original reports

Valproate and Retinoic Acid in Combination With Decitabine in Elderly Nonfit Patients With Acute Myeloid Leukemia: Results of a Multicenter, Randomized, 2 × 2, Phase II Trial

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abstract

PURPOSE DNA-hypomethylating agents are studied in combination with other epigenetic drugs, such as histone deacetylase inhibitors or differentiation inducers (eg, retinoids), in myeloid neoplasias. A randomized, phase II trial with a 2 × 2 factorial design was conducted to investigate the effects of the histone deacetylase inhibitor valproate and all-*trans* retinoic acid (ATRA) in treatment-naive elderly patients with acute myeloid leukemia (AML).

PATIENTS AND METHODS Two hundred patients (median age, 76 years; range, 61-92 years) ineligible for induction chemotherapy received decitabine (20 mg/m^2 intravenously, days 1 to 5) alone (n = 47) or in combination with valproate (n = 57), ATRA (n = 46), or valproate + ATRA (n = 50). The primary endpoint was objective response, defined as complete and partial remission, tested at a one-sided significance level of $\alpha = .10$. Key secondary endpoints were overall survival, event-free survival, and progression-free survival and safety.

RESULTS The addition of ATRA resulted in a higher remission rate (21.9% with ATRA *v* 13.5% without ATRA; odds ratio, 1.80; 95% CI, 0.86 to 3.79; one-sided $P = .06$). For valproate, no effect was observed (17.8% with valproate *v* 17.2% without valproate; odds ratio, 1.06; 95% CI, 0.51 to 2.21; one-sided $P = .44$). Median overall survival was 8.2 months with ATRA *v* 5.1 months without ATRA (hazard ratio, 0.65; 95% CI, 0.48 to 0.89; two-sided $P = .006$). Improved survival was observed across risk groups, including patients with adverse cytogenetics, and was associated with longer response duration. With valproate, no survival difference was observed. Toxicities were predominantly hematologic, without relevant differences between the 4 arms.

CONCLUSION The addition of ATRA to decitabine resulted in a higher remission rate and a clinically meaningful survival extension in these patients with difficult-to-treat disease, without added toxicity.

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INTRODUCTION

Treatment of elderly patients with acute myeloid leukemia (AML) considered nonfit for standard induction chemotherapy still poses a major unmet clinical need.[1] Recently, 2 DNA-hypomethylating agents (HMAs), decitabine (5-aza-2′-deoxycytidine) and azacitidine (5-azacytidine), with possible mechanisms of action that include gene reactivation (eg, of tumor suppressors) and induction of endogenous retroviruses,[2-4] were approved for treatment of AML in these patients. Both agents show some survival improvement compared with conventional-care regimens, such as low-dose cytarabine,[5,6] and have marked activity in patients with adverse genetic profiles.[7-10] Because outcomes with single-agent HMAs are still unsatisfactory, rational combinations with other agents are being investigated (eg, histone deacetylase inhibitors), which offer in vitro synergism with HMAs as 2 complementary epigenetic mechanisms of gene reactivation).[11] So far, results of randomized trials have been inconsistent.[12]

All-*trans* retinoic acid (ATRA), a powerful inducer of in vivo blast differentiation in acute promyelocytic leukemia (APL),[13] has no single-agent activity in other subtypes of AML. However, preclinical studies demonstrating an at-least-additive effect when ATRA was combined with an HMA in AML cell lines[14,15] have

ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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prompted several nonrandomized, phase II trials in AML and myelodysplastic syndromes,[7,16,17] which demonstrated good feasibility of this combination without unexpected toxicities.

On the basis of encouraging results with decitabine + ATRA in almost 100 elderly, medically nonfit patients with AML[7] and the rationale that the combination of an HMA with valproate might be superior to single-agent HMA treatment,[18] the DECIDER trial (DECItabine, DEacetylase inhibition, Retinoic acid; AMLSG14-09) investigated valproate and ATRA in combination with decitabine.

PATIENTS AND METHODS

Trial Design, Objectives, Patients, and Treatments

This trial was a prospective, randomized, observer-blind, active-control, parallel-group, multicenter, phase II trial. The objective of the trial was the investigation of the efficacy and safety of valproate and ATRA in combination with decitabine in older and nonfit patients with AML. The trial had a 2 × 2 design, in which patients were randomly assigned to 1 of 4 treatment arms: decitabine, decitabine + valproate, decitabine + ATRA, or decitabine + valproate + ATRA.[19] Inclusion and exclusion criteria as well as study treatments and procedures are described in the Data Supplement. The study and all participating sites were approved by the central ethics committee (University of Freiburg) and the respective local ethics committees. Patients' written consent to participate in this clinical trial and its translational research program was obtained before any study-specific procedures occurred. This trial was registered at ClinicalTrials.gov identifier: NCT00867672, at EU Clinical Trials Register (EudraCT No. 2009-009916-33), and at German Clinical Trials Register (No. DRKS00000733).

Study Endpoints

The primary endpoint was objective response, defined as complete remission (with [CR] or without [CRi] regeneration of platelets and neutrophils) or partial remission (PR), per 2010 European LeukemiaNet recommendations.[20] Central review was conducted by an independent hematopathologist (A.M.M.) who was blind to treatment arms (Data Supplement).

Secondary endpoints for evaluation of efficacy were overall survival (OS), event-free survival (EFS), progression-free survival (PFS), overall best response (CR, CRi, PR, antileukemic effect[7]; Data Supplement). Other secondary endpoints were quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire (EORTC QLQ-C30); number of nights in hospital; and safety and toxicity, evaluated by means of adverse events (AEs) occurring from the first administration until 4 weeks after the last administration of study drug and by deaths.

Statistical Analysis

Sample size calculation was based on the primary endpoint (objective response), assuming a response rate of 25% with decitabine alone.[7] The effect of valproate was investigated by comparing the combined treatment arms of decitabine + valproate and decitabine + valproate + ATRA (called the VPA group) versus the combined treatment arms of decitabine-only and decitabine + ATRA (called the no-VPA group). The effect of ATRA was investigated by comparing the combined treatment arms of decitabine + ATRA and decitabine + valproate + ATRA (called the ATRA group) versus decitabine-only and decitabine + valproate (called the no-ATRA group). According to the phase II design of the study, both tests were planned at a one-sided significance level of $\alpha = .10$. For a power of 80%, assuming an increase of the response rate to 40% with valproate or ATRA, 176 patients were necessary, and the planned sample size was 200 patients. Efficacy analyses were performed in the full analysis set, which included all randomly assigned patients for whom treatment was started. For analyses of the primary endpoint, logistic regression was used; for analyses of the time-to-event endpoints OS, EFS, and PFS, Cox regression was used. Primary analyses were conducted without adjustment for patient and disease characteristics, and adjusted analyses were done as sensitivity analyses (Data Supplement).

RESULTS

Study Patients and Treatment

Between December 2011 and February 2015, 204 patients were randomly assigned at 27 centers. Four patients were excluded from all subsequent analyses, because no study treatment was administered, so 200 patients constituted the full analysis set (Fig 1). All patients received the allocated study treatment. The median patient age was 76 years (interquartile range, 72-79 years; range, 61-92 years). Eastern Cooperative Oncology Group performance status of the patients was 0 in 19%, 1 in 61%, 2 in 20%, and 3 in a single patient. Overall, 52% of patients had hematopoietic cell transplantation comorbidity index (HCT-CI) score ≥ 3 according to Sorror et al.[21] A total of 18.5% had leukocytes ≥ 30,000/μL at screening and thus received, according to protocol, a short course of hydroxyurea to achieve cytoreduction to < 30,000/μL before the start of decitabine. In addition, 30% of patients had adverse genetics by 2010 European LeukemiaNet criteria[20]; a monosomal karyotype, strongly associated with *TP53* mutations,[22] was present in 23.5%; mutations of *FLT3* and *NPM1* were found in 12.0% and 9.4%, respectively. A total of 51% had an antecedent hematologic disorder, and 13.5% had treatment-related AML. Patient characteristics overall were balanced across treatment arms (Table 1; Data Supplement).

To objectify reasons for ineligibility for induction chemotherapy, the factors amounting to this mutual decision of the physician and patient were captured at inclusion (Data Supplement). The most frequent reasons given were higher age (57%), patient wish (57%), reduced performance status (44%), and antecedent hematologic disorder (34%).

A median of 3 decitabine cycles were administered: 2 cycles in the decitabine-only arm, 3 in the decitabine + valproate arm, 5.5 in the decitabine + ATRA arm, and 4 in the decitabine + valproate + ATRA arm. Treatment with valproate was stopped, whereas decitabine was continued, in 7 patients in the decitabine + valproate arm and in 15 patients in decitabine + valproate + ATRA arm; treatment with ATRA was stopped, but decitabine was continued, in 8 patients in decitabine + ATRA arm and in 8 patients in decitabine + valproate + ATRA arm. Reasons for the eventual end of study treatment are displayed in Figure 1. In total, 169 patients were followed until death, 20 patients were followed until the study's end, and 11 patients withdrew from the study prematurely (Fig 1).

Objective Response

Thirty-five patients attained an objective response, with a median time to best response of 5.6 months (interquartile range, 3.7-8.7 months; range, 1.7-21.7 months). The objective response rate was 17.5% (decitabine-only, 8.5%; decitabine + valproate, 17.5%; decitabine + ATRA, 26.1%; decitabine + valproate + ATRA, 18.0%; Table 2; Data Supplement).

Because the test of the multiplicative interaction between valproate and ATRA resulted in a P value $> .05$, the effects of valproate and ATRA were estimated from a model that included their main effects only and disregarded the interactive effect (Table 2). No effect of valproate addition on the primary endpoint could be detected (17.8% with valproate *v* 17.2% without valproate; odds ratio, 1.06; 95% CI, 0.51 to 2.21; 80% CI, 0.65 to 1.71; one-sided $P = .44$). A comparison of ATRA versus no ATRA showed a statistically significant effect of ATRA (21.9% *v* 13.5%) at a one-sided significance level of $\alpha = .10$: the odds ratio was 1.80 (95% CI, 0.86 to 3.79; 80% CI, 1.11 to 2.93; one-sided $P = .06$). Sensitivity analyses adjusting for clinical center and bone marrow blasts (which showed an effect on objective response) revealed similar results (Data Supplement).

OS and EFS

The median follow-up for OS was 25.1 months. In total, 169 patients died, the median OS time was 6.2 months (95% CI, 4.7-7.7 months), and the 1-year OS rate was 27% (95% CI, 21% to 34%). With respect to EFS, 182 events occurred (n = 16 were disease relapse, n = 71 were disease progression, n = 16 were other out-of-study treatment, and n = 79 were death).

The median OS times by treatment arm (Table 2; Fig 2A) were 4.8 months with decitabine-only, 6.1 months with decitabine + valproate, 8.4 months with decitabine + ATRA, and 7.7 months with decitabine + valproate + ATRA. Treatment effects again were estimated and tested from a model disregarding the interactive effect between valproate and ATRA (because testing for this effect resulted in $P = .47$; Table 2). The addition of valproate did not affect OS (Fig 2B): the median OS time was 6.2 months and the

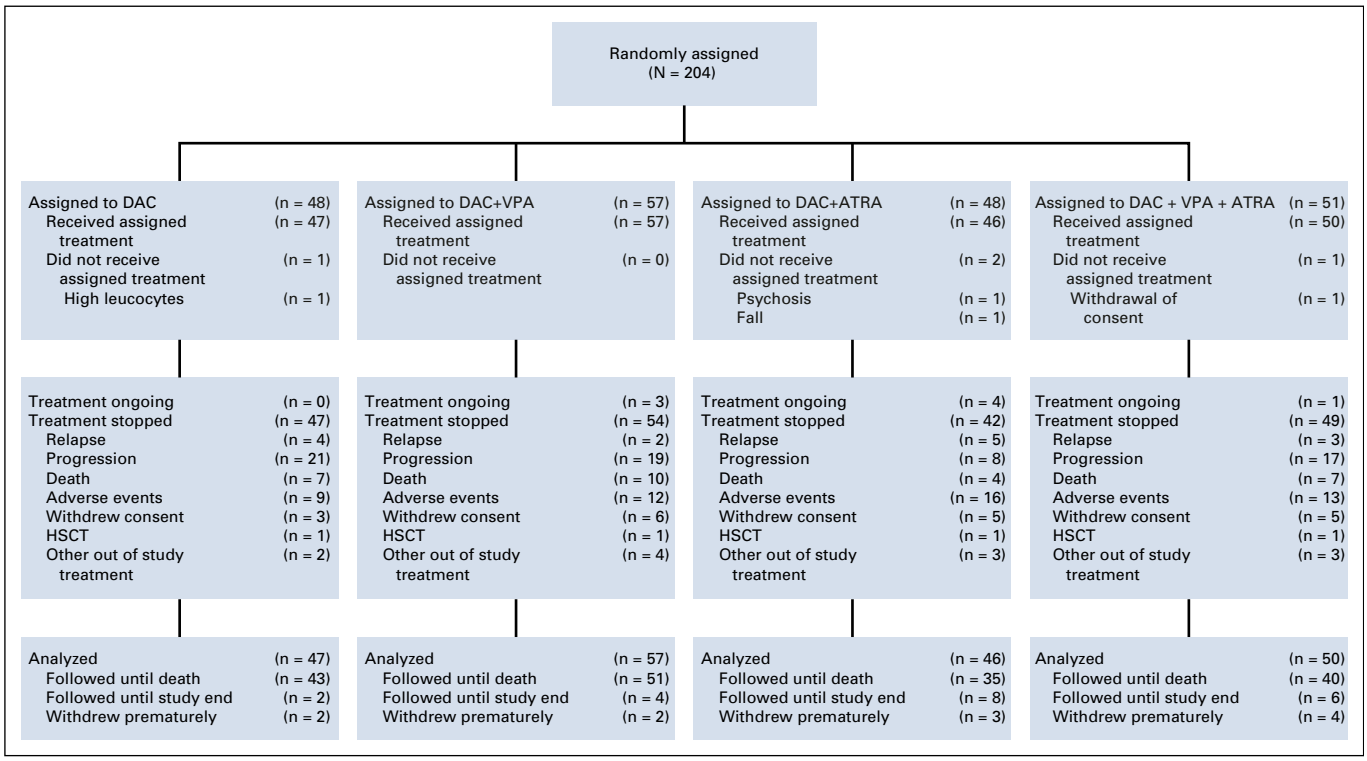


FIG 1. CONSORT diagram showing patient disposition from random assignment to analysis. Forty-three additional patients were reported as screening failures. ATRA, all-*trans* retinoic acid; DAC, decitabine; HSCT, hematopoietic stem cell transplantation; VPA, valproate.

TABLE 1. Patient and Disease Characteristics by Randomly Assigned Treatment

Variable	DAC (n = 47)	DAC + VPA (n = 57)	DAC + ATRA (n = 46)	DAC + VPA + ATRA (n = 50)	Total (N = 200)
Sex					
Male	31 (66.0)	38 (66.7)	28 (60.9)	31 (62.0)	128 (64.0)
Female	16 (34.0)	19 (33.3)	18 (39.1)	19 (38.0)	72 (36.0)
Age, years					
Median (IQR, range)	75 (72-79, 61-92)	76 (72-77, 67-77)	77 (73-80, 61-90)	77 (74-80, 61-84)	76 (72-79, 61-92)
< 70	5 (10.6)	5 (8.8)	5 (10.9)	7 (14.0)	22 (11.0)
70-74	18 (38.3)	20 (35.1)	11 (23.9)	9 (18.0)	58 (29.0)
75-79	15 (31.9)	24 (42.1)	18 (39.1)	21 (42.0)	78 (39.0)
≥ 80	9 (19.2)	8 (14.0)	12 (26.1)	13 (26.0)	42 (21.0)
ECOG PS					
0	11 (23.4)	10 (17.5)	7 (15.2)	10 (20.0)	38 (19.0)
1	27 (57.5)	35 (61.4)	29 (63.0)	31 (62.0)	122 (61.0)
2-3*	9 (19.2)	12 (21.1)	10 (21.7)	9 (18.0)	40 (20.0)
Comorbidity index†					
Median (IQR, range)	2 (1-4, 0-10)	3 (1-5, 0-12)	3 (1-4, 0-10)	2 (0-4, 0-10)	3 (1-4, 0-12)
0	9 (19.2)	7 (12.3)	10 (21.7)	13 (26.0)	39 (19.5)
1-2	15 (31.9)	18 (31.6)	11 (23.9)	13 (26.0)	57 (28.5)
3-4	12 (25.5)	17 (29.8)	14 (30.4)	14 (28.0)	57 (28.5)
≥ 5	11 (23.4)	15 (26.3)	11 (23.9)	10 (20.0)	47 (23.5)
Prior hematologic disorder					
No	22 (46.8)	30 (52.6)	21 (45.7)	25 (50.0)	98 (49.0)
Yes	25 (53.2)	27 (47.4)	25 (54.3)	25 (50.0)	102 (51.0)
Treatment-related AML					
No	41 (87.2)	49 (86.0)	37 (80.4)	46 (92.0)	173 (86.5)
Yes	6 (12.8)	8 (14.0)	9 (19.6)	4 (8.0)	27 (13.5)
White-blood-cell count per μL‡					
Median (IQR)	2.5 (1.4-32.4)	4.1 (1.9-7.6)	7.2 (2.1-20.2)	3.4 (1.7-28.2)	4.1 (1.7-17.5)
< 5,000	27 (57.5)	35 (61.4)	20 (43.5)	28 (56.0)	110 (55.0)
5,000-29,999	8 (17.0)	18 (31.6)	16 (34.8)	11 (22.0)	53 (26.5)
≥ 30,000	12 (25.5)	4 (7.0)	10 (21.7)	11 (22.0)	37 (18.5)
Platelet count per μL					
Median (IQR)	47 (26-102)	48 (35-83)	57 (23-121)	72 (39-135)	53 (31-100)
< 50,000	25 (53.2)	31 (54.4)	22 (47.8)	18 (36.0)	96 (48.0)
≥ 50,000	22 (46.8)	26 (45.6)	24 (52.2)	32 (64.0)	104 (52.0)
Serum lactate dehydrogenase, U/L					
Median (IQR)	273 (210-607)	230 (196-414)	350 (237-504)	297 (214-571)	296 (208-508)
< 300	24 (51.1)	35 (61.4)	17 (37.0)	26 (52.0)	102 (51.0)
≥ 300	23 (48.9)	22 (38.6)	29 (63.0)	24 (48.0)	98 (49.0)
Hemoglobin, g/dL					
Median (IQR)	9.1 (8.3-10.2)	9.2 (8.4-10.3)	9.3 (8.1-10.1)	8.9 (7.9-9.9)	9.1 (8.2-10.1)
< 8	7 (14.9)	11 (19.3)	11 (23.9)	14 (28.0)	43 (21.5)
≥ 8	40 (85.1)	46 (80.7)	35 (76.1)	36 (72.0)	157 (78.5)

(continued on following page)

TABLE 1. Patient and Disease Characteristics by Randomly Assigned Treatment (continued)

Variable	DAC (n = 47)	DAC + VPA (n = 57)	DAC + ATRA (n = 46)	DAC + VPA + ATRA (n = 50)	Total (N = 200)
Bone marrow blasts, %					
Median (IQR)	48 (25-64)	43 (26-73)	69 (40-84)	48 (29-73)	50 (28-80)
< 50	23 (51.1)	30 (52.6)	18 (39.1)	25 (51.0)	96 (48.7)
≥ 50	22 (48.9)	27 (47.4)	28 (60.9)	24 (49.0)	101 (51.3)
Missing	2	0	0	1	3
2010 European LeukemiaNet genetic risk classification					
Favorable	4 (8.5)	5 (8.8)	3 (6.5)	3 (6.0)	15 (7.5)
Intermediate-I	13 (27.7)	13 (22.8)	16 (34.8)	15 (30.0)	57 (28.5)
Intermediate-II	9 (19.2)	15 (26.3)	11 (23.9)	15 (30.0)	50 (25.0)
Adverse	16 (34.0)	22 (38.6)	11 (23.9)	11 (22.0)	60 (30.0)
Not available	5 (10.6)	2 (3.5)	5 (10.9)	6 (12.0)	18 (9.0)
FLT3-ITD					
No	40 (87.0)	52 (96.3)	41 (91.1)	46 (93.9)	179 (92.2)
Yes	6 (13.0)	2 (3.7)	4 (8.9)	3 (6.1)	15 (7.8)
Missing	1	3	1	1	6
FLT3-TKD					
No	44 (97.8)	52 (96.3)	41 (93.2)	47 (95.9)	184 (95.8)
Yes	1 (2.2)	2 (3.7)	3 (6.8)	2 (4.1)	8 (4.2)
Missing	2	3	2	1	8
NPM1					
No	37 (84.1)	52 (96.3)	39 (86.7)	46 (93.9)	174 (90.6)
Yes	7 (15.9)	2 (3.7)	6 (13.3)	3 (6.1)	18 (9.4)
Missing	3	3	1	1	8
MK					
No	32 (76.2)	38 (69.1)	35 (83.3)	35 (79.6)	140 (76.5)
Yes	10 (23.8)	17 (30.9)	7 (16.7)	9 (20.4)	43 (23.5)
Missing	5	2	4	6	17
Reasons for ineligibility for induction chemotherapy					
Patient's age	27 (57.5)	30 (52.6)	27 (58.7)	30 (60.0)	114 (57.0)
Patient's wish	32 (68.1)	37 (64.9)	21(45.7)	24 (48.0)	114 (57.0)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: AML, acute myeloid leukemia; ATRA, all-*trans* retinoic acid; DAC, decitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; FLT3, fms-like tyrosine kinase 3; ITD, internal tandem duplication; IQR, interquartile range; MK, monosomal karyotype; NPM1, nucleophosmin-1; TKD, tyrosine kinase domain; VPA, valproate.

*One patient in the decitabine arm had a performance status 3.

†According to the hematopoietic cell transplantation comorbidity index.

‡White-blood-cell count at time of screening, prior to cytoreduction as per protocol.

1-year OS rate was 27.9% with valproate versus 6.4 months and 26.8% without valproate (hazard ratio [HR], 0.94; 95% CI, 0.70 to 1.28; two-sided $P = .71$). In a multivariable analysis adjusting for performance status, comorbidities, serum lactate dehydrogenase level, hemoglobin level, and genetic risk, as well as in a multivariable model stratifying for center, this result remained unchanged (Data Supplement). Similarly, the addition of valproate did not affect EFS (HR, 0.90; 95% CI, 0.67 to 1.21; two-sided $P = .48$; Data Supplement). The median OS time and the 1-year OS rate were higher in patients treated with ATRA (8.2 months and 35.3%, respectively) than in patients not treated with ATRA (5.1 months and 20.3%, respectively). The HR was 0.65 (95% CI, 0.48 to 0.89; two-sided

TABLE 2. Effect of Treatment on Objective Response and Overall Survival

	Objective Response				Overall Survival				
Treatment	Objective Response Rate %, (95% CI)	Odds Ratio	95% CI	*P*	1-Year Overall Survival Rate %, (95% CI)	Median Overall Survival, Months (95% CI)	Hazard Ratio	95% CI	*P*
Comparison of 4 groups				.20					.043
Decitabine	8.5 (2.4 to 20.4)	1.00	—		16 (7 to 28)	4.8 (2.8 to 7.6)	1.00	—	
Decitabine + VPA	17.5 (8.8 to 29.9)	2.29	(0.67 to 7.83)		24 (14 to 36)	6.1 (3.2 to 7.2)	0.85	(0.57 to 1.28)	
Decitabine + ATRA	26.1 (14.3 to 41.1)	3.79	(1.12 to 12.8)		38 (24 to 52)	8.4 (4.0 to 14.0)	0.58	(0.37 to 0.91)	
Decitabine + VPA + ATRA	18.0 (8.6 to 31.4)	2.36	(0.67 to 8.26)		33 (20 to 46)	7.7 (4.6 to 11.2)	0.62	(0.40 to 0.95)	
Effects of VPA and ATRA with interaction between VPA and ATRA									
Effect of VPA *v* no VPA									
Without ATRA		2.29	(0.67 to 7.83)	.19			0.85	(0.57 to 1.28)	.44
With ATRA		0.62	(0.23 to 1.65)	.34			1.07	(0.68 to 1.68)	.78
Effect of ATRA *v* no ATRA									
Without VPA		3.79	(1.12 to 12.8)	.032			0.58	(0.37 to 0.91)	.017
With VPA		1.03	(0.38 to 2.79)	.95			0.72	(0.48 to 1.10)	.13
Interaction		0.27	(0.06 to 1.31)	.104			1.25	(0.68 to 2.31)	.47
Effects of VPA and ATRA without interaction between VPA and ATRA									
Effect of VPA *v* no VPA		1.06	(0.51 to 2.21)*	.88*			0.94	(0.70 to 1.28)	.71
VPA	17.8 (11.0 to 26.3)				28 (20 to 37)	6.2 (4.5 to 8.9)			
no VPA	17.2 (10.2 to 26.4)				27 (18 to 36)	6.4 (3.9 to 8.4)			
Effect of ATRA *v* no ATRA		1.80	(0.86 to 3.79)*	.12*			0.65	(0.48 to 0.89)	.006
ATRA	21.9 (14.1 to 31.5)				35 (26 to 45)	8.2 (4.7 to 11.2)			
no ATRA	13.5 (7.6 to 21.6)				20 (13 to 29)	5.1 (3.8 to 6.9)			

NOTE. Objective response is defined as attainment of a complete remission (with or without hematopoietic recovery) or partial remission, with the analyses unadjusted for patient and disease characteristics and the effect estimated from a logistic regression model. For the effect of treatment on overall survival, the analyses were unadjusted for patient and disease characteristics, and the effect was estimated from a Cox regression model. *P* values are two-sided.

Abbreviations: ATRA, all-*trans* retinoic acid; VPA, valproate.

*For correspondence with a one-sided test at $\alpha = .10$, effect of VPA with an 80% CI of the odds ratio of 0.65 to 1.71, one-sided $P = .44$; effect of ATRA with an 80% CI of the odds ratio of 1.11 to 2.93, one-sided $P = .06$.

$P = .006$; Table 2; Fig 2C). This treatment effect was similar in multivariable analysis after adjustment (Data Supplement), with an HR of 0.60 (95% CI, 0.43 to 0.84; two-sided $P = .003$). The result also remained stable after stratification for clinical center (HR, 0.65; 95% CI, 0.47 to 0.91; two-sided $P = .012$). Patients receiving ATRA also had longer EFS than those not receiving ATRA (HR, 0.66; 95% CI, 0.49 to 0.89; two-sided $P = .007$; Data Supplement).

The positive effect of ATRA on OS is not readily explained solely by its positive effect on objective response. Rather, its positive effect is caused by other mechanisms, leading to prolonged survival after attainement of response. This is illustrated in an exploratory descriptive analysis (Fig 2D-F), showing that the ATRA group had a higher survival probability with overall best response (CR/CRi + PR + antileukemic effect) compared with the no-ATRA group, with a mean survival with response of 7.2 months in the ATRA group compared with 4.1 months in the no-ATRA group (areas under the curves shown in Fig 2F). Interestingly, the estimated probability of survival without attaining response (Fig 2G-I) also was higher in the ATRA group than in the no-ATRA group (area under the curve, 5.8 months with ATRA *v* 4.2 months without ATRA; Fig 2I), indicating that ATRA may prolong the stable-disease phase.

The stability of the effects of treatment on OS was evaluated in several subgroups that were defined by patient baseline characteristics. Regarding valproate (Fig 3A), no interactive

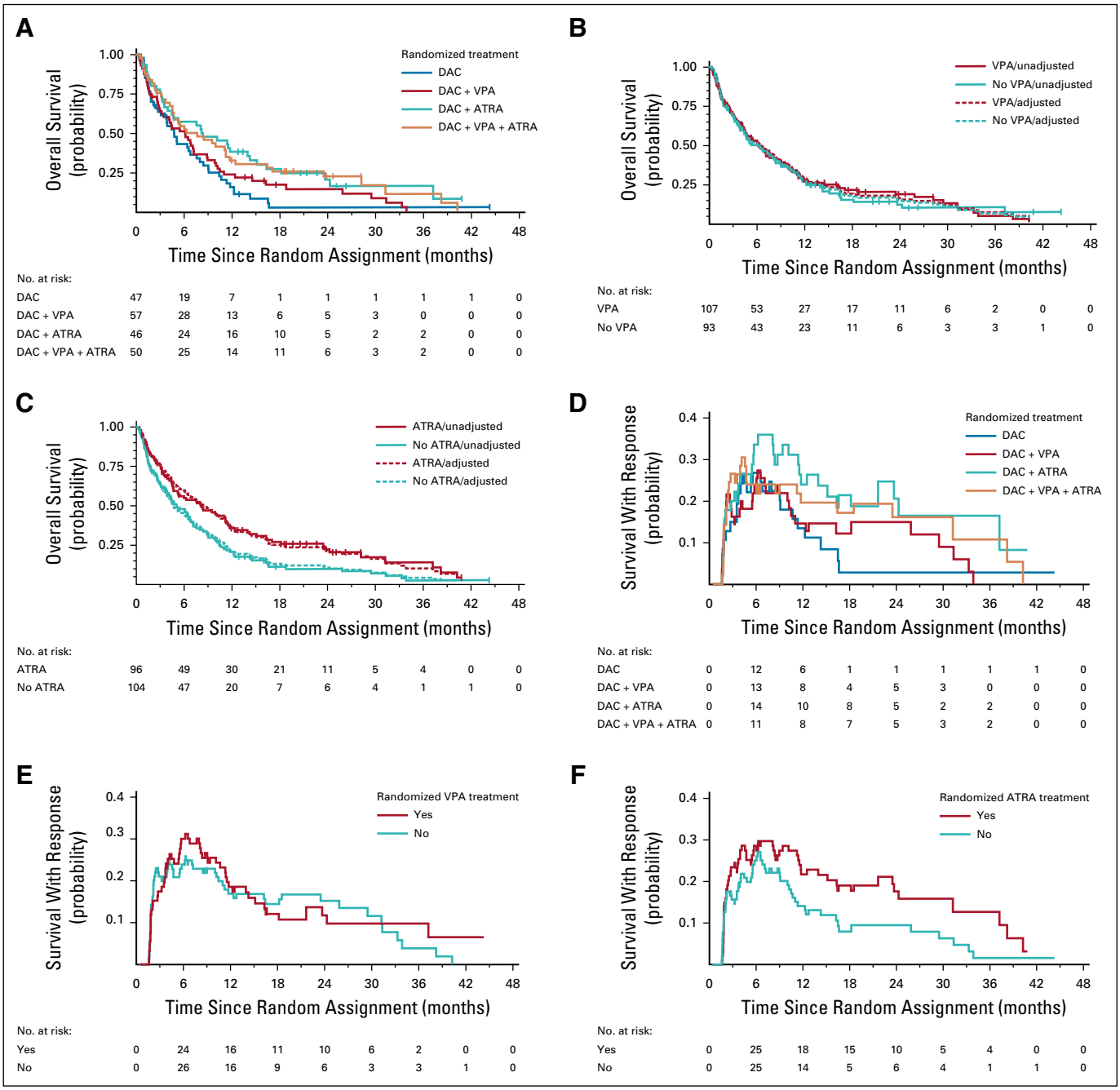


FIG 2. Effect of treatment on (panels A-C) overall survival (OS), (panels D-F) survival with response, and (panels G-I) survival without response. (A) OS rates by randomized treatment, for each treatment arm, estimated by the Kaplan-Meier method. (B) OS rates by randomized combination treatment, with (red) or without (aqua) valproate (VPA). Solid curves represent unadjusted rates estimated by the Kaplan-Meier method; broken curves, adjusted for all-*trans* retinoic acid (ATRA) treatment, performance status, comorbidity index, serum lactate dehydrogenase level, hemoglobin level, and genetic risk (2010 European LeukemiaNet classification[20]) estimated from a Cox regression model. (C) OS rates by randomized combination treatment, with (red) or without (aqua) ATRA. Solid curves represent unadjusted rates estimated by the Kaplan-Meier method; broken curves, adjusted for VPA treatment, performance status, comorbidity index, serum lactate dehydrogenase level, hemoglobin level, and genetic risk (2010 European LeukemiaNet classification[20]) estimated from a Cox regression model. (D) Probability of survival with response by randomly assigned treatment, for each treatment arm, with response defined as attaining a complete remission (with or without hematopoietic recovery), partial remission, or antileukemic effect as best response, estimated by the Aalen-Johansen method. (E, F) Probability of survival with response by randomly assigned combination treatment, with (red) or without (aqua) (E) VPA or (F) ATRA, with response defined as for (D) estimated by the Aalen-Johansen method.

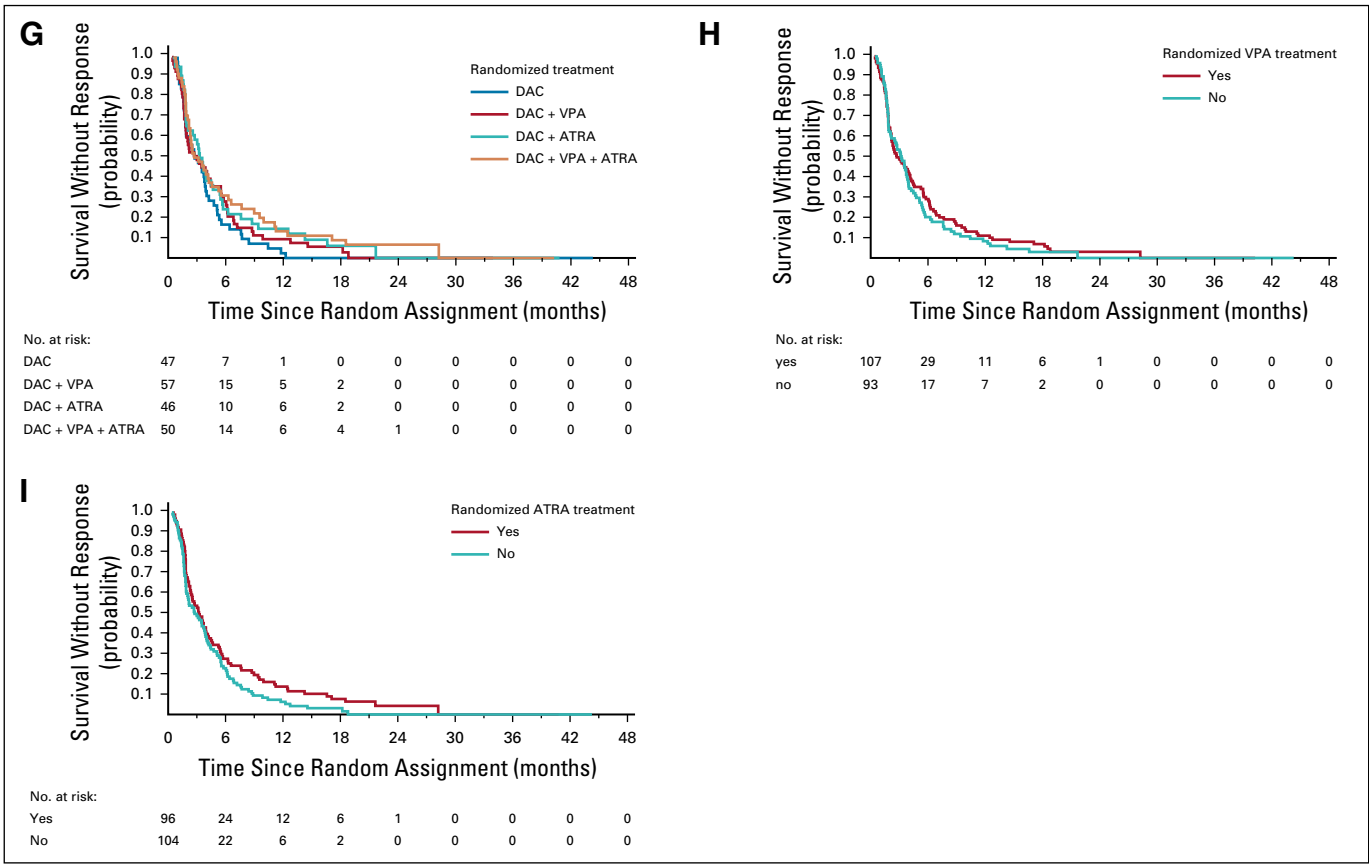


FIG 2. (Continued). (G) Probability of survival without response by randomly assigned treatment, for each treatment arm, with response defined as attaining a complete or partial remission or an antileukemic effect, estimated by the Aalen-Johansen method. (H, I) Probability of survival without response by randomly assigned combination treatment, with (red) or without (aqua) (H) VPA or (I) ATRA, with response defined as for (G) estimated by the Aalen-Johansen method. DAC, decitabine.

effects with *P* values < .05 could be detected. All estimated HRs varied around 1.0, with 95% CIs largely overlapping the equality of treatment groups. Regarding ATRA (Fig 3B), interactive effects between treatment and HCT-CI, and between treatment and sex, showed *P* values < or close to .05, suggesting stronger beneficial effects of ATRA in patients without comorbidities and in women. However, the multiplicity of analyses must be taken into account in these subgroup analyses. In general, the beneficial effect of ATRA with estimated HRs < 1.0 was present in all patient subgroups. Interestingly, this benefit was similar in the different genetic risk groups (Fig 3B; Data Supplement). Results for secondary endpoints of PFS, overall best response, quality of life, and number of nights in hospital are provided in the Data Supplement.

Safety

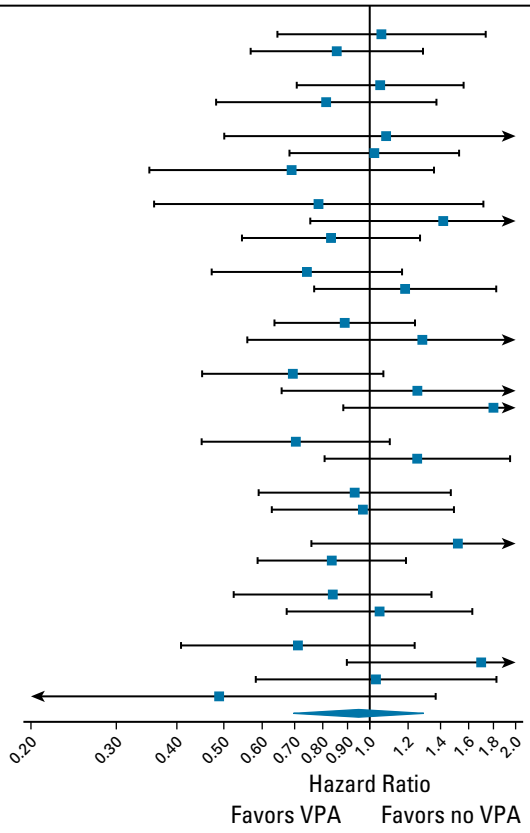
As listed in Table 3, grade 3-5 treatment-emergent AEs were predominantly hematologic or infectious and overall did not show relevant differences between the 4 treatment arms. The frequency of grade 3-5 AEs occurring in patients receiving ATRA also was comparable to that of the no-ATRA group (albeit with the longer median survival associated with ATRA; Data Supplement). Fatal serious AEs judged by the investigator to be related to decitabine occurred in 3.5% of patients, whereas no relationships of fatal serious AEs to valproate or ATRA were observed. The descriptive comparison of the valproate versus no-valproate and ATRA *v* no-ATRA groups showed that the reported AEs and adverse drug reactions were in line with the corresponding applicable Summary of Product Characteristics and/or the underlying disease.

DISCUSSION

Presently, a plethora of AML studies (several of them in phase III) is aimed at identifying a combination of a hypomethylating drug with a second agent that might demonstrate superiority over hypomethylating monotherapy. This includes BCL-2 inhibition,[23,24] novel cytotoxic agents,[25] mutant-IDH inhibition,[26] tyrosine kinase inhibition,[27] anti-CD33 antibodies,[28] and biologicals such as retinoids.[7,29] Retinoids have been clinically investigated as noncytotoxic antineoplastic drugs in many solid tumors and hematologic malignancies, with established roles so far limited to APL, neuroblastoma, and squamous cell carcinoma.[13,30] Since

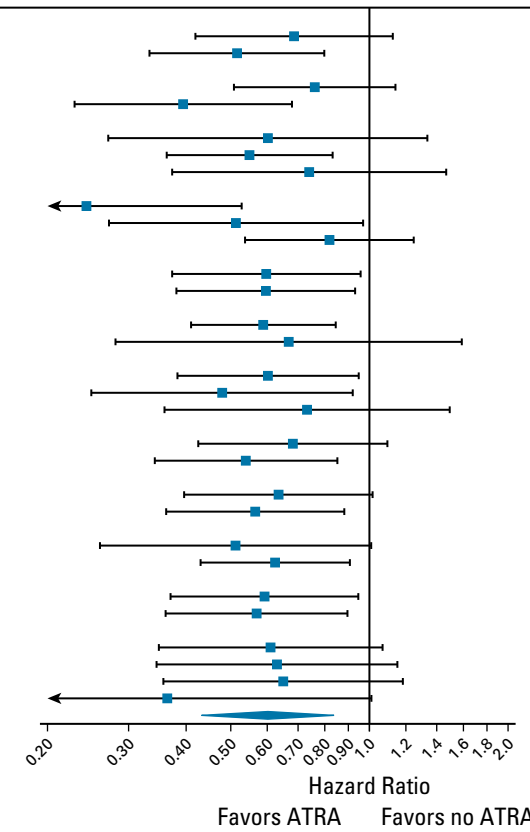
A

	n	HR	95% CI	*P* for Interaction
Age, years				
< 75 years	80	1.057	(0.645 to 1.735)	.5242
≥ 75 years	120	0.855	(0.568 to 1.288)	
Sex				
Male	128	1.051	(0.707 to 1.562)	.4519
Female	72	0.813	(0.482 to 1.373)	
ECOG				
0	38	1.081	(0.501 to 2.333)	.5742
1	122	1.022	(0.683 to 1.529)	
2–3	40	0.690	(0.351 to 1.357)	
HCT–CI				
0	39	0.784	(0.359 to 1.716)	.3585
1–2	57	1.418	(0.754 to 2.669)	
≥ 3	104	0.832	(0.545 to 1.270)	
Prior hem. disorder				
no	98	0.742	(0.472 to 1.166)	.1469
yes	102	1.183	(0.768 to 1.824)	
tAML				
no	173	0.888	(0.636 to 1.240)	.4191
yes	27	1.284	(0.559 to 2.949)	
WBC				
< 5,000 [µl]	110	0.694	(0.451 to 1.067)	.0614
5,000-29,999 [µl]	53	1.254	(0.658 to 2.390)	
≥ 30,000 [µl]	37	1.800	(0.882 to 3.671)	
Plt				
< 50,000 [µl]	96	0.704	(0.450 to 1.100)	.0738
≥ 50,000 [µl]	104	1.253	(0.807 to 1.948)	
LDH				
< 300 [U/l]	102	0.931	(0.590 to 1.470)	.9049
≥ 300 [U/l]	98	0.968	(0.628 to 1.492)	
Hb				
< 8 [g/dl]	43	1.520	(0.758 to 3.048)	.1368
≥ 8 [g/dl]	157	0.835	(0.587 to 1.188)	
Blasts				
< 50 [%]	98	0.839	(0.524 to 1.341)	.5109
≥ 50 [%]	101	1.048	(0.674 to 1.628)	
2010 ELN genetic risk				
Good/Intl	72	0.711	(0.408 to 1.238)	.1090
Int II	50	1.698	(0.897 to 3.215)	
Poor	60	1.030	(0.582 to 1.826)	
NA	18	0.489	(0.175 to 1.368)	
All	**200**	**0.949**	**(0.696 to 1.293)**	



B

	n	HR	95% CI	*P* for Interaction
Age, years				
< 75 years	80	0.686	(0.419 to 1.124)	.3884
≥ 75 years	120	0.516	(0.333 to 0.798)	
Sex				
Male	128	0.761	(0.508 to 1.139)	.0516
Female	72	0.394	(0.229 to 0.679)	
ECOG				
0	38	0.602	(0.271 to 1.336)	.7622
1	122	0.549	(0.363 to 0.832)	
2–3	40	0.740	(0.373 to 1.468)	
HCT–CI				
0	39	0.243	(0.112 to 0.528)	.0207
1–2	57	0.513	(0.272 to 0.969)	
≥ 3	104	0.819	(0.537 to 1.248)	
Prior hem. disorder				
no	98	0.597	(0.373 to 0.957)	.9938
yes	102	0.596	(0.381 to 0.931)	
tAML				
no	173	0.588	(0.410 to 0.845)	.7929
yes	27	0.668	(0.281 to 1.587)	
WBC				
< 5,000 [µl]	110	0.602	(0.383 to 0.948)	.6869
5,000-29,999 [µl]	53	0.479	(0.249 to 0.920)	
≥ 30,000 [µl]	37	0.732	(0.359 to 1.494)	
Plt				
< 50,000 [µl]	96	0.682	(0.425 to 1.094)	.4789
≥ 50,000 [µl]	104	0.539	(0.342 to 0.852)	
LDH				
< 300 [U/l]	102	0.635	(0.396 to 1.016)	.7189
≥ 300 [U/l]	98	0.565	(0.362 to 0.882)	
Hb				
< 8 [g/dl]	43	0.512	(0.260 to 1.009)	.6145
≥ 8 [g/dl]	157	0.624	(0.430 to 0.907)	
Blasts				
< 50 [%]	98	0.592	(0.370 to 0.946)	.9025
≥ 50 [%]	101	0.569	(0.361 to 0.896)	
2010 ELN genetic risk				
Good/Intl	72	0.610	(0.349 to 1.068)	.7938
Int II	50	0.630	(0.345 to 1.150)	
Poor	60	0.650	(0.357 to 1.182)	
NA	18	0.364	(0.131 to 1.010)	
All	**200**	**0.602**	**(0.432 to 0.838)**	



the introduction of ATRA as a well-tolerated, highly effective differentiation inducer in APL, efforts studying combination therapies have been undertaken to explore its usefulness in other AML subtypes, particularly in elderly, nonfit patients. However, a large, randomized trial did not demonstrate an effect of ATRA when combined with low-dose cytarabine.[31] A major benefit of ATRA added to standard chemotherapy might be limited to patients with favorable-risk genetics.[32,33]

The rationale for combining ATRA with HMAs is based on the concept of reactivation of ATRA signaling by epigenetic derepression of silenced genes. Momparler et al[14] first demonstrated an additive antiproliferative and differentiating effect of decitabine and ATRA in HL-60 cells. Since then, several single-arm phase II studies in AML/myelodysplastic syndrome combining ATRA with decitabine[7,34] or azacitidine[16,17] were reported, with encouraging tolerance of this combination. Similarly, the combination of valproate with ATRA was investigated in AML and demonstrated a very acceptable toxicity profile and recurrent clinical responses.[35-39]

In this study, we asked whether valproate and ATRA combined with decitabine could improve objective response and OS compared with decitabine alone. For valproate, no clinical benefit was noted—a result that is in line with those of Issa et al.[40] The addition of ATRA, however, resulted in an increase in the objective response rate compared with patients not receiving ATRA (21.9% *v* 13.5%; one-sided $P = .06$), thus showing a significant effect at a one-sided alpha = .10, prespecified for this phase II study.[41,42] Notably, in patients receiving ATRA, OS also was prolonged, constituting a clinically meaningful effect that was reflected in prolonged EFS and PFS as well and that was observed also in patients with adverse-risk genetics. This treatment combination was not associated with relevant additional toxicities compared with decitabine alone, and it proved readily feasible.

It has to be considered why an, in absolute numbers, moderate improvement in response resulted in a clinically relevant survival extension. The observed cooperativity between decitabine and ATRA did not appear to involve in vivo differentiation (absence of differentiation syndrome). Rather, the addition of ATRA appeared to delay time to progression and thus prolong overall survival (Figs 2F, 2I). It is therefore tempting to speculate that ATRA may prolong survival by delaying the development of decitabine resistance, prompting investigations on resistance mechanisms in vivo.

A possible suggestion of an antagonistic effect between valproate and ATRA was observed, even if the statistical tests of the interactive effects with respect to objective response and with respect to OS showed P values $> .05$ (Table 2; Data Supplement). The effect of ATRA was larger in the no-VPA group than in the VPA group. Interestingly, Noack et al[43] observed that, in vitro, APL cells were protected by ATRA from the cytotoxic effect of the pan–histone deacetylase inhibitor vorinostat.

The CR rate in the decitabine-only arm (6.4%) was lower than anticipated on the basis of the predecessor, single-arm, phase II trial, in which a CR rate of 13.0% was noted.[7] Patients in that previous trial were younger by 3 years (median age, 72 *v* 75 years) than those in the control arm of DECIDER, with otherwise overall similar characteristics. In the previous trial, time on treatment had been longer, with a median of 12 weeks (2 treatment cycles of 6-week durations) compared with a median of 8 weeks in the DECIDER trial (2 treatment cycles of 4-week durations). Continued treatment with HMAs for at least 4 to 6 cycles is crucial to obtain optimal responses, because HMAs are slow-acting drugs. In that regard, in the DACO-16 pivotal trial of decitabine versus treatment choice, a median of 4 decitabine cycles (4-week duration) was administered, with a resultant CR rate of 15.7%. The median patient age in the DACO-16 trial was 73 years, and the incidence of secondary AML was 36% (*v* 47% in the decitabine-only arm of this trial)—both factors that may account at least in part for the differences in outcome.

The decision-making process to advise elderly patients with AML for or against induction chemotherapy is complex and takes both patient- and disease-related factors into account.[44-46] A total of 179 patients (89.5%) had at least one of the following unfavorable conditions regarding induction chemotherapy: a prior hematologic disorder, Eastern Cooperative Oncology Group performance status of 3, an HCT-CI of ≥ 3, reduced activities of daily living, or increased fatigue. We interrogated these and other clinical parameters as reasons indicated by the treating physician to recommend nonintensive treatment rather than induction. Usually, more than a single clinical parameter was given as a reason (Data Supplement); patient age was the most frequent, together with patient wish. The wish of the patient is probably often informed by the physician's personal views on the risks versus benefits of induction chemotherapy, which can be

FIG 3. Effect of treatment on overall survival in different subgroups by baseline patient and disease characteristics. *P* values refer to the test of the respective hypothesis of no interaction. (A) Effect of valproate (VPA) treatment, adjusted for treatment with all-*trans* retinoic acid (ATRA), performance status, comorbidity index, serum lactate dehydrogenase level, hemoglobin level, and genetic risk estimated from a Cox regression model including VPA treatment and the respective patient and disease characteristic as main effects and their multiplicative interaction. (B) Effect of ATRA treatment, adjusted for treatment with VPA, performance status, comorbidity index, serum lactate dehydrogenase level, hemoglobin level, and genetic risk estimated from a Cox regression model including ATRA treatment and the respective patient and disease characteristic as main effects and their multiplicative interaction. ECOG, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet classification[20]; Hb, hemoglobin; HCT-CI, hematopoietic cell transplantation comorbidity index; LDH, serum lactate dehydrogenase; Plt, platelets; tAML, treatment-related AML; WBC, white-blood-cell count.

TABLE 3. Grade 3-5 Treatment-Emergent Adverse Events by Treatment Arm

	No. (%) of Patients With at Least One Adverse Event of Grade 3-5 Defined by MedDRA Preferred Term				
MedDRA Preferred Term and Maximum Grade	DAC (n = 47)	DAC + VPA (n = 57)	DAC + ATRA (n = 46)	DAC + VPA + ATRA (n = 50)	Total (N = 200)
Thrombocytopenia or platelet count decreased					
3-5	12 (25.5)	20 (35.1)	16 (34.8)	19 (38.0)	67 (33.5)
3	3 (6.4)	0 (0.0)	2 (4.3)	2 (4.0)	7 (3.5)
4	9 (19.1)	19 (33.3)	14 (30.4)	17 (34.0)	59 (29.5)
5	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.5)
Anemia or hemoglobin decreased					
3-5	10 (21.3)	13 (22.8)	14 (30.4)	10 (20.0)	47 (23.5)
3	10 (21.3)	13 (22.8)	14 (30.4)	10 (20.0)	47 (23.5)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia					
3-5	12 (25.5)	12 (21.1)	7 (15.2)	9 (18.0)	40 (20.0)
3	6 (12.8)	5 (8.8)	4 (8.7)	6 (12.0)	21 (10.5)
4	2 (4.3)	1 (1.8)	1 (2.2)	0 (0.0)	4 (2.0)
5	4 (8.5)	6 (10.5)	2 (4.3)	3 (6.0)	15 (7.5)
Leukopenia or white blood cell count decreased					
3-5	6 (12.8)	13 (22.8)	12 (26.1)	7 (14.0)	38 (19.0)
3	2 (4.3)	5 (8.8)	5 (10.9)	1 (2.0)	13 (6.5)
4	4 (8.5)	8 (14.0)	7 (15.2)	6 (12.0)	25 (12.5)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile neutropenia					
3-5	10 (21.3)	8 (14.0)	8 (17.4)	10 (20.0)	36 (18.0)
3	9 (19.1)	5 (8.8)	6 (13.0)	8 (16.0)	28 (14.0)
4	1 (2.1)	0 (0.0)	1 (2.2)	2 (4.0)	4 (2.0)
5	0 (0.0)	3 (5.3)	1 (2.2)	0 (0.0)	4 (2.0)
Neutropenia or neutrophil count decreased					
3-5	7 (14.9)	8 (14.0)	8 (17.4)	12 (24.0)	35 (17.5)
3	0 (0.0)	1 (1.8)	2 (4.3)	0 (0.0)	3 (1.5)
4	7 (14.9)	7 (12.3)	5 (10.9)	12 (24.0)	31 (15.5)
5	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.5)
General physical health deterioration					
3-5	2 (4.3)	4 (7.0)	2 (4.3)	5 (10.0)	13 (6.5)
3	1 (2.1)	4 (7.0)	1 (2.2)	4 (8.0)	10 (5.0)
4	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.5)
5	1 (2.1)	0 (0.0)	0 (0.0)	1 (2.0)	2 (1.0)

NOTE. Events are shown that occurred in ≥ 10% of patients in any treatment group (by decreasing frequency in total). Events were coded using the MedDRA and were graded for severity using Common Terminology Criteria for Adverse Events, version 4.0. Data are No. (%) unless otherwise indicated.
Abbreviations: ATRA, all-*trans* retinoic acid; DAC, decitabine; MedDRA, Medical Dictionary for Regulatory Activities; VPA, valproate.

quite subjective, as elegantly shown in a recent prospective study performed by a French consortium.[47] Considering that approximately 10% of our patients did not have any of the above-mentioned unfavorable conditions, it is possible that a subset of patients enrolled in this trial also would have benefitted from intensive therapy.

The recent results in older patients with AML treated with venetoclax combined with decitabine or azacitidine also are very encouraging[24] and resulted in approval of this treatment combination by the US Food and Drug Administration. Given the favorable safety profile of decitabine + ATRA, it is rational to investigate a triplet therapy of

decitabine + ATRA + venetoclax. In vitro studies in AML cell lines demonstrated cooperativity of this drug combination (unpublished data), and a randomized clinical trial (investigating the value of ATRA added to decitabine + venetoclax in a placebo-controlled fashion) appears warranted.

In conclusion, the addition of ATRA to decitabine improved the outcome of elderly, mostly frail patients with AML compared with decitabine alone. Given also the favorable tolerability of this combination, decitabine + ATRA provides a clinically meaningful advantage compared with decitabine monotherapy. The results therefore warrant confirmation in a placebo-controlled randomized trial and a search for biomarkers to predict response to this combination treatment.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.01053.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Valproate and Retinoic Acid in Combination With Decitabine in Elderly Nonfit Patients With Acute Myeloid Leukemia: Results of a Multicenter, Randomized, 2 × 2, Phase II Trial

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