Phase II Trial of Vorinostat With Idarubicin and Cytarabine for Patients With Newly Diagnosed Acute Myelogenous Leukemia or Myelodysplastic Syndrome

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ABSTRACT

Purpose

To evaluate the safety and efficacy of the combination of the histone deacetylase inhibitor vorinostat with idarubicin and ara-C (cytarabine) in patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS).

Patients and Methods

Patients with previously untreated AML or higher-risk MDS age 15 to 65 years with appropriate organ function and no core-binding factor abnormality were candidates. Induction therapy was vorinostat 500 mg orally three times a day (days 1 to 3), idarubicin 12 mg/m² intravenously (IV) daily × 3 (days 4 to 6), and cytarabine 1.5 g/m² IV as a continuous infusion daily for 3 or 4 days (days 4 to 7). Patients in remission could be treated with five cycles of consolidation therapy and up to 12 months of maintenance therapy with single-agent vorinostat. The study was designed to stop early if either excess toxicity or low probability of median event-free survival (EFS) of more than 28 weeks was likely.

Results

After a three-patient run-in phase, 75 patients were treated. Median age was 52 years (range, 19 to 65 years), 29 patients (39%) were cytogenetically normal, and 11 (15%) had *FLT-3* internal tandem duplication (ITD). No excess vorinostat-related toxicity was observed. Induction mortality was 4%. EFS was 47 weeks (range, 3 to 134 weeks), and overall survival was 82 weeks (range, 3 to 134 weeks). Overall response rate (ORR) was 85%, including 76% complete response (CR) and 9% in CR with incomplete platelet recovery. ORR was 93% in diploid patients and 100% in *FLT-3* ITD patients. Levels of *NRF2* and *CYBB* were associated with longer survival.

Conclusion

The combination of vorinostat with idarubicin and cytarabine is safe and active in AML.

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INTRODUCTION

Outcomes in patients with acute myelogenous leukemia (AML) can be improved by incorporating new front-line agents¹ or by adding a third drug to standard therapy.^{2,3} Standard therapy for AML at the MD Anderson Cancer Center (MDACC) consists of the combination of idarubicin with high-dose continuous infusion ara-C (cytarabine). This so-called IA program has been safely combined with other agents such as tipifarnib² and sorafenib.³ Vorinostat is a histone deacetylase inhibitor (HDACI) with limited but single-agent activity in AML⁴ that is approved in the United States to treat specific subsets of patients with cutaneous T-cell lymphoma.⁵ We hypothesized that the addition of vorinostat as

an investigative agent to IA could improve results in first-line AML therapy. This was based on data that indicated synergism between vorinostat and DNA topoisomerase II inhibitors^{6,7} and safety of the combination in a phase I trial.⁸ On the basis of these data, we conducted a phase II study to explore the safety and activity of vorinostat with IA in AML. This study had a Bayesian design with predefined stopping rules for toxicity and event-free survival (EFS).

PATIENTS AND METHODS

All patients were treated at MDACC under protocol 2007-0835 (Data Supplement) following institutional guidelines. In the protocol, EFS is referred to as progression-free survival.

Patient Eligibility

Patients age 15 to 65 years old with AML according to WHO⁹ criteria or with INT-2/high-risk myelodysplastic syndrome according to the International Prognostic Scoring System (IPSS)¹⁰ were eligible. The study had two phases: an initial run-in phase for patients with relapsed or refractory AML and the actual phase II portion for previously untreated patients with AML. Patients could have received prior therapy for myelodysplastic syndrome (blasts < 10%). An Eastern Cooperative Oncology Group (ECOG) performance status of less than 3 and a creatinine and total bilirubin of ≤ 2 mg/dL were required. Patients with cardiac ejection fraction (EF) less than 50%; those who were pregnant; those with t(15;17), inv16, or t(8;21); and those with severe active comorbidity were excluded.

Therapy and Evaluation

During induction, vorinostat 500 mg was administered orally three times a day on days 1 to 3. This dose was derived from our phase I trial of idarubicin and vorinostat.⁸ On day 4, idarubicin was started at a dose of 12 mg/m² daily $\times$ 3 (days 4 to 6) with cytarabine at a dose of 1.5 gm/m² daily administered as a continuous infusion for 4 days (days 4 to 7) in patients younger than age 60 years or for 3 days (days 4 to 6) in those older than age 60 years. Up to two cycles of induction therapy could be administered if response was not achieved with the first cycle. Patients in remission could receive up to five cycles of consolidation therapy with vorinostat at 500 mg orally three times per day (days 1 to 3), idarubicin 8 mg/m² daily $\times$ 2 days (days 4 through 5), and cytarabine 0.75 gm/m² as a continuous infusion daily $\times$ 3 days (days 4 through 6). Steroids (salumetrol 50 mg intravenously on the same days as cytarabine) were used with cytarabine administration to prevent fever and rash. Patients who completed induction and consolidation therapy could be treated with single-agent vorinostat (200 mg orally 3 times a day for 14 days every 28 days) for up to 12 cycles. Criteria for dose adjustments are shown in the Data Supplement. Patients older than age 49 years were admitted to a laminar flow room. Baseline evaluation included echocardiogram and ECGs, basic laboratory analysis, bone marrow aspiration, and biopsy with cytogenetic and molecular studies. Bone marrow examination was repeated on days 21 and 28 of the first cycle and as needed thereafter. Cytogenetic and gene mutation (*NPM1*, *RAS*, and *FLT-3*) analysis were performed in clinical laboratories at MDACC.

Response Definition and Assessment of Toxicity

Complete response (CR) included normalization of marrow blasts ($\leq 5\%$ blasts) and of peripheral blood counts (neutrophil count ≥ 1 K/ μ L; platelet count $> 100 \times$ K/ μ L). CR with incomplete platelet recovery (CRp) was the same as CR but with platelets less than $100 \times$ K/ μ L. CR duration was calculated from time of CR until relapse. EFS was calculated from the beginning of treatment until an event, including resistance, partial response, relapse, or death from any cause. Survival was plotted by the Kaplan-Meier method and compared by using the log-rank test. Differences in subgroups by different covariates were evaluated by using the χ^2 test for nominal values and the Mann-Whitney *U* test and Fisher's exact test for continuous variables. Toxicity was assessed by using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical Design

The objective of this trial was to provide an early assessment of efficacy (phase IIA) of vorinostat when used in combination with IA. Because we had limited experience with the administration of vorinostat with IA, first we planned a run-in phase in which vorinostat was used at the highest dose level with IA. If no toxicity was observed in the first three patients, then the study would move to the actual phase II portion of the trial. Details of statistical design are shown in the Data Supplement. The study had two stopping rules: for toxicity and for EFS. We assumed that EFS followed an exponential distribution and that the treatment would be considered successful if a median EFS of at least 28 weeks was achieved. The trial was monitored every 6 months by an independent statistician (N.B.B.). The study would stop early if the probability of median EFS being ≥ 28 weeks (compared with data from the trial) was less than 0.02. The study was also monitored for unacceptable vorinostat-related severe toxicity. The study was to stop early if an unacceptable toxicity rate more than 10% at 6 months (compared with data from the trial) was more than 0.99.

Table 1. Patient Characteristics (N = 75)

Characteristics	No.	%
Age, years		
Median	52	
Range	19-65	
Male sex	39	52
Secondary disease	16	21
BM blasts $\geq 20\%$	68	90
FAB		
M0-M2	26	35
M4	12	16
M5	11	15
M6	2	3
Mixed	1	1
RAEB	2	3
RAEB-T	11	15
Unknown/not done	10	13
WBC, K/ μ L		
Median	5.0	
Range	0.7-110.6	
Platelets, K/ μ L		
Median	42	
Range	6-534	
Hgb, g/dL		
Median	8.7	
Range	2.0-12.9	
ANC, K/ μ L		
Median	0.713	
Range	0-33.456	
% BM blasts		
Median	40	
Range	11-95	
% PB blasts		
Median	14	
Range	0-92	
Creatinine, mg/dL		
Median	0.9	
Range	0.4-1.6	
Total bilirubin, mg/dL		
Median	0.3	
Range	0.2-1.7	
Cytogenetics		
Diploid	29	39
-5/-7	17	23
Other	26	35
Inadequate	3	4
<i>FLT-3</i> ITD status		
Positive	11	15
Negative	57	76
Not done	7	9
<i>RAS</i> mutation		
Positive	10	13
Negative	53	71
Not done	12	16
<i>NPM1</i> mutation		
Positive	10	13
Negative	42	56
Not done	23	31

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; FAB, French-American-British; Hgb, hemoglobin; ITD, internal tandem duplication; PB, peripheral blood; RAEB, refractory anemia with excess blasts; RAEB-T, RAEB in transformation.

Correlative Studies

Peripheral blood mononuclear cells were isolated, as previously described, on days 0, 3, 7, and 28 of the first cycle of therapy.¹¹ The following biomarkers were evaluated: histone acetylation, beclin levels, mRNA levels of TIMP1, interleukin-6 (IL-6), MMP9, p38MAPK, NRF2, CYBB, FOXO3, SOD1, SOD2, and GST-Pi. Induction of histone H3 acetylation and beclin levels were analyzed by Western blot as previously described.^{11,12} Antibodies for acetylated H3 were from Millipore (Billerica, MA); antibodies for beclin were from Cell Signaling Technology (Danvers, MA). Total cellular RNA was extracted with Trizol (Invitrogen, Carlsbad, CA). Reverse transcription was performed by using Moloney murine leukemia virus reverse transcription enzyme (Invitrogen) according to the manufacturer's protocol. For expression levels of IL-6, p38MAPK, TIMP1, and MMP9, primers and probes were purchased from Applied Biosystems (Carlsbad, CA) and analyzed with TaqMan Universal PCR Master Mix by using an ABI 7700 sequencing detection system (Applied Biosystems). Primers for NRF2, CYBB, FOXO3, SOD1, SOD2, and GST-Pi were synthesized by Invitrogen, real-time polymerase chain reaction was performed by using ABI 7700 sequencing detection system and SYBR Green reagents (Invitrogen).

RESULTS

From April 2008 to March 2010, 78 patients were treated: three in the run-in phase and 75 in the phase II portion. Three patients with relapsed AML were treated in the run-in phase. None of the three patients suffered significant vorinostat-related toxicity (data not shown). The study then moved to the formal phase II portion.

Patient Characteristics

In total, 75 patients were treated in the phase II portion of the study. Characteristics are detailed in Table 1. Median age was 52 years (range, 19 to 65 years), 21% of patients had therapy-related disease, seven (13%) had bone marrow blasts of 10% to 19%, 29 (39%) had diploid cytogenetics, and 11 (15%) had *FLT*-3 internal tandem duplication (ITD). Four patients (5%) had received prior therapy for blasts less than 10%. Only 18 patients (24%) did not have any of the following characteristics: secondary disease, abnormal cytogenetics, or *FLT*-3 ITD.

Table 2. Most Frequent Adverse Events During Induction Therapy

Adverse Event	No. of Patients			Total %
	Grade 1 to 2	Grade 3 to 4	Total	
Cardiac	4	7	11	15
Diarrhea	26	27	53	72
Edema/swelling	4	0	4	5
Gastrointestinal, other (mucositis, typhilitis, colitis)	18	11	29	39
Hemorrhage/bleeding	8	5	13	18
Hepatic	6	8	14	19
Metabolic, hypomagnesemia	1	0	1	1
Nausea/vomiting	40	8	48	65
Neurologic	2	1	3	4
Pain	2	0	2	3
Rash/cellulitis/hand-foot syndrome	25	3	28	38
Renal	3	2	5	7
Respiratory	0	2	2	3
Thrombosis/deep vein thrombosis	2	0	2	3

Toxicity

No excess toxicity was observed with IA vorinostat compared with historical experience with IA. Death at induction was documented in three patients (4%). Table 2 summarizes the most frequent toxicities observed during induction therapy. They were primarily gastrointestinal, including diarrhea (72%), nausea and vomiting (65%), and other gastrointestinal toxicity (39%). Skin toxicity was documented in 38% of patients. Grade 3 to 4 diarrhea was observed in 36% of patients, other GI toxicity in 14%, and nausea and vomiting in 10%. Severe skin toxicity was observed in only 4% of patients. Because of the potential for excess cardiac toxicity, cardiac EF was evaluated before therapy and at the end of cycle 1. Median EF was 60% at baseline and 55% at end of cycle 1 (P = not significant). Only one patient had irreversible EF reduction in the setting of sepsis and induction death.

Overall Survival and EFS

With a median follow-up of 82 weeks (range, 5 to 132 weeks), median overall survival (OS) for the whole group was 82 weeks (range, 3 to 134 weeks), and EFS was 47 weeks (range, 3 to 134 weeks; Figs 1A and 1C). Details of the results are provided in Table 3. Median OS and EFS for patients with *FLT*-3 ITD were 91 weeks (range, 6 to 134 weeks)

Fig 1. (A) Overall survival and (B) event-free survival of all patients by molecular cytogenetic subset. -5/-7 cytogenetics. Misc, miscellaneous.

Table 3. Clinical Responses and Survival

Patient Characteristic	CR		CRp		ORR		95% CI	EFS (weeks)	Range	OS (weeks)	Range
	No.	%	No.	%	No.	%					
All patients	57	76	7	9	64	85	0.75 to 0.91	47	3-134	82	3-134
<i>FLT-3</i> ITD	10	91	1	9	11	100	0.73 to 0.99	66	6-134	91	6-134
<i>FLT-3</i> WT	42	71	5	8	47	80	0.61 to 0.82	47	4-100	72	5-122
<i>NPM1</i> +/ <i>FLT-3</i> WT	6	100	0		6	100	0.59 to 0.99	29	6-91	N/R	6-91
<i>NPM1</i> +/ <i>FLT-3</i> ITD	2	67	1	33	3	100	0.39 to 0.99	N/R	5-134	N/R	5-134
<i>NPM1</i> -/ <i>FLT-3</i> WT	24	69	3	9	27	78	0.56 to 0.84	23	5-97	46	5-110
<i>NPM1</i> -/ <i>FLT-3</i> ITD	5	100	0		5	100	0.54 to 0.99	68	51-89	N/R	51-105
Diploid*	25	86	2	7	27	93	0.77 to 0.97	68	5-134	105	5-134
-5/-7	9	53	1	6	10	59	0.35 to 0.78	14	3-92	34	3-92
Miscellaneous CG	23	79	4	14	27	93	0.77 to 0.97	N/R	5-119	92	5-119

CG, cytogenetics; CR, complete remission; CRp, complete remission with incomplete platelet recovery; EFS, event-free survival; ITD, internal tandem duplication; Miscellaneous CG, nondiploid non -5/-7; N/R, not reached; ORR, overall response rate; OS, overall survival; WT, wild type.

*Diploid includes *FLT-3* ITD patients.

and 66 weeks (range, 6 to 134 weeks), respectively (Fig 1). There was a trend toward better survival in the *FLT-3* ITD patients versus the unmutated group ($P = .067$). The characteristics of *FLT-3* ITD patients are shown in the Data Supplement. Patients with diploid cytogenetics had a median OS of 105 weeks (range, 5 to 134 weeks) and a median EFS of 68 weeks (range, 5 to 134 weeks; Fig 1). There was a trend toward better survival in the diploid patients versus nondiploid patients ($P = .09$). Survival was poorer in patients with -5/-7 cyto-

genetics: OS was 34 weeks (range, 3 to 92 weeks), and EFS was 14 weeks (range, 3 to 92 weeks). In contrast, nondiploid non -5/-7 patients had a median OS of 92 weeks (range, 5 to 119 weeks), and EFS was not reached (range, 5 to 119 weeks).

Clinical Responses

Responses are summarized in Table 3. CR was documented in 57 patients (76%) and CRp in an additional seven patients (9%) for an

Fig 2. Gene expression of genes involved in resistance and reactive oxygen species sequentially during therapy. Gene expression was normalized to glyceraldehyde phosphate dehydrogenase and was measured sequentially during the first course of therapy. D, day.

overall response rate (ORR) of 85% (95% CI, 75% to 91%). No differences in response were observed in patients younger than or older than 60 years. Seven patients (9%) received two cycles of induction therapy and four (44%) responded (two with CR and two with CRp). When analyzed on the basis of molecular or cytogenetic features, 10 of the 11 patients with *FLT-3* ITD achieved a CR and one achieved a CRp (ORR, 100%). All six *NPM1* mutated/*FLT-3* wild-type patients achieved CR. The presence of Ras mutations had no impact on response. Of the diploid patients, 25 (86%) achieved a CR and two achieved a CRp (7%; ORR, 93%). Patients with other cytogenetic alterations, excluding $-5/-7$, had an ORR of 93%, including 23 patients (79%) with a CR and four patients with a CRp (14%). Only nine patients (53%) with $-5/-7$ achieved a CR and one patient (6%) achieved a CRp for an ORR of 64%.

Consolidation and Maintenance Therapy

The median number of consolidation cycles was two (range, two to five). This was because of the number of patients who did not respond to therapy ($n = 11$), those who received transplantation ($n = 19$), and those who relapsed ($n = 27$). Sixty-six percent required reduction of vorinostat dose during consolidation, frequently due to myelosuppression or gastrointestinal toxicity. The median dose of vorinostat administered during consolidation was 400 mg (range, 100 to 500 mg) orally three times a day for 3 days. Thirteen patients (17%) received maintenance therapy with single-agent vorinostat with a median of five cycles.

Outcome of Patients Undergoing SCT

Nineteen patients (25%) underwent stem-cell transplantation (SCT) during their first CR. Their characteristics are shown in the Data Supplement. All patients had achieved CR/CRp before SCT. Different preparative regimens were used. Eleven (57%) received transplantations from an unrelated donor, including two umbilical cords and two with antigen mismatch. Fifteen patients (79%) received ablative preparative regimens. Median OS and EFS had not been reached (Appendix Fig A1, online only) in the 19 patients who received transplantations.

Molecular Markers

Robust induction of histone H3 acetylation was documented in 13 (32%) of 40 patients evaluated (Appendix Fig A2, online only). Because response rate was 100% in the 40 patients analyzed, no correlation was observed between acetylation and response. No induction of beclin was observed in any of the patients (data not shown). Baseline levels of genes analyzed are shown in Appendix Figure A3 (online only). mRNA upregulation occurred in all genes starting as early as day 3 of therapy (Fig 2). No association with response and gene expression was observed because a majority of patients analyzed had achieved a CR. Upregulation ($>$ two-fold at day 3) of *NRF2* and *CYBB* was associated with longer survival (Fig 3). No association between age or cytogenetics was found with *NRF2* or *CYBB*.

DISCUSSION

Standard therapy for younger patients with AML consists of the combination of an anthracycline with cytarabine.¹³ Long-term survival is usually achieved in patients with favorable cytogenetics or with mo-

Fig 3. Overall survival based on levels of (A) *NRF2* and (B) *CYBB*.

lecular features such as mutation of *NPM1*.¹⁴ In the remaining patients (those with abnormal cytogenetics or the presence of *FLT-3* ITD¹⁵), outcome is significantly poorer. Recently, the use of high-dose daunorubicin in combination with cytarabine has been associated with increased survival in younger patients with AML.¹³

In this study, we combined IA with vorinostat on the basis of our prior experience with single-agent vorinostat in relapsed or refractory AML⁴ and on the basis of in vitro data that demonstrated a sequence-dependent synergistic antileukemia effect of the combination of vorinostat with anthracyclines and cytarabine.^{6,7} A phase I clinical trial of idarubicin with higher doses of vorinostat demonstrated the safety of the combination.⁸ The study contained an initial run-in phase in which the highest dose of vorinostat was used. After treating three patients, the study was opened to previously untreated patients with AML. The study did not meet either of the two stopping rules and was considered statistically successful. The combination of vorinostat and IA did not result in excess toxicity compared with standard IA. A relatively high rate of diarrhea and gastrointestinal toxicity was observed in patients treated in this trial but this was similar to the result observed with the combination of IA and tipifarnib² or standard IA. Induction mortality (4%) was low. EFS was 47 weeks in excess of the 7 months that had been set up as the stopping rule. The combination was active: the ORR was 85%, including 76% of patients in CR and 9%

in CRp. This response rate is significant in view of the poor prognostic characteristics of the patients treated in this study. Use of vorinostat IA did not result in poor outcomes with SCT. Nineteen patients (25%) received SCT using different types of preparative programs and donor sources. Outcomes in patients receiving SCT were excellent, with median OS and EFS not having been reached at the time this article was submitted for publication.

This study also explored potential biomarkers that could explain mechanisms of sensitivity or resistance to the therapy. We evaluated four parameters: histone acetylation⁴; beclin^{12,16}; levels of *TIMP1*, *IL-6*, and *MMP9* as markers of chemotherapy resistance¹⁷; and a reactive oxygen species pathway (*NRF2*, *CYBB*, *FOXO3*, *SOD1*, *SOD2*, and *GST-Pi*) involved in HDACI resistance.¹⁸ We could detect significant levels of histone acetylation in 30% of patients. This low rate is probably related to the low sensitivity of the assay used (Western blot) as opposed to that of other assays such as enzyme-linked immunosorbent assay.⁴ Beclin is a surrogate marker of autophagy.¹² HDACIs have been shown to induce autophagy in vitro.^{12,19,20} We could not detect increased beclin levels in any of the samples analyzed. These data do not imply that autophagy has no role in the antileukemia effect observed here but that measurement of beclin by Western blot is not a reliable marker in primary patient samples. Finally, we explored up-regulation at the mRNA levels of a series of genes involved in chemotherapy resistance¹⁷ and reactive oxygen species.¹⁸ All of these genes were found to be upregulated during therapy. Of importance, levels of the transcription factor *NRF2* and *CYBB* were associated with a trend toward improved survival. These results are of significant importance because both *NRF2*, a transcription factor involved in antioxidant response,¹⁸ and *CYBB* were shown to be involved in a pathway mediating resistance to HDACI.¹⁸ We also performed molecular analysis by using conventional cytogenetic and/or molecular analysis and more exploratory mechanistic approaches. As discussed earlier and as expected, cytogenetic patterns were clearly associated with response rates. Surprisingly, the presence of *FLT-3* ITD was associated with a 100% ORR. These data should be viewed with caution, because the patient cohort studied was small.

This study has several limitations intrinsic to the design of early phase II clinical trials; therefore, results should be considered preliminary and the analysis of molecular biomarkers exploratory. A randomized study will be needed to demonstrate the contribution of vorinostat to IA in AML. One question is whether vorinostat IA is superior to IA or to other more traditional 7 + 3 schemas.¹³ Analysis of response indicates that response rates are higher with vorinostat IA versus IA (Data Supplement). In terms of comparison with the most recent 7 + 3 data, it should be noted that ECOG-1900 (E1900)¹³ included patients with favorable cytogenetics.^{13,21} In the intermediate-risk group, CR was 59% in E1900 compared with a range of 79% to 86% in our study. In the unfavorable prognosis group, CR in E1900 was 52% compared with 53% to 79% in vorinostat IA. CR rates were higher in the *FLT-3* ITD subset with vorinostat IA compared with E1900 (91% v 67%). These data indicate that response rates with vorinostat IA are not inferior to those observed with IA or with

modern 7 + 3 strategies. Second, this study was not powered to demonstrate an improved survival rate compared with other strategies. The population of patients treated here had poor characteristics that made it difficult to identify a matching historical cohort at MDACC for survival analysis (data not shown). That said, survival was not different from that reported with IA tipifarnib² or sorafenib.³ It is difficult to compare survival between E1900 and our study, because we excluded patients with favorable cytogenetics and because survival data for both the favorable- and intermediate-risk groups in E1900 were plotted together. Furthermore, a significant fraction of patients received allogeneic SCT, which should be taken into account when analyzing these survival data. It should be noted that survival data were not censored for transplantation.

In summary, the combination of vorinostat with IA is associated with high induction response rates. Toxicity and EFS rules were not met, and the study exceeded expectations. Ongoing studies at MDACC are further evaluating the activity of vorinostat IA in *FLT-3*-mutated AML, and a randomized study comparing it to either standard IA or 7 + 3 therapy is planned for 2012. More studies on the impact of specific molecular pathways (*FLT-3*, *NRF2*, *CYBB*) need to be performed and could result in future target interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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