BH3 Profiling Discriminates Response to Cytarabine-Based Treatment of Acute Myelogenous Leukemia

William E. Pierceall1, Steven M. Komblau2,3, Nicole E. Carlson1, Xueling Huang4, Noel Blake1, Ryan Lena1, Michael Elashoff1, Marina Konopleva2,3, Michael H. Cardone1, and Michael Andreeff2,3

Abstract

As acute myelogenous leukemia (AML) patient response to cytarabine-based standard-of-care treatment is variable, stratification into subgroups by biomarker-predicted response may lead to improved clinical outcomes. Here, we assess cell mitochondrial depolarization to proapoptotic signaling BH3-only peptides as a surrogate for the function of Bcl-2 family proteins to address clinical response to cytarabine-based therapy in patients with AML (N = 62). Peripheral blood mononuclear cell (PBMC) or bone marrow aspirate specimens were obtained from newly diagnosed patients with AML, viably preserved, and assayed by flow cytometry following BH3 profile assay with individual BH3 peptides. Mann–Whitney analysis indicates biomarker correlation with response to induction therapy: Notably, BIM priming was highly significant (P = 2 × 10−10) with a compelling sensitivity/specificity profile [area under curve (AUC) = 0.83; 95% confidence interval (CI), 0.73–0.94; P = 2 × 10−10]. Multivariate analysis indicates improved profiles for BIM readout + patient age (AUC = 0.89; 95% CI, 0.81–0.97) and BIM + patient age + cytogenetic status (AUC = 0.91; 95% CI, 0.83–0.98). When patients were stratified by cytogenetic status, BIM readout was significant for both intermediate (P = 0.0017; AUC = 0.88; 95% CI, 0.71–1.04) and unfavorable (P = 0.023; AUC = 0.79; 95% CI, 0.58–1.00) risk groups, demonstrating predictive power independent of cytogenetics. Additional analyses of secondary clinical endpoints displayed correlation between overall survival (P = 0.037) and event-free survival (P = 0.044) when patients were stratified into tertiles by BIM peptide response. Taken together, these results highlight the potential utility of BH3 profiling in personalized diagnostics of AML by offering actionable information for patient management decisions. Mol Cancer Ther; 12(12); 2940–9. ©2013 AACR.

Introduction

Acute myelogenous leukemia (AML) is the second most common leukemia, with approximately 14,600 newly diagnosed cases and 10,400 related deaths annually in the United States (1, 2). Response rates generally are inverse to patient age; the outcomes for the majority of patients treated with standard-of-care regimens (cytarabine + anthracycline) remain poor, with approximately 25% of patients surviving 3 or more years (2, 3). Although aggressive treatments have improved outcome in young patients, patients older than 60, comprising the majority of AML cases, remain a therapeutic enigma. The development of personalized diagnostic tests that could identify patients that will benefit from conventional cytarabine + anthracycline regimens, and conversely direct those unlikely to benefit to alternative therapies, could potentially improve response rates and minimize toxicity.

Prognostic markers for AML have been identified including age and performance status but by themselves these are not therapeutically leverageable. A number of prognostic molecular events have been identified in AML including translocations and mutations in MLL, AML/ETO, Fli1-ITD, NPM1, CEBPalpha, IDH1, IDH2, RUNX1, and WT1 and in epigenetic modifying genes such as TET2 and ASXL1 (4–6), and changes in cell signaling protein profiles (7, 8). Though these events carry prognostic significance, the heterogeneity of patient response with a given molecular event demonstrates that other factors must be involved in regulating the biology of the leukemic blast and, consequently, the relative sensitivity to a given therapy. Impairment of apoptosis is a hallmark of AML and Bcl-2 family proteins comprise key modulators of such at the mitochondrial level. It has been proposed that steady-state expression levels of these proteins would confer prognostic information in AML. To date,
however, these measurements have not provided a predictive biomarker for incorporation into routine clinical use due to conflicting outcomes relevance data (9–11). Differential expression in AML subtypes has been cited as a confounding factor, limiting clinical utility of this approach (11).

The study of pathways in the context of constituent component expression and measured changes in response to perturbation has demonstrated to yield important prognostic information (12, 13). The underlying principle of BH3 profiling is that mitochondrial depolarization following BH3 peptide exposure serves as a functional biomarker for cellular response to proapoptotic cues (14–17). Early conceptual investigations into mitochondrial profiling have drawn correlations between therapeutic efficacy and BH3 peptide-derived metrics (18–21). This study offers translational and statistical evidence for the clinical utility of BH3 profiling in discriminating response to standard-of-care–based therapeutic management of AML.

Materials and Methods

AML patient cohort

Newly diagnosed AML patient samples were obtained from peripheral blood draw or bone marrow aspirate collection before induction chemotherapy administration at The University of Texas MD Anderson Cancer Center (MDACC; Houston, TX) between September 1999 and March 2007 (22). Specimens were acquired during routine diagnostic assessments in accordance with the regulations and protocols (Lab 01-473) approved by the investigational review board of MDACC. Informed consent was obtained in accordance with the Declaration of Helsinki. Patients were selected for inclusion in this study on the basis of the availability of cryopreserved cells from the larger pool of 511 cases from a population treated with cytarabine-based regimens. Following Ficoll purification, CD3/CD19 cell depletion removed contaminating T and B cells and cells were cryopreserved in liquid N2.

Patient treatment

All 62 patients were treated with high-dose ara-C (HDAC)-based chemotherapy (cytarabine + anthracycline [n = 48], cytarabine + nonanthracycline [n = 7], and cytarabine + fludarabine [n = 8]; one patient received cytarabine + nonanthracycline and cytarabine + fludarabine on subsequent cycles [no response on either cycle]). Complete response (CR) denotes normal bone marrow morphology, absolute neutrophil count greater than 1,000, platelet count more than 100K and rising hemoglobin. Relapse is more than 5% blasts in the bone marrow or blasts in the peripheral blood in a patient formerly in CR. Primary refractory (no response, NR) denotes residual leukemia after 2 cycles of induction chemotherapy. For statistical analyses, CR denotes patients who exhibited response, with or without subsequent relapse and NR shows primary refractory.

Cytogenetic risk status determination

Cytogenetic risk determination was performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified cytogenetics laboratory at MDACC. Patient risk-group assignment was carried out according to Cancer and Leukemia Group B (CALGB): favorable = inv16, t(8:21), T(15:17); intermediate = diploid, –y, insufficient metaphases; unfavorable = all others, −5, −7, +8, t(6;9), 11q, PH1+, miscellaneous.

BH3 profiling

AML specimens were stained with antibodies CD45-V450 (BD Biosciences), CD3-Biotin (BD Biosciences), and CD20-Biotin (eBiosciences). Secondary antibody was Streptavidin-APC (BD Biosciences). Specimens were permeabilized with digitonin (Sigma-Aldrich) and incubated with JC-1 mitochondrial dye (Enzo Life Sciences) and peptides (BIM 100 μmol/L, BIM 0.1 μmol/L, PUMA 100 μmol/L, PUMA 10 μmol/L, NOXA 100 μmol/L, BAD 100 μmol/L, BMF 100 μmol/L, HRK 100 μmol/L, or PUMA2A 100 μmol/L) or dimethyl sulfoxide (DMSO; 1%) or carbonyl cyanide m-chlorophenyl hydrazone (CCCP; 10 μmol/L) at room temperature. Samples were run in duplicate except in cases in which insufficient viable cells were available.

Samples were analyzed on a FACS CantoII (BD Biosciences) using BD FACS Diva software. The blast population was identified as CD45 dim, CD3 and CD20 −. Intensely stained CD45 cells (mature lymphocytes) were excluded from analyses as described previously (20, 21). The quantifiable propensity of a proapoptotic peptide to induce mitochondrial depolarization relative to an uncoupling reagent control is referred to as percentage priming. For the blast population this was calculated using the median signal intensity of the PE channel normalized for DMSO as background (negative control) and CCCP served as 100% priming (positive control). For calculation of percentage priming, the following formula is used:

\[
\text{Percentage priming} = \left[1 - \frac{\text{Peptide} - \text{CCCP}}{\text{DMSO} - \text{CCCP}}\right] \times 100
\]

Statistical analysis

Biomarkers were analyzed by testing the association between the biomarker status (percentage priming) and responder or nonresponder classification. Univariate comparisons were made using Mann–Whitney test; all reported P values are two sided. The threshold for significance was \(P < 0.05\). The primary analysis to account for multiple comparisons (7 biomarkers). Secondary analyses used a threshold of \(P < 0.05\) and are only reported when the primary analysis for a marker was significant. The predictive ability of markers was assessed using the area under the curve (AUC) statistic. Multivariate analyses were performed using logistic regression and significant adjustment variables from Table 1 (age, cytogenetic risk status).
overall survival (OS) and event-free survival (EFS) were tested for significant correlation with percentage priming by log-rank test for trend. Patients having received stem cell transplant were censured from OS analyses. Analyses were performed using SAS software, version 9.2 (SAS Institute Inc.), R version 2.14.2 (R Core Team), and/or GraphPad Prism version 5.04.

**RPPA methodology**

Proteomic profiling was performed on AML patient samples using validated methods described previously.
Slides were analyzed using Vigene Tech Microvigene the signal at a dilution of 1:15,000 (24). The stained primary antibody against total BCL2L1 (Epitomics) expression controls. Slides were probed with validated dilutions onto slides along with normalization and (7, 23). Patient samples were printed in five serial patient age, cytogenetic variables (Table 1). Mann–Whitney analyses were performed to test for association between clinical variables and chemotherapeutic response. Patient age, cytogenetic status were formed to test for association between clinical variables (Table 1). Mann–Whitney analyses were performed to test for association between clinical variables and chemotherapeutic response.

### Results

**Patient cohort characteristics**

Patients with AML were stratified by cytarabine-based regimen response status relative to clinical pathologic variables (Table 1). Mann–Whitney analyses were performed to test for association between clinical variables and chemotherapeutic response. Patient age, cytogenetic risk, and treatment displayed statistically significant association relative to response ($P = 0.008$, $P = 0.003$, and $P = 0.0001$, respectively). Age and cytogenetic status were subsequently used in multivariate analyses for BH3 profiling biomarkers.

**BH3 profiling of patient specimens**

Of 62 viably preserved AML patient specimens that were BH3 profiled, 61 provided analyzable data (an overall technical success rate of 98.4%). The one sample that was eliminated from consideration before statistical analysis contained insufficient viable cells by trypan blue exclusion to continue with analysis. Representative data are shown in Supplementary Fig. S1 of two NR (low priming of biomarker panel) and two CR patients (high priming of biomarker panel). Note that the overall coefficient of variation for repeat samples from individual patients is generally 3% to 5%, indicative of a technically robust assay with limited run-to-run variability.

Among the biomarker peptides assayed, BIM(0.1) elicited priming scores correlated with response with pronounced significance ($P = 1.8 \times 10^{-6}$). It is worth noting that the site from which the specimen was drawn (peripheral blood or bone marrow) did not influence analysis as priming scores were significantly associated with response for peripheral blood and bone marrow specimens analyzed independently as subsets (data not shown). Analyses of other BH3 profiling biomarkers assayed are indicated in Table 2. In addition to BIM(0.1), PUMA(10) displayed (borderline) significant association with response ($P = 0.0064$; Supplementary Fig. S2). NOXA, BAD, HRK, BMF, and PUMA2A did not display significant correlation ($P > 0.007$) with response.

When the BIM(0.1) priming scores of individual patients are segregated into responder and nonresponder groups (Fig. 1A), a clear trend emerges. Patients with AML likely to exhibit response to cytarabine-based therapy display higher BIM(0.1) readout (percentage priming $= 36.8 \pm 21.2$ SD) than patients not likely to respond (percentage priming $= 13.2 \pm 13.4$ SD). In establishing sensitivity and specificity of this biomarker, receiver operator characteristic (ROC) plot depiction indicates an AUC of 0.83 (95% CI, 0.73–0.94; Fig. 1B), an indication of the ability of the biomarker to correctly discriminate individual specimens. Interestingly, a single biomarker may identify 89.7% of responders, whereas at the same time 59.1% of those patients unlikely to respond. With a more stringent sensitivity cutoff of 92.3%, specificity still identifies 54.6% of unlikely responders.

Age and cytogenetics have been recognized as prognostic factors in AML and that was true in this dataset as well (Table 1). To determine whether the addition of BIM (0.1)% priming biomarker added prognostic information beyond that of age and cytogenetics, each was serially added to BIM(0.1)% priming in multivariate analyses. The addition of patient age to BIM(0.1) yields an increase in

<table>
<thead>
<tr>
<th>Mean percentage priming ±/– SD</th>
<th>P</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BH3 Peptide</strong></td>
<td><strong>NR</strong></td>
<td><strong>CR</strong></td>
</tr>
<tr>
<td><strong>BIM</strong></td>
<td>70.1 ± 32.6</td>
<td>88.2 ± 17.6</td>
</tr>
<tr>
<td><strong>BIM(0.1)</strong></td>
<td>13.8 ± 13.4</td>
<td>36.8 ± 21.2</td>
</tr>
<tr>
<td><strong>PUMA</strong></td>
<td>44.7 ± 29.5</td>
<td>64.0 ± 22.7</td>
</tr>
<tr>
<td><strong>PUMA(10)</strong></td>
<td>33.3 ± 24.3</td>
<td>50.4 ± 23.7</td>
</tr>
<tr>
<td><strong>NOXA</strong></td>
<td>26.3 ± 15.5</td>
<td>35.1 ± 24.9</td>
</tr>
<tr>
<td><strong>BAD</strong></td>
<td>32.2 ± 29.6</td>
<td>52.7 ± 24.3</td>
</tr>
<tr>
<td><strong>BMF</strong></td>
<td>45.6 ± 31.6</td>
<td>64.4 ± 24.9</td>
</tr>
<tr>
<td><strong>HRK</strong></td>
<td>20.8 ± 22.4</td>
<td>36.6 ± 22.4</td>
</tr>
<tr>
<td><strong>PUMA2A</strong></td>
<td>10.8 ± 19.5</td>
<td>16.1 ± 18.9</td>
</tr>
</tbody>
</table>

NOTE: Summary of the mean percentage priming (± SD), P values, and AUC for all profiling biomarkers analyzed for nonresponse (NR) and clinical response (CR) AML patient specimens. BIM(0.1) was identified as a highly significant biomarker ($P < 0.001$ and AUC $> 0.80$) and PUMA(10) was also (borderline) statistically significant ($P < 0.007$). Statistical significance was determined by Mann–Whitney analysis.
AUC to 0.89 from previous BIM(0.1) AUC = 0.83 alone (Fig. 1C). Furthermore, when BIM(0.1) is adjusted for patient age and cytogenetic risk, then AUC further increases to 0.91. Within this latter adjustment, more than 90% sensitivity is achieved with identification concurrent with segregation of more than 70% of the likely nonresponders (Fig. 1C).

Patients were stratified by cytogenetic risk status and analyzed by Mann–Whitney test for response discrimination. In the intermediate risk subgroup, BIM(0.1) was significantly associated (n = 33 [8 NR, 25 CR]; P = 0.0017; AUC, 0.88; 95% CI, 0.71–1.04), with further discriminating response, and in the unfavorable group BIM(0.1) was also significant (n = 23 [14 NR, 9 CR]; P = 0.023; AUC, 0.79; 95% CI, 0.58–1.00; Fig. 2A, B and G, H). The P values are somewhat diminished relative to BIM(0.1) analysis of the combined cohort due to reduced statistical power from the subgrouped number of patients. Interestingly, both BAD and HRK analysis yielded significant P values in response discrimination (n = 33 [8 NR, 25 CR]; P = 0.0017; AUC, 88; 95% CI, 0.74–1.00 and P = 0.0055; AUC, 0.87; 95% CI, 0.75–1.00, respectively), however, this was only observed for the intermediate risk-group (Fig. 2C and E). Although sensitivity and specificity assessment by ROC analyses of these biomarkers in response discrimination gives AUCs of 0.88 for BIM(0.1), 0.88 for BAD, and 0.87 for HRK in the intermediate group and 0.79 for BIM(0.1) for the unfavorable group (Fig. 2B, D, F, and H, respectively), these AUCs may benefit from somewhat imbalanced sub-groupings for responders versus nonresponders in the independent subgroups. Statistical analysis was not possible for favorable patients versus nonresponders (n = 5).

**Comparison of BIM(0.1) BH3 profiling percentage priming and BIM (BCL2L11) protein levels**

We sought to assess whether BIM BH3 profiling response discrimination is merely redundant with BIM protein levels in AML patient specimens within this study. We find that no correlation exists between BIM protein level and percentage priming (Fig. 3A) yielding an R² = 0.04. Samples analyzed were limited to those having data for both BCL2L22 protein and BH3 profiling BIM(0.1) (n = 43; 20 NR, 23 CR).

BH3 profiling of BIM(0.1) maintains a significant P value (P = 0.0048) for response discrimination with a notable AUC of 0.75 (95% CI, 0.60–0.90; Fig. 3B and C) in this subset for which both BH3 profiling and reverse phase protein array (RPPA) data exist from the total patients cohort. The power of the analysis is reduced relative to our earlier analyses as the sample size decreases from n = 62 to n = 43 and many of the samples that did not have RPPA data were among the highest scoring BH3-profiling specimens. The P value and AUC for response discrimination for this same subset of specimens for BCL2L11 protein level is P = 0.33; AUC = 0.61 (95% CI, 0.44–0.79; Fig. 3D and E). These data provide strong evidence that BH3 profiling is not correlated with overall protein levels and that BH3 profiling may offer a new
paradigm by which to predict cytarabine response in patients with AML.

**Secondary clinical endpoints: overall survival and event-free survival**

BH3-profiling biomarkers were also analyzed for correlation with the secondary clinical endpoints OS and EFS. Interestingly, when the patient cohort is divided into tertiles by BIM percentage priming (high, intermediate, and low), corresponding OS yielded a median of 262.2, 192.1, and 32.7 weeks, respectively ($P = 0.037$; Fig. 4A). When analysis of tertiles was conducted for EFS, the median EFS was 26.1, 71.3, and 160.7 weeks for low priming, intermediate priming, and high priming tertiles, respectively ($P = 0.044$; Fig. 4B). All other peptides displayed a nonsignificant association on tertile-segregated patients ($P > 0.1$, data not shown). These data are consistent with our earlier assessment of the importance of BIM(0.1) in discriminating clinical outcomes for cytarabine-treated patients with AML.

Figure 2. BH3 peptides response prediction stratified by cytogenetic status. Response prediction stratified by intermediate cytogenetic status (A–F) depicted in dot plots (A, C, and E) and ROC plots (B, D, and F) for BIM(0.1) (A and B), BAD (C and D), or HRK (E and F) or unfavorable cytogenetic status for BIM(0.1) as a dot plot (G) and ROC plot (H). BIM (0.1), BAD, and HRK were all statistically significant for intermediate cytogenetic status ($P < 0.01$ and AUC > 0.85). Statistical significance was determined by Mann–Whitney analysis. Mean ± SD for each set is indicated on dot plots.
Discussion

This study highlights the potential clinical utility of BH3-profiling biomarkers in discriminating patient response to standard-of-care (cytarabine-based) chemotherapeutic regimens for patients with AML. Namely, a single BH3–profiling biomarker (BIM\[0.1\]) used in conjunction with patient age and cytogenetic status delivers a sensitivity and specificity profile with an AUC > 0.9. Interestingly, the two most interesting biomarkers in this study (BIM \[P = 10^{-6}\] and potentially PUMA \[P = 0.0064\]) display functional roles in the BH3 proteins “activator” class, directly binding to and modulating Bax/Bak. The other biomarkers assessed here (NOXA, BAD, and HRK) are classified as “sensitizers” by engaging specific antiapoptotic proteins (MCL-1, BCL-2, and BCL-xL) and are not significantly associated with outcomes.

Although the statistics achieved with a limited number of patients are impressive, this study is limited in several aspects that must be addressed in future studies. This study used patient specimens that were collected and viably cryopreserved. However, analytic scrutiny of prospective collection versus viably frozen technically has indicated that the test will be used to direct treatments of patients as they present in real time. Furthermore, a skewed dataset with more long-term CR and more primary refractory cases was selected for this study. The range of priming and correlation with clinical endpoints will need to be assessed in randomized cohorts more representative of an unselected population including intermediate response endpoints (i.e., CRi, CRp).

Although the current cohort comprises a first test set that provided notable predictive capability, additional studies are required to confirm the present findings. Still, even
Although static protein levels have not been conclusively shown to correlate with clinical outcomes, other investigational studies highlight the importance of BIM as a key regulatory node in apoptosis following chemotherapy in AML. Zhang and colleagues (25) showed that sorafenib treatment resulted in BIM upregulation and activation of the intrinsic apoptotic pathway. Conversely, decreasing BIM expression significantly abrogated sorafenib-induced apoptosis. In separate studies, intrinsic apoptosis pathway response to MEK inhibitors and FLT3 inhibitors was regulated through levels of both BIM and PUMA (26, 27), although at least in the case of FLT3 inhibitors, BIM apparently plays the more key role. Finally, Grocek and colleagues have reported that cytarabine-mediated apoptosis in AML following vitamin D3 treatment occurs through modulation of miR-23 and subsequently BIM levels (28). Taken together, these studies underscore the functional importance of BIM (not directly assessed by static expression levels) as addressed by BH3 profiling for assessing proapoptotic response to AML treatment.

Recent studies have addressed the potential utility of BH3 profiling for predicting chemotherapeutic response in patients with AML. Ni Chonghaile and colleagues (20) used a small cohort of 15 patients (6 NR, 9 CR). Although this cohort was of statistically low power and specific therapeutic treatment of patients was not addressed, BIM BH3 profiling was significant for general chemotherapeutic response. Vo and colleagues (21) found correlation between BH3 profiling of CD34+ stem cells and response to induction chemotherapy comprising daunorubicin, etoposide, or mitoxantrone in patients with AML and BH3 profiling of BIM was used to identify patients that could likely benefit from allogenic stem cell transplant. In this study, no significant correlation was observed between BH3 profiling and cytarabine efficacy in cell lines or patient-derived specimens. As cytarabine remains a key component of standard-of-care treatment of patients with AML, our study sought to focus on defining the medical utility of mitochondrial response as actionable information for patient management using a statistically powered cohort of patients uniformly treated with cytarabine-based therapy. BH3 profiling cutoff points from this cohort come into focus and alongside additional patient information such as age and cytogenetic risk status, improved sensitivity and specificity profiles herein serve as a harbinger for the potential clinical application for such a diagnostic.

Application of personalized medicine approaches in patient management decisions carries certain considerations that cannot be discounted. Given that most patients will receive standard-of-care chemotherapy, one may want to avoid targeting a specific biomarker status whereby a patient likely to benefit from treatment is misclassified even if there is improvement in the overall clinical endpoints of the patient group overall. Resolved that a 10% false-negative rate is acceptable, the question to be addressed is how many of the patients...

With a 62-patient cohort, the BIM(0.1) P value is notable (P = 1.8 x 10^-6). When placed in the context of patient age and cytogenetic status (P = 0.008 and 0.003, respectively), BIM(0.1) significance is strikingly juxtaposed to clinicopathologic variables already accepted to be associated with clinical outcomes.

A key question addressed here was whether a significant BH3-profiling metric is merely redundant with BH3-only protein expression. Our results indicate BH3 profiling and protein expression are decidedly not correlated and response is only predicted by the more functional of the two metrics (BH3 profiling). Protein levels alone do not assess the context in which these expressions occur, including phosphorylation state, subcellular location, or the broader context of similar measurements for directly or indirectly cooperating proteins. Still, although the analyses here were directed to response, it is plausible that BH3 protein levels may show trends coincident with other clinical endpoints (S.M. Kornblau; unpublished data).
unlikely to respond can be moved to a different treatment? On the basis of the current data, theoretically applying a preliminary cutoff point for patients with BIM(0.1) priming at ≥15% would identify ≥90% of likely responders who should receive cytarabine, whereas 55% to 60% of likely nonresponders would be spared the treatment (negative predictive value). Furthermore, when age and cytogenetic status are considered in the context of BIM(0.1) priming, then ≥90% sensitivity may be achieved concurrently with classifying ≥70% of nonresponders. Additional BH3 profiling biomarkers and algorithms may have application in discriminating response to alternative therapies for patients not deemed suitable for cytarabine-based regimens.

Disclosures of Potential Conflicts of Interest
M. Elashoff is a consultant/advisory board member for Eutropics Pharmaceuticals. M.H. Cardone has a commercial research grant and ownership interest in Eutropics Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Conception and design: W.E. Pierceall, N.E. Carlson, M.H. Cardone
Development of methodology: W.E. Pierceall, N.E. Carlson

References

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.E. Pierceall, S.M. Kornblau, N.E. Carlson, N. Blake, R. Lena.

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W.E. Pierceall, S.M. Kornblau, N.E. Carlson, X. Huang, N. Blake, R. Lena, M. Elashoff, M. Konopleva, M. Andreeff.

Writing, review, and/or revision of the manuscript: W.E. Pierceall, S.M. Kornblau, N.E. Carlson, X. Huang, N. Blake, R. Lena, M. Konopleva, M.H. Cardone, M. Andreeff.

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.E. Pierceall, S.M. Kornblau, N.E. Carlson, N. Blake, R. Lena, M.H. Cardone.

Study supervision: W.E. Pierceall, M. Andreeff.

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