50% (5/10) in cohort E (venetoclax 600 mg; Figure 1C).

Delayed platelet recovery after consolidation was also evident, affecting 50% (2/4) and 83% (5/6) in cohorts F and G, respectively (Figure 1B). Concerningly, 5 of 6 patients in cohort G had persistent thrombocytopenia beyond day 100 of first consolidation (Figure 1B). Delayed platelet recovery after first consolidation was observed in 56% (9/16) in cohorts A through D, and 60% (6/10) in cohort E (Figure 1B,D). Therefore, persistent postconsolidation thrombocytopenia featured at both dose levels of venetoclax incorporating posaconazole, with toxicity appearing to be greater at the venetoclax 100-mg dose level.

Omitting idarubicin from consolidation improves hematopoietic recovery

Our original consolidation included cytarabine 100 mg/m^2 IV on days 1 to 2 and a single dose of idarubicin 12 mg/m^2 on day 2 with venetoclax given on days −7 to +7. To mitigate delays in postconsolidation hematologic recovery, 2 changes were implemented in cohort H (supplemental Figure 1). The first was to commence posaconazole prophylaxis on day 8 of induction, avoiding overlap with venetoclax. The second was to amend consolidation to a LDAC plus venetoclax regimen, enabling idarubicin as a potential cause of platelet progenitor toxicity to be omitted. This approach reduced hematopoietic toxicity after consolidation, with median time to neutrophil and platelet recovery of 37 and 46 days, respectively (Figure 1C-D). Importantly, no patient had postconsolidation thrombocytopenia persisting beyond day 100 (Figure 1D). The median number of consolidation LDAC/venetoclax cycles delivered in cohort H was 2 (range, 1-4).

Clinical outcomes

Of 85 patients enrolled, 27 (32%) remain alive at data cutoff. CAVEAT induction was associated with very low rates of tumor lysis syndrome (3/85 [4%]; laboratory only) and 30-day mortality (3/85 [4%]). Notably, grade ≥3 gastrointestinal toxicities were low in cohorts F through H (5/34 [15%]), affirming the low rates noted in cohorts A to E (supplemental Tables 1 and 2).

For the entire study, overall response rate (ORR; CR + CR with partial hematologic recovery [CRh] + CRi) was 75%, with CR in 56% (Figure 2A). Median OS was 19.3 months (95% confidence interval, 11.1-31.3), with 2-year OS of 48% and 3-year OS of 33% (Figure 2B). Outcomes were significantly better in de novo than secondary disease, with ORR of 88% vs 54%, CR of 75% vs 27%, and a longer median OS of 33.1 vs 8.0 months (Figure 2C). For patients in cohort H, median OS has not been reached (minimum follow-up: 9.8 months), compared with 33.2 months in cohort E (consolidation with cytarabine/idarubicin/venetoclax; supplemental Figure 2). There were no significant differences in RFS when cohort H was compared with combined cohorts D through G (venetoclax dose ≥400 mg); with median RFS of ~20 months for both subgroups (supplemental Figure 4B). Three (19%) patients in cohort H proceeded to allogeneic hematopoietic cell transplant (HCT) in first CR, with a median time to HCT of 139 days from first remission (range, 91-243). Because cohort H delivered the best balance between safety and efficacy, this dose level is recommended for future studies.

Genomic determinants of clinical outcome

The ELN 2022 classification stratifies IC outcomes into 3 prognostic subgroups, with inferior outcomes in older adults (≥60 years) treated intensively; for example, 2-year OS of ~35% for those with favorable-risk AML and <20% for patients with intermediate- or adverse-risk AML.[7] For patients in the CAVEAT study, 2-year OS for ELN 2022 favorable, intermediate, or adverse risk were 77%, 54%, and 36%, respectively (Figure 2D). Within the ELN 2022 adverse-risk group, 2-year OS outcomes for patients with myelodysplasia-related cytogenetic abnormalities (n = 20) or myelodysplasia-related gene mutations (n = 31) were 19% and 47%, respectively.

Molecular determinants of clinical response and OS for the most frequently occurring gene variants was assessed. CR was highest for patients with *IDH1/2* (75%) or *NPM1* mutations (81%) and lowest for mutated *TP53* (27%; Figure 2A). Two-year OS was highest for patients with either *IDH1/2*- (76%), *SRSF2*- (72%), or *NPM1*-mutated (69%) AML and lowest for *TP53* mutant (13%) disease (Figure 2E-H; supplemental Figure 3).

Sustained chemotherapy-free remission associated with NPM1- and/or IDH2-mutated AML

For patients achieving remission, median RFS was 15.6 months (supplemental Figure 4A). The median time on the chemotherapy phase for patients achieving remission was 3.9 months (range, 1.0-9.9). Thereafter, patients received venetoclax monotherapy

Table 1. Patient characteristics and clinical outcomes

	Total (N = 85)	A 50 mg (n = 8)	B 100 mg (n = 8)	C 200 mg (n = 9)	D 400 mg (n = 8)	E 600 mg (n = 18)	F 50 mg + POSA (n = 9)	G 100 mg + POSA (n = 9)	H 600 mg (n = 16)	CR + CRh + CRi	Median OS, mo (95% CI)
Median age, y (range)	71 (63-80)	73 (68-80)	70 (65-77)	73 (63-80)	70 (64-78)	71 (67-77)	73 (67-75)	70 (66-76)	69 (63-75)	–	–
De novo AML, n (%)	52 (61)	3 (38)	5 (62)	6 (67)	5 (62)	9 (50)	6 (67)	6 (67)	12 (75)	88%	33.1 (19.3-54.3)
Secondary AML, n (%)	33 (39)	5 (63)	3 (38)	3 (33)	3 (38)	9 (50)	3 (33)	3 (33)	4 (25)	54%	8.0 (4.6-13.2)
t-AML, n (%)	6 (7)	1 (12)	–	–	1 (12)	1 (5)	–	1 (11)	2 (13)	33%	17.0 (0.9 to NA)
Prior MDS, n (%)	17 (20)	4 (50)	2 (25)	3 (33)	1 (12)	5 (28)	2 (22)	–	–	59%	7.2 (3.7-15.1)
Prior CMML, n (%)	5 (6)	–	1 (13)	–	–	2 (11)	1 (11)	1 (11)	–	60%	6.3 (0.8 to NA)
Prior MPN, n (%)	5 (6)	–	–	–	1 (12)	2 (11)	–	–	2 (13)	40%	8.6 (0.3 to NA)
Prior HMA, n (%)	16 (19)	3 (38)	3 (38)	2 (22)	2 (25)	6 (33)	–	–	–	44%	5.7 (1.4-8.8)
ELN 2022, n (%)											
Favorable	18 (21)	1 (12)	1 (12)	2 (22)	1 (12)	2 (11)	3 (33)	4 (44)	4 (25)	89%	54.3 (12.5 to NA)
Intermediate	16 (19)	1 (12)	2 (25)	2 (22)	3 (38)	4 (22)	–	1 (11)	3 (19)	81%	29.4 (3.5 to NA)
Adverse	51 (60)	6 (75)	5 (62)	5 (56)	4 (50)	12 (67)	6 (67)	4 (44)	9 (56)	69%	13.2 (8.0 to 20.1)
Selected mutations, n (%)											
NPM1	20 (24)	1 (12)	1 (12)	3 (33)	1 (12)	3 (17)	3 (33)	4 (44)	4 (25)	85%	43.9 (5.5 to NA)
IDH2	18 (21)	–	–	1 (11)	2 (25)	5 (28)	2 (22)	3 (33)	5 (31)	89%	58.5 (33.2 to NA)
IDH1	8 (9)	1 (12)	1 (12)	–	1 (12)	4 (22)	–	–	1 (6)	88%	34.8 (3.45 to NA)
FLT3-ITD	6 (7)	–	1 (12)	2 (22)	1 (12)	1 (5)	–	–	1 (6)	83%	17.5 (0.8 to NA)
NRAS	18 (21)	–	4 (50)	2 (22)	3 (38)	4 (22)	2 (22)	1 (11)	2 (13)	89%	15.1 (6.3-24.1)
KRAS	6 (7)	–	1 (12)	1 (12)	1 (12)	2 (11)	–	1 (11)	–	100%	8.1 (5.3 to NA)
TP53	15 (18)	3 (38)	1 (12)	3 (33)	2 (25)	3 (17)	–	–	3 (19)	40%	4.6 (1.2-8.4)
CR + CRh + CRi	75%	63%	76%	100%	63%	67%	55%	100%	81%		

CI, confidence interval; CMML, chronic myelomonocytic leukemia; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NA, not assessable; POSA, posaconazole; t-AML, therapy-related AML.

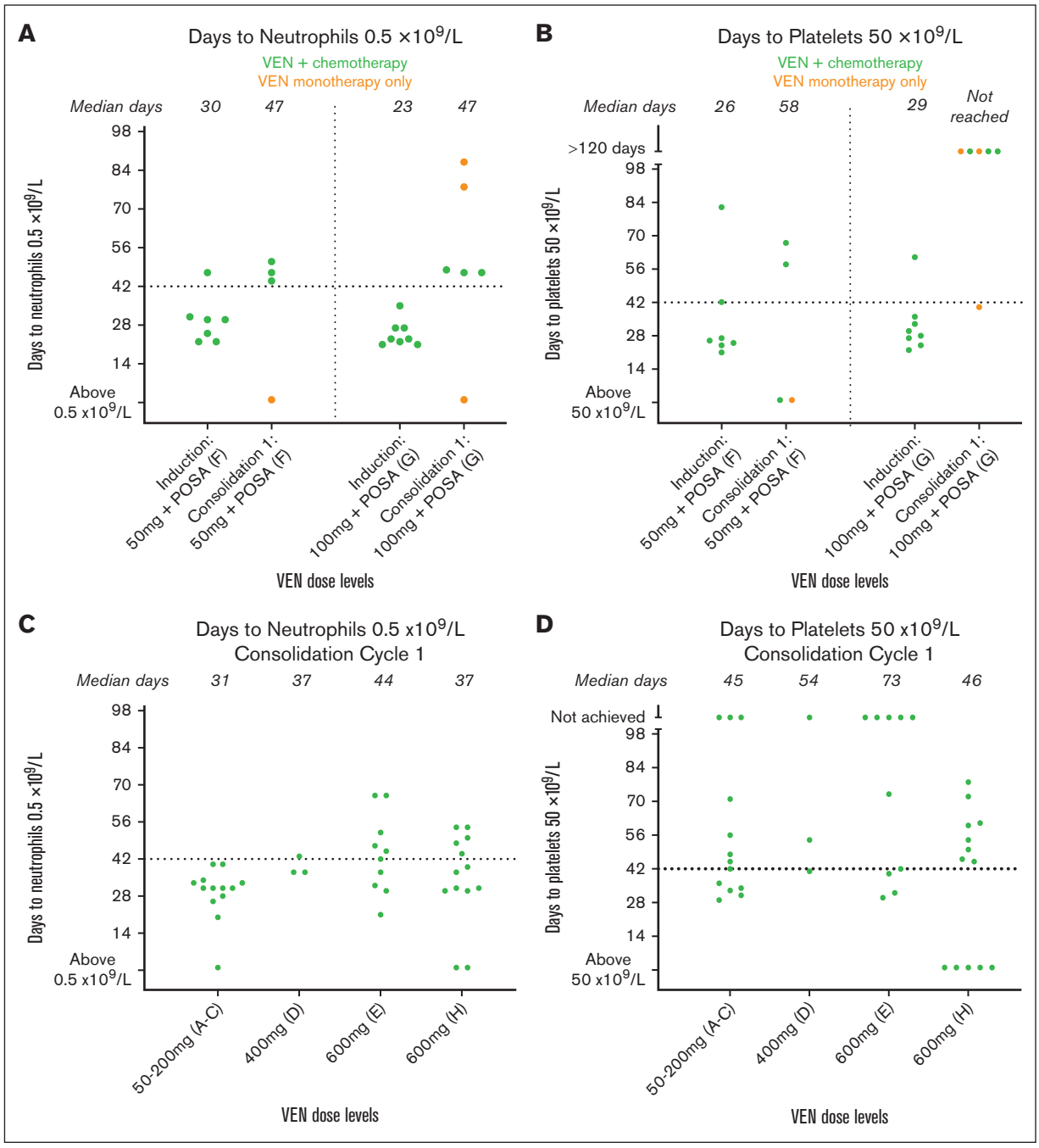

Figure 1. Time to hematologic recovery. (A-B) Hematologic recovery for POSA-augmented cohorts F (VEN 50 mg) and H (VEN 100 mg) during induction and consolidation cycle 1: (A) days to neutrophil recovery, ≥0.5 × 10^9/L; and (B) days to platelet recovery, ≥50 × 10^9/L. (C-D) Hematologic recovery for non–POSA-augmented cohorts A to E and H during consolidation cycle 1: (C) days to neutrophil recovery, ≥0.5 × 10^9/L; and (D) days to platelet recovery, ≥50 × 10^9/L. Individual patient data are shown. Orange points indicate patients who received VEN monotherapy as consolidation. POSA, posaconazole; VEN, venetoclax.

maintenance (n = 28), followed by treatment-free remission (TFR) as part of an observation phase (TFR; n = 30; supplemental Figure 5A). Upon completion of induction and consolidation, the median duration of TFR was 17.9 months (range, 1.0-63.8). AML relapse occurred in 14 of 30 (47%) patients with TFR. Among the 16 patients remaining relapse free at data cutoff, the median duration of TFR was 30.4 months, and 11 have *NPM1* and/or *IDH2* mutations (supplemental Figure 5A).

Across the whole study, 21 of 41 (51%) who relapsed harbored a kinase-activating mutation at diagnosis, affecting *N/KRAS* (n = 17), *FLT3*-ITD (n = 4), *CSF3R* (n = 2), *PTPN11* (n = 2), or *KIT* (n = 1; supplemental Figure 5A). Furthermore, 4 patients acquired new kinase-activating mutations at relapse in *N/KRAS*, *FLT3*-TKD, *JAK2*, and *PTPN11* (supplemental Figure 5B-C). Other variants emerging at relapse included pathogenic *TP53* (n = 2), *PHF6* (n = 2), *EZH2* (n = 2), or *BAX* (n = 4) abnormalities.[8] Patients

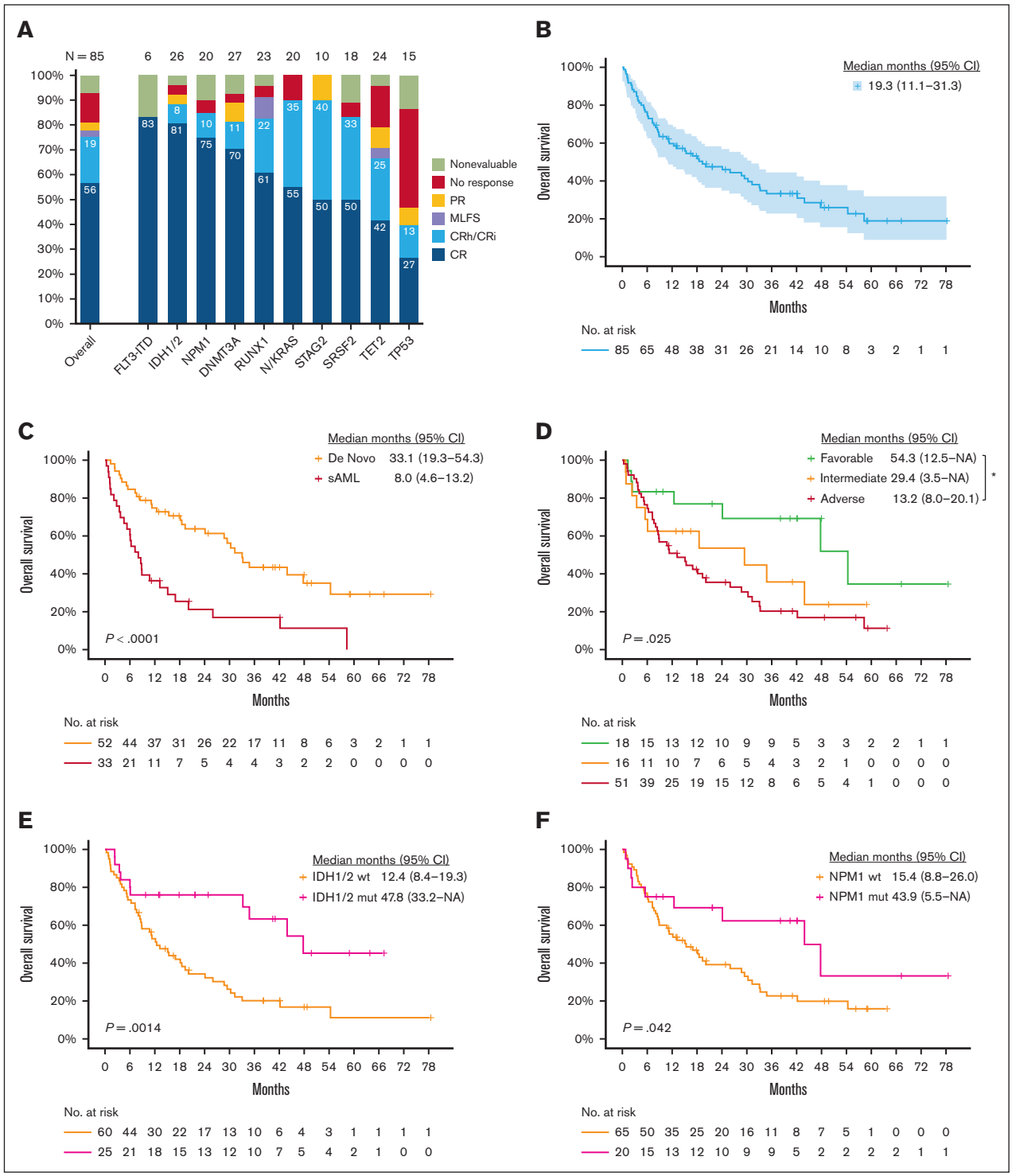

Figure 2. Clinical outcomes after CAVEAT therapy. (A) Clinical response (best response at any time on study) for all patients and by key molecular subgroups (most frequently occurring gene mutations). (B) OS of all patients. (C) OS stratified by de novo vs secondary AML. (D) OS stratified by ELN 2022 risk classification[5]: pairwise comparisons between the 3 risk groups show significant differences only between favorable and adverse risk ($P = .02$; *, corrected for multiple testing), with nonsignificant P values for favorable vs intermediate ($P = .218$) and intermediate vs adverse ($P = 1.00$). (E-H) OS stratified by mutation status: (E) *IDH1/2* mut vs wt, (F) *NPM1* mut vs wt, (G) *TP53* mut vs wt, and (H) *SRSF2* mut vs wt. CI, confidence interval; CRh, CR with partial hematologic recovery; CRi, CR with incomplete count recovery; mut, mutant; MLFS, morphologic leukemia free state; NA, not assessable; wt, wild-type.

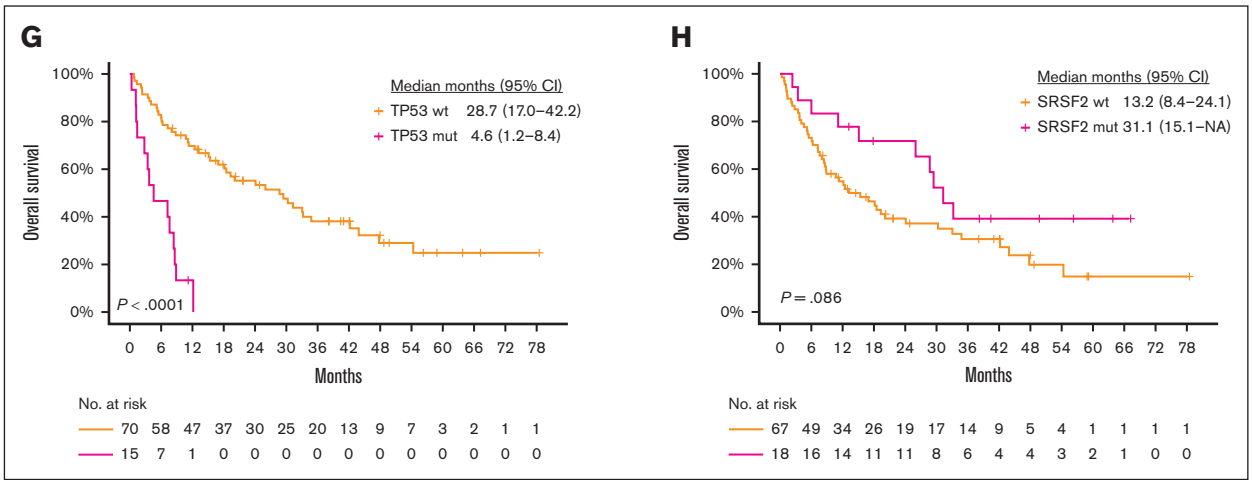

Figure 2 (continued)

refractory to CAVEAT therapy commonly had *TP53* abnormalities (8/13; 62%; supplemental Figure 5B).

Discussion

This final analysis of the CAVEAT study, including 85 patients and almost 42 months median follow-up, highlights the excellent tolerance of the regimen and promising survival in fit, but elderly patients. The time-limited exposure to cytotoxic chemotherapy and long-duration of TFR (median, 17.9 months) affords obvious benefits to elderly patients and resource-constrained health services. The population most likely to benefit are patients with de novo AML, especially those with *NPM1* and/or *IDH1/2* mutations. For de novo AML, response rates of 88% were associated with 33 months median survival. For fit older patients, CAVEAT therapy using the cohort H induction schedule provides high rates of remission, with limited systemic toxicity. Evaluation of long-term efficacy was not confounded by high rates of transplant censoring, with only 5 (6%) patients proceeding to allogeneic HCT. It is not clear why rates of HCT in the CAVEAT study were low, because transplant intent was not collected as part of the study protocol. Possible explanations include (1) HCT in patients aged >65 years was less commonly practiced in Australia when this protocol was activated (June 2016); (2) reduced physician inclination to allograft patients with *NPM1* mutation (24% of the study population) achieving measurable residual disease remission; and (3) HCT was not stipulated in the study protocol, which could have inadvertently discouraged transplant consideration.

In older, unfit patients with AML treated with venetoclax plus azacitidine, cumulative myelosuppression resulting in delayed post-remission neutrophil and platelet recovery is an important concern. Among patients receiving venetoclax in combination with IC, the first induction cycle is often well tolerated. However, after anthracycline-containing consolidation chemotherapy, prolongation of platelet recovery is a known problem, potentially exacerbated by the pharmacokinetic interaction between venetoclax and strong antifungal azoles and association with interpatient variability in venetoclax drug levels.[6,9-12] In the CAVEAT study, delayed hematopoietic recovery after therapy was notable after cytarabine-idarubicin-venetoclax consolidation, limiting the number of chemotherapy-venetoclax cycles able to be delivered. Amelioration of prolonged hematopoietic recovery observed in cohorts D through G was achieved by omitting idarubicin from consolidation, combining venetoclax with LDAC during the consolidation phase in cohort H, and commencing posaconazole only after completing venetoclax during induction. Despite the reduced intensity of chemotherapy delivered during consolidation (venetoclax + LDAC) to patients in cohort H, RFS did not appear compromised, compared with patients in cohorts D to G (supplemental Figure 2). However, it should be cautioned that with the small number of patients examined in cohort H (n = 16) and with a relatively short follow-up (median, 16.1 months), further exploration is required to confirm that long-term efficacy has not been compromised by this reduced-intensity consolidation approach.

In the CAVEAT study, 28 of 85 (33%) patients received maintenance venetoclax. Since completion of the CAVEAT study, oral azacitidine maintenance has become standard of care, based on the results of the phase 3 QUAZAR trial showing improved survival for patients aged ≥55 years not proceeding to allogeneic HCT.[13] For patients aged >65 years, we propose that CAVEAT induction with/without consolidation followed by either allogeneic HCT or oral azacitidine maintenance would seem a highly attractive treatment option, based on high response rates and limited toxicity associated with this "chemotherapy-lite" approach. Studies examining the feasibility of combining maintenance azacitidine with venetoclax after chemotherapy-induced remission are in progress and aimed at further improving elderly AML outcomes with reduced reliance on chemotherapy. Future studies are necessary, however, to verify if such approaches can be proven to enhance long-term disease control and patient-reported outcomes.

In conclusion, in this elderly AML population, the final analysis of the CAVEAT study confirms high rates of response and durable remission in older patients with de novo AML. Our analysis provides guidance regarding the optimal dose of venetoclax, posaconazole scheduling, and consolidation chemotherapy intensity least likely to result in prolonged marrow suppression after therapy. The CAVEAT regimen is a highly effective, minimally toxic, and time-limited treatment option, representing an attractive treatment option for fit, older patients with AML.

Acknowledgments

The authors thank all investigators, study staff, trial management committee, patients, and their families for participation in this study. Venetoclax generously provided by AbbVie.

This trial was principally supported by a grant from the Victorian Cancer Agency. The research was also supported, in part, by grants and fellowships from National Health and Medical Research Council (NHMRC; 1126843) of Australia and an equipment grant from the Australian Cancer Research Foundation. A.W.R. is supported by NHMRC Practitioner Fellowship (1079560) and investigator grant (1174902). A.H.W. and A.W.R. are supported by a Synergy grant (2011139).

Authorship

Contribution: A.H.W., A.W.R., J.R., and C.C.C. designed the research; C.C.C., A.H.W., A.W.R., C.Y.F., S.B.T., S.L., M.A., I.S.T., S.F., and T.-C.T. contributed patients and/or performed clinical data collection; C.C.C., N.S.A., and A.I. provided molecular sequencing data of patient samples; C.C.C., A.H.W., and J.R. performed data analysis and interpretation; C.C.C. and A.H.W. wrote the manuscript; and all authors read and approved the final version of the manuscript.

Conflict-of-interest disclosure: C.C.C. has participated in advisory board meetings for AbbVie, Pfizer, and Sumitomo Pharma Oncology, and received honoraria from Otsuka, Bristol Myers Squibb (BMS), AstraZeneca, AbbVie, and Pfizer. S.L. has received honoraria for speaker's bureau from AbbVie. I.S.T. has received honoraria from Jazz Pharmaceuticals, Novartis, and Pfizer. C.Y.F. has consulted for, served on advisory boards of, or received honoraria for speakers bureau from Astellas, AbbVie, BeiGene, BMS, Jazz Pharmaceuticals, Limbic, Novartis, Novotech, Otsuka, and Pfizer, and received research funding from Jazz Pharmaceuticals and Astellas. S.F. has consulted for, served on advisory boards of, and received honoraria for speakers' bureaus from Astellas, AbbVie, Amgen, BMS, Gilead/Kite, Jazz Pharmaceuticals, Limbic, Novartis, and Pfizer, and has received research funding from Amgen. J.R. holds stock in Novartis AG, Sandoz AG, and Alcon AG, and his employer, Alfred Health, receives funds from AbbVie for his involvement in 1 research project. A.H.W. has served on advisory boards for Novartis, AstraZeneca, Astellas, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Amgen, Roche, Pfizer, AbbVie, Servier, Gilead, BMS, and BeiGene; has consulted for AbbVie, Servier, Novartis, Shoreline, and Aculeus; receives research funding to the institution from Novartis, AbbVie, Servier, BMS, Janssen, Syndax, Astex, AstraZeneca, and Amgen; and serves on speakers' bureaus for AbbVie, Novartis, BMS, Servier, and Astellas. A.H.W., A.W.R., and N.S.A. are employees of the Walter and Eliza Hall Institute (WEHI). WEHI receives milestone and royalty payments related to the development of venetoclax. Current and past employees of WEHI may be eligible for financial benefits related to these payments. A.H.W., A.W.R., and N.S.A. receive such a financial benefit. A.W.R. is an inventor on a patent related to venetoclax. The remaining authors declare no competing financial interests.

ORCID profiles: S.L., 0000-0001-6294-2691; C.Y.F., 0000-0001-5773-103X; S.B.T., 0000-0001-7755-8326; I.S.T., 0000-0001-7417-4343; N.S.A., 0000-0003-2093-1403; M.A., 0000-0001-8653-4844; J.R., 0000-0002-8825-8625; A.W.R., 0000-0002-7341-5720; A.H.W., 0000-0002-7514-3298.

Correspondence: Andrew H. Wei, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, 305 Grattan St, Melbourne, VIC 3000, Australia; email: andrew.wei@petermac.org.

References

1. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
2. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145.
3. Chua CC, Roberts AW, Reynolds J, et al. Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT): a phase Ib dose-escalation study of venetoclax combined with modified intensive chemotherapy. *J Clin Oncol*. 2020;38(30):3506-3517.
4. Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy:results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood*. 2007;109(12):5129-5135.
5. Döhner H, Wei AH, Appelbaum FR, 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.
6. Agarwal SK, DiNardo CD, Potluri J, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clin Therapeut*. 2017;39(2):359-367.
7. Mrózek K, Kohlschmidt J, Blachly JS, et al. Outcome prediction by the 2022 European LeukemiaNet genetic-risk classification for adults with acute myeloid leukemia: an alliance study. *Leukemia*. 2023;37(4):788-798.
8. DiNardo C, Tiong I, Quaglieri A, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood*. 2020;135(11):791-803.
9. Kawedia J, Rausch CR, Li X, et al. Prospective pharmacokinetic evaluation of venetoclax (VEN) in AML demonstrates significant and variable drug interactions with azole antifungals that increase ven exposure, reduce clearance, and necessitate re-evaluation of dose adjustments. *Blood*. 2023;142(suppl 1):2885.
10. De Gregori S, Gelli E, Capone M, et al. Pharmacokinetics of venetoclax co-administered with posaconazole in patients with acute myeloid leukemia. *Pharmaceutics*. 2023;15(6):1680.

11. Jen WY, Takahashi K, Loghavi S, et al. FLAG-IDA+ venetoclax in newly diagnosed (ND) or relapsed/refractory (RR) AML [abstract]. *J Clin Oncol*. 2024; 42(suppl 16):6519.

12. Otsuki A, Kumondai M, Kobayashi D, et al. Plasma venetoclax concentrations in patients with acute myeloid leukemia treated with CYP3A4 inhibitors. *Yakugaku Zasshi*. 2024;144(7):775-779.

13. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26): 2526-2537.