Prolonged Administration of Azacitidine With or Without Entinostat for Myelodysplastic Syndrome and Acute Myeloid Leukemia With Myelodysplasia-Related Changes: Results of the US Leukemia Intergroup Trial E1905

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ABSTRACT

Purpose

Although azacitidine (AZA) improves survival in patients with high-risk myelodysplastic syndrome, the overall response remains approximately 50%. Entinostat is a histone deacetylase inhibitor that has been combined with AZA with significant clinical activity in a previous phase I dose finding study.

Design

Open label phase II randomized trial comparing AZA 50 mg/m²/d given for 10 days ± entinostat 4 mg/m²/d day 3 and day 10. All subtypes of myelodysplasia, chronic myelomonocytic leukemia, and acute myeloid leukemia with myelodysplasia-related changes were eligible for the study. The primary objective was the rate of hematologic normalization (HN; complete remission + partial remission + trilineage hematological improvement).

Results

One hundred forty-nine patients were analyzed, including 97 patients with myelodysplastic syndrome and 52 patients with acute myeloid leukemia. In the AZA group, 32% (95% CI, 22% to 44%) experienced HN and 27% (95% CI, 17% to 39%) in the AZA + entinostat group. Both arms exceeded the HN rate of historical control (Cancer and Leukemia Group B 9221 trial), but only the AZA group fulfilled the primary objective of the study. Rates of overall hematologic response were 46% and 44%, respectively. Median overall survivals were 18 months for the AZA group and 13 months for the AZA + entinostat group. The combination arm led to less demethylation compared with the monotherapy arm, suggesting pharmacodynamic antagonism.

Conclusion

Addition of entinostat to AZA did not increase clinical response as defined by the protocol and was associated with pharmacodynamic antagonism. However, the prolonged administration of AZA by itself seems to increase HN rate compared with standard dosing and warrants additional investigation.

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INTRODUCTION

Until recently, no treatment has demonstrated a survival benefit for patients with myelodysplastic syndrome (MDS).¹ A major breakthrough in our understanding of the pathophysiology of these diseases has been the demonstration of the role of an impaired epigenetic regulation in the progression of MDS to acute myeloid leukemia (AML).²⁻⁴ and resistance to conventional treatment.⁵ DNA promoter methylation downregulates expression of key genes affecting cell fate through their impact on cell cycle or apoptosis.⁶ Such epigenetic marks can be reversed

by DNA methyltransferase inhibitors (DNMTis), such as azacitidine (AZA) and decitabine. Post-translational modification of histone tails, such as deacetylation or methylation, are also implicated in the silencing of transcription.⁷ Histone deacetylase inhibitors (HDACis, valproic acid, sodium phenylbutyrate, vorinostat, entinostat, and others) synergistically induce re-expression of genes whose expression is silenced through promoter methylation when administered in vitro after a DNMTi.⁸

AZA has become the treatment standard for high-risk MDS since randomized trials demonstrated improved survival compared with standard

therapies. The US registration trial Cancer and Leukemia Group B (CALGB) 9221 study^{9,10} for AZA and the US intergroup study¹¹ for decitabine demonstrated hematologic responses for patients with MDS treated with DNMTi. CALGB 9221 trial revealed a trilineage (TL) response rate (hematologic normalization [HN]: complete remission [CR] plus partial remission [PR] plus TL hematologic improvement as defined by International Working Group [IWG] 2000 criteria¹²) of 16% with AZA as compared with < 5% in the best supportive care arm. More recently, these results were confirmed for AZA in a phase III study in high risk MDS¹³ and AML with MDS-related changes (AML-MRC) and bone marrow blasts between 20% and 30% (formerly refractory anemia with excess blasts in transformation).¹⁴ The latter study also demonstrated a significant improvement in overall survival (OS) as compared with conventional care regimens (median OS, 24 months for AZA v 15 months in control arm).

Despite increased survival, 40% to 50% of AZA-treated patients will not respond and even more will continue to require blood products. Outcomes might be improved through alternative dose or scheduling of AZA, which might be more pharmacodynamically optimal. Combinations of DNMTi with HDACi are hypothesized to act synergistically in countering epigenetic suppression and may improve responses.^{15,16} Phase I and II studies have demonstrated that treatment with HDACi in this population of patients is feasible but associated with a limited response rate.¹⁷⁻¹⁹ The orally bioavailable benzamide HDACi entinostat inhibits the class I HDAC enzymes, which are specifically involved in chromatin modification and has shown activity in a monotherapy phase I trial.²⁰ In a previous phase I pilot study (J0443 study; clinical trial information: NCT00101179), we found that the combination of AZA and the entinostat was effective and tolerable for patients with MDS and AML-MRC. This trial was built on a 10-day schedule of AZA, which had been developed to optimize DNA methylation through prolonged administration of lower daily dose designed to cause less cell cycle inhibition.²¹ The recommended phase II schedule was AZA 50 mg/m²/d subcutaneously (SC) for 10 days (500 mg/m²/cycle) and entinostat 4 mg/m²/d orally on day 3 and day 10 of AZA each 28 days.

In the present study from the North American Leukemia Intergroup (includes Eastern Oncology Group, Southwest Oncology Group, and CALGB), E1905 study, we aimed to improve the response rate of AZA through administration of the 10-day schedule with or without addition of entinostat in MDS and AML-MRC. The monotherapy arm was included to provide formal phase II testing of this novel AZA schedule.

PATIENTS AND METHODS

Patients

All patients included in this study fulfilled the following criteria: diagnosis of MDS, chronic myelomonocytic leukemia (CMML) or AML-MRC according to WHO classification²²; patients with MDS and CMML could have any International Prognostic Scoring System (IPSS)²³ score, but patients with low or intermediate-1 MDS were required to have a platelet count < 50 G/L and/or an absolute neutrophil count < 0.5 G/L; patients with AML could have AML-MRC according to the WHO without signs of rapidly progressive disease (WBC count < 30 g/L or doubling time below 4 weeks and WBC count < 20 g/L) including former refractory anemia with excess blasts in transformation from French-American-British classification; and therapy-related

MDS or AML were not eligible. Patients with previous exposure to DNMTi, entinostat, induction chemotherapy, or stem-cell transplantation were also ineligible. The study was approved by the internal review board of each participating center. All patients gave their signed informed consent for the use of the clinical and biologic data. The cytogenetic risk group assessment used the IPSS stratification for all patients.

Protocol Design

E1905 study was a phase II 1:1 randomized trial evaluating the efficacy of AZA alone 50 mg/m²/d SC for 10 days (days 1 to 10, arm A) and AZA with the addition of entinostat 4 mg/m²/d orally on day 3 and day 10 (arm B). Each cycle was of 28 days duration. Patients were stratified according to disease (MDS IPSS high/intermediate-2 versus MDS low/intermediate-1 versus CMML versus AML-MRC). After six cycles of treatment, patients with documented clinical response continued for the lesser of a total of 24 cycles or until disease progression.

The primary objective was to determine whether either arm significantly increased the rate of HN compared with historical CALGB 9221 results. The aim was to achieve a doubling of HN rate as compared with CALGB 9221 (ie, 30% HN). In the protocol, HN was defined by achieving CR, PR, or major TL hematological improvement. Additional data on protocol design are described in the Data Supplement.

Protocol Evaluation

The clinical response and cytogenetic response (CyR) assessment used IWG 2000 criteria.¹² Clinical data, biologic data (bone marrow smears, biopsy sections, and cytogenetics), and response assessment were centrally reviewed. Other types of major hematological improvements (in one or two lineages) were also registered but were not included in response as defined per protocol objectives. Toxicities were assessed by using Common Terminology Criteria for Adverse Events (version 3) definitions.

Statistical Analysis

Two-stage designs were employed for each arm. An underlying true HN rate of 30% was considered evidence that the treatment merited further study, whereas 16% would be of no clinical interest. First, 31 eligible patients per arm were accrued to this study. If at least six patients experienced HN, accrual would continue to 68 eligible patients. If 15 or more HNs were seen in 68 eligible patients, we would conclude that the treatment warranted further study. This design has a power of 90% and one-sided type I error of 0.1. Allowing for a 10% rate of ineligibility, the total accrual for both arms was targeted at 150 patients. Additional statistical methodology is described in the Data Supplement.

Correlatives Studies

Material and methods for DNA methylation by HELP, microarray analysis, and methyl specific polymerase chain reaction are described in the Data Supplement.

RESULTS

Patients' Characteristics

Between December 2006 and December 2010, 150 patients were accrued and 149 analyzed (one death before treatment in arm A [see CONSORT diagram in Fig 1]), including 92 patients with MDS, 5 patients with CMML, and 52 patients with AML. Median age was 72 years (range, 25 to 87 years). Twenty-four patients (16%) were previously treated (previous low-dose chemotherapy, 10; previous immunotherapy, 5; previous other treatment, 13). IPSS intermediate-2/high risk patients represented 71% (n = 65) of the MDS cohort. Poor risk cytogenetics were found in 37% of the patients. Table 1 describes the other main clinical and biologic characteristics of these patients. There was no difference in patient characteristics between the two arms besides previous treatment exposure.

Fig 1. CONSORT diagram of the E1905 protocol.

Treatment Administration and Toxicities

The median duration of each cycle was 28 days, the median number of administered cycles was six (range, 1 to 24 cycles), and 33% of the patients received three cycles or fewer. The median number of administered cycles was six¹⁻²⁴ in both arms. The most frequent reasons for stopping treatment were disease progression ($n = 33$), treatment-related toxicity ($n = 30$), absence of response ($n = 17$), consent withdrawal ($n = 19$), and end of the protocol (ie, 24 cycles, $n = 10$; Data Supplement). A total of nine patients died while on study (multi-organ failure: one in each arm; infections: four in arm A, two in arm B; sudden death: one in arm B). There was no difference between the two arms regarding treatment discontinuation. Toxicities in both arms were acceptable. Table 2 summarizes the most common severe toxicities observed. One hundred thirty patients (87%; 84% in arm A; 91% in arm B; $P = .23$) experienced grade 3 or grade 4 toxicities, including hematological toxicities. Severe treatment-related nonhematological adverse events were reported in 75 (50%) of the patients (43% in arm A; 57% in arm B; $P = .10$). As mentioned in Table 2, infection, including neutropenic fever, was the most frequent severe adverse event (38% and 47%, respectively). There was a trend for more grade 3 to 4 fatigue in arm B as compared with arm A (23% v 12%; $P = .12$). Moreover, there was a marked tendency for grade 4 thrombocytopenia in arm B (53% in arm A versus 64% in arm B, respectively; $P = .19$).

Response

The HN rates were in arm A: 32% (95% CI, 22% to 44%, including 12% CR, 8% PR, and 12% TL); and in arm B: 27% (95% CI, 17% to 39%, including 8% CR, 7% PR, 12% TL). For both arms, their 95% CIs lie entirely above 16%, the HN rate of historical CALGB control. Arm A reached the objectives of the protocol by exceeding 30% of HN. Non-TL hematological improvement was achieved in an additional 14% of patients in arm A and 17% of patients in arm B. Table 3 shows the details of the response evaluation. Total hematologic response was 46% and 44%. The median time to first response was 4 months in both arms, and the median time to best response was 6 months in both arms (range, 1 to 14). Median duration of response was 12 months in both arms ($P =$ not significant).

Cytogenetic Response

We analyzed all patients with cytogenetic abnormalities at baseline or appearing during treatment, and with available cytogenetic

Table 1. Patient Demographics and Clinical Characteristics

	Whole Population (N = 149)		AZA Alone (arm A; n = 74)		AZA + Entinostat (arm B; n = 75)		P
	No.	%	No.	%	No.	%	
Age (years)							.74
Median	72		72		72		
Range	25-87		25-87		30-86		
Sex ratio	102		50		52		.86
Male	102		50		52		
Female	47		24		23		
Disease classification							
IPSS low/intermediate-1 MDS*	27	18	13	18	14	19	
IPSS intermediate-2/high MDS	65	44	33	45	32	43	
CMML	5	3	2	3	3	4	
AML-MRC	52	35	26	35	26	35	1.00
Bone marrow blast counts							.93
Median (%)	14		14.5		13		
Range	0-95		0-95		0-90		
IPSS cytogenetic risk stratification							
Favorable	43	29	20	27	23	31	.44
Intermediate	22	15	8	11	14	19	
High risk	55	37	30	41	25	33	
Missing	19	13	10	14	9	12	
Unacceptable for analysis	10	7	6	8	4	5	
RBC transfusion dependency	98		50	68	48	64	.86
Platelets transfusion dependency	40	27	20	27	20	26.7	1.00
Previous treatment before protocol inclusion	24	16	6	8	18	24	.01

NOTE. Treatment preceding inclusion included AML-like chemotherapy, immunotherapy, and IMiDs.

Abbreviations: AML, acute myeloid leukemia; AML-MRC, AML with MDS-related changes; AZA, azacitidine; CMML, chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome.

*IPSS stratification was assessed only for patient with MDS and excluding AML.

follow-up (cycle 6). Of 149 patients, 76 had baseline cytogenetic abnormalities. Forty-five patients had informative cytogenetic follow-up (including four cases with normal karyotype at baseline). Table 4 displays the rates of CyR among the different cytogenetic groups of patients. The rate of overall CyR was 49% and included 21% complete CyR and 28% partial CyR. CyR did not differ between the two treatment arms. CyR and clinical response were highly correlated ($P < .001$): eight of nine patients with complete CyR had a clinical response, and 11 of 12 patients with partial CyR had a clinical response. The cytogenetic responders have more low/intermediate-1 MDS as compared with nonresponders ($P = .08$). No differences were found in other baseline characteristics examined (data not shown).

Survival Analysis

With a median follow-up of 30 months, 21 patients were alive and 128 had died. The median OS was 18 months in arm A and 13 months in arm B (Fig 2A). For patients with MDS and patients with CMML, the median OS was 21.2 months in arm A and 14.7 months in arm B (Fig 2B). For patients with AML, the median OS was 7.1 months in arm A and 5.3 months in arm B (Fig 2C).

Table 2. Report of the Most Common Grade 3 and 4 Common Terminology Criteria for Adverse Events Drug-Related Adverse Events

	Arm A, Grade 3		Arm A, Grade 4		Arm B, Grade 3		Arm B, Grade 4	
	No.	%	No.	%	No.	%	No.	%
Hematological toxicities								
Anemia	31	42	8	11	31	42	6	8
Thrombocytopenia	14	19	39	53	9	12	48	64
Neutropenia	3	4	51	69	5	7	49	66
Nonhematological toxicities	28	38	4	5	34	45	9	12
Fatigue/asthenia	9	12			18	24	1	1
Confusion/dizziness	1	1	1	1	5	7		
Nausea/vomiting	2	3			4	5		
Infection	25	34	3	4	31	42	4	5
Hyponatremia	1	1			9	12		
Hypoalbuminemia	1	1			6	8		

NOTE. Patients may appear in more than one adverse event (AE). All AEs were evaluated according to Common Terminology Criteria for Adverse Events version 3 definitions. We listed here all AEs with a frequency of 5% or more in at least one arm.

Abbreviations: Arm A, azacitidine alone; Arm B, azacitidine + entinostat.

Correlative Studies

Genome-wide DNA methylation studies were performed for 99 specimens: 56 baseline specimens, 24 from day 15 and 19 from day 29. For our initial analysis, we compared the baseline DNA methylation profiles to those obtained at day +15 after treatment initiation, irrespective of treatment arm, for 21 patients for whom we had paired specimens. This comparison revealed a global loss of DNA methylation after treatment with an AZA-containing regimen (Fig 3A) comparable with that observed in our analysis of the patients included in the phase I trial.²⁴ We observed that DNA demethylation for patients on the combination arm, while still trending towards overall demethylation, was of a significantly lesser magnitude than that observed in the AZA single agent arm with none of the probe sets in the comparison for the combined treatment arm reaching our stringent significance cutoff (Fig 3B). We also performed a direct comparison between responder and nonresponder patients. We did not detect a distinct

Table 3. Response Evaluation

	Arm A		Arm B	
	No.	%	No.	%
CR	9	12.2	6	8
PR	6	8.1	5	6.7
TL	9	12.2	9	12
Hematological normalization rate (CR + PR + TL)	24	32.5	20	26.7
HI, not TL	10	13.5	13	17.3
HI-bilineage	4	5.4	8	10.6
HI-unilineage	6	8.1	5	6.7
Not evaluable	0		1	1.3
No change/stable	36	48.6	40	53.3
Progression/relapse	4	5.4	1	1.3

NOTE. Response was evaluated according to International Working Group 2000 criteria.

Abbreviations: Arm A, azacitidine alone; Arm B, azacitidine + entinostat; CR, complete response; HI, hematologic improvement; PR, partial response; TL, trilineage.

Table 4. Analysis of Cytogenetic Response Among the Different Cytogenetic Risk Groups

	Evaluable	CCyR		PCyR		NR		Progression*	
		No.	%	No.	%	No.	%	No.	%
Favorable Cy risk group	7	0		1	14	2	29	4	57
Intermediate Cy risk group	14	3	21	3	21	4	29	4	29
Unfavorable Cy risk group (including Chr 7 abnormalities)	24	6	25	8	33	6	25	4	17
Monosomy 7 or deletion 7q	12	3	25	1	8	6	50	2	17

Cytogenetic clustering was assessed by using International Prognostic Scoring System classification. Response evaluation was performed according to International Working Group 2000 criteria. Of 76 patients who had cytogenetic abnormalities at baseline, 20 did not have informative follow-up, and 11 died before cycle 6.

Abbreviations: CCyR, complete cytogenetic response; Cy, cytogenetic; NR, nonresponder; PCyR, partial cytogenetic response.

*Among 12 patients with cytogenetic progression, four patients showed an increased frequency of a known aberration, and eight patients showed new or additional aberration including four cases affecting patients with normal karyotype at baseline (including two patients with acquired monosomy 7). The cytogenetic responders have more low/intermediate-1 myelodysplastic syndrome as compared with nonresponders ($P = .08$). No differences were found in other baseline characteristics examined (data not shown).

DNA methylation pattern at baseline that correlated with response to therapy (data not shown).

In parallel, methylation specific polymerase chain reaction was evaluated for 80 patients at baseline and 40 patients during follow-up (day 15 and/or day 28). There was no correlation with response for *P15* or *CDH1*. Baseline *SOCS1* methylation trended towards lower response when overall response rate was as follows: median baseline methylation was 13% for responding patients versus 39% for nonresponding patients ($P = .008$; Fig 3C). The same trend was confirmed in a multivariable analysis model integrating pretreatment variables ($P = .006$). There was no correlation between *SOCS1* methylation and patient characteristics at baseline or quality of response (CR + PR v other; $P = .3$). Among patients with a significant initial *SOCS1* methylation (promoter methylation above 20%, $n = 42$), the median methylation ratio at baseline was 60% and decreased at day 15 (42%; $P = .008$) and day 28 (47%; $P = .10$) as compared with baseline (Fig 3D).

DISCUSSION

This study, to our knowledge, is the first randomized study comparing AZA and a combination of AZA and an HDAC inhibitor. Entinostat was selected because it is orally bioavailable, selectively targets class I HDAC enzymes, has a long half-life (4.5 days), and can be safely combined with AZA.

Our study evaluated a more prolonged use of AZA delivering a lower daily dose over 10 days with a total dose per cycle comparable with the US Food and Drug Administration- and European Medicines Agency-labeled 7-day schedule. Because AZA nucleosides need to be first incorporated into DNA during S phase and then require additional cell cycling to effect methylation reversal, the 10-day schedule could be pharmacodynamically superior to the standard schedule. In fact, the rate of HN (the primary end point of this study) in response

Fig 2. Kaplan-Meier representation of the azacitidine alone (arm A) and the azacitidine + entinostat (arm B) regimens for overall population (A), patients with myelodysplastic syndrome and chronic myelomonocytic leukemia (B), and patients with acute myeloid leukemia (C). Survival is represented from the day of first administration of treatment to the date of death or last follow-up. Arm A is in blue and arm B is in gold. CNSR, censored.

to AZA monotherapy, 50 mg/m²/d for 10 days, was twice that observed in the reference C9221 study, therefore fulfilling the efficacy criteria defined as the trial objective. A previous study had evaluated different schedules of AZA aiming to demonstrate that shorter (5 days) or more convenient schedules of AZA (5 days treated, weekend off, 2 days treatment: 5-2-2) can give hematologic response rates similar to those obtained with the conventional 7-day schedule.²⁵ In

the Lyons et al²⁵ study, one arm of treatment used AZA for 10 days by using a 5 days per week, 2 consecutive weeks schedule (5-2-5). In this last study, transfusion dependency was the primary objective, and a majority of patients were low-risk MDS. In patients who were thrombocytopenic, the 5-2-5 schedule led to a higher rate of transfusion independence compared with the other two schedules, suggesting a potential benefit of this schedule in relatively higher-risk patients.

In E1905, the absence of a positive clinical effect with the addition of entinostat was mirrored by a lower extent of promoter methylation reversal found in patients receiving the combination. Entinostat is a potent cell cycle inhibitor. Using concomitant administration of AZA with entinostat, it is likely that AZA incorporation and subsequent cell cycling were inhibited by the HDACi, leading to a less effective change in promoter methylation. The demethylation effect of the combination arm in the current study appeared to be less than previously reported in the phase I study.²⁴ Given that the phase I study included a range of different combination doses and that few patients were available for methylation analysis from each of the different dose ranges, it is hard to determine whether the lesser demethylation effect observed in the current study is due to the specific dose combination used in this trial. If it is true that the current combination results in less effective demethylation because of the cell cycle inhibition effect induced by entinostat, then HDACi should be administered after the completion of AZA administration; such sequential addition was required for the demonstration of *in vitro* synergy.⁸ As with similar trials, a promoter DNA methylation signature predictive of response, or a profile of change in methylation with treatment predictive of response, was not identified in the present study.^{21,26}

A slight excess of chronic hematological toxicities was seen in the combination arm (in particular thrombocytopenia), which may have influenced these results because the objective of the trial was hematological normalization. The use of IWG 2006 response criteria may be, today, more appropriate to evaluate compounds with such toxicity profile by refining blood counts threshold for the definition of CR, PR, or hematological improvement and introducing bone marrow blast clearance (marrow CR) as a significant response to therapy. Finally, the choice of HDACi by itself could be questioned, as recent reports suggest a higher response rate with a combination of AZA and vorinostat in a phase I dose escalation trial.^{27,28} The vorinostat combination data serves as one arm of the current US Leukemia Intergroup randomized phase II study in high risk MDS (S1117). One of the main differences between entinostat and vorinostat is the panel of cellular targets: entinostat specifically targets the nuclear histone deacetylases, whereas vorinostat is a nonclass-selective inhibitor that targets histone deacetylases, as well as other protein deacetylases inside and outside the nucleus. These other deacetylases are responsible for the action of this drug on P53 or Beta-catenin pathways, among others.

The possible correlation of *SOCS1* methylation with response rate will need to be confirmed in additional prospective studies with larger series of patients but is in line with recent data on the potential impact of *SOCS1* on myeloid neoplasm pathogenesis.²⁹ Confirmation of improved response after prolonged administration of lower daily doses of AZA will require direct comparison to the currently approved dose regimen. The design of such a study will need to integrate OS criteria as trial objectives considering the survival benefit demonstrated in the AZA001 study. Regarding these survival data, the OS of our cohort seemed shorter than the AZA001 study, but there are notable differences in the composition of the patient cohorts; the

Fig 3. DNA methylation changes evaluated by HpaII tiny fragment enrichment by ligation-mediated polymerase chain reaction (HELP): (A) Comparison between baseline and day 15 for overall population; (B) comparison of the treatment arms at day 15. And by methyl-specific polymerase chain reaction (MSP): (C) Correlation of *SOCS1* methylation and clinical response; (D) time-dependent methylation pattern of *SOCS1* promoter. (A) Heatmap representation of 139 differentially methylated regions at day 15 compared with baseline for the 21 patients with paired specimens on both treatment arms. Each row represents a probe set on the array and each column represents a patient. (B) Dot plot representation of methylation difference (x-axis) versus statistical significance (y-axis) for patients on arm A (left) and arm B (right). Red dots indicate probe sets that reached our significance cutoff in each comparison. (C) Median *SOCS1* promoter DNA methylation for responders (ie, patients with hematological normalization: complete remission [CR], partial remission [PR], or trilineage hematological), nonresponders, and patients who experienced CR or PR. Median *SOCS1* methylation was significantly higher in nonresponders as compared with responders (42% v 13%, respectively; $P = .03$). Patients with CR or PR showed no difference as compared with other patients ($P = .3$). There was no correlation of methylation decrease with clinical response or with treatment arm. (D) Only patients with baseline methylation of *SOCS1* were represented in this figure; median *SOCS1* promoter methylation decreased between baseline and day 15 ($P = .008$), or between baseline and day 28 ($P = .10$). HpaII, *Haemophilus parainfluenzae* II restriction enzyme; MspI *Moraxella* sp. I restriction enzyme.

participation of patients with AML in E1905 may have had a possible negative impact on response and survival. The decision to cap the number of treatment cycles at 24 may have also limited survival benefit.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a

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