report is the first to describe the use of blinatumomab in the treatment of CD19+ MPAL and to establish its efficacy in controlling this rare type of acute leukemia.

Although the survival of patients with MPAL has improved in recent years, primarily due to incorporation of allo-HSCT into treatment, the overall prognosis remains poor. The risk of death from MPAL is 59% and 26% higher than for ALL and AML, respectively.⁶ In the absence of prospective clinical trials, MPAL treatment is guided by retrospective studies and is based on ALL regimens. Given high relapse rates with chemotherapy, targeted approaches may improve outcomes.

B/myeloid MPAL blasts express CD19. In this report, we aimed to study the efficacy of blinatumomab in the treatment of two patients with CD19+ MPAL. The clinical hypothesis was that treatment of these patients with CD19+ MPAL with blinatumomab, along with a tyrosine kinase inhibitor for Ph(+) disease in the first patient, would result in the achievement of sustained MRD-negative CR and maintenance of MRD-negative CR in the first and second patient, respectively. Our patients had short periods of myelosuppression and few adverse events, which led to overall improved functional status after therapy. Both patients were able to proceed to allo-HSCT, thus far resulting in sustained MRD-negative clinical remissions. The poor outcomes of R/R MPAL with chemotherapy underscore the need for a prospective clinical study of targeted therapy in this patient population. We suggest that blinatumomab is an excellent candidate for this purpose.

CONFLICT OF INTEREST
A.E. is a Global Oncology Advisory Board Member for Amgen and has served as a consultant to Amgen.

ORCID
Vu H. Duong https://orcid.org/0000-0003-0278-7727

Firas El Chaer and Omer M. Ali contributed equally to this study.

REFERENCES
Blood circulation through the placenta is similar to blood circulation through the spleen. In the spleen, some blood flows directly from arterioles to venules, without intervening capillaries, whereas other blood is shunted into the low pressure pools in the sinusoids. Plasma preferentially flows directly to the venules, described as “plasma skimming”, while the blood cells are sequestered in the sinusoids. Platelet counts in splenic blood are 7-fold greater than platelet counts in peripheral blood. In normal adults, one-third of all circulating platelets

<p>| TABLE 1  Comparison of peripheral and placental intervillous space blood counts in women with scheduled cesarean sections |
|---------------------|---------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Blood cells</th>
<th>Median (range)</th>
<th>Placental blood (corrected)</th>
<th>Absolute difference between medians</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.9 (8.0-14.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>9.50 (5.60-12.99)</td>
<td>9.94 (1.64-23.16)</td>
<td>+0.44</td>
<td>.0285</td>
</tr>
<tr>
<td>Neutrophils (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>6.50 (3.46-9.51)</td>
<td>6.40 (1.11-17.61)</td>
<td>−0.10</td>
<td>.2231</td>
</tr>
<tr>
<td>Lymphocytes (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>2.05 (1.21-4.81)</td>
<td>2.44 (0.04-6.69)</td>
<td>+0.39</td>
<td>.0012</td>
</tr>
<tr>
<td>Platelets (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>233 (98-340)</td>
<td>164 (18-728)</td>
<td>−69</td>
<td>.0285</td>
</tr>
</tbody>
</table>

The 20 women with placental blood samples that had fetal blood contamination ≤ 13.5%<sup>c</sup>

<table>
<thead>
<tr>
<th>Blood cells</th>
<th>Median (range)</th>
<th>Placental blood (corrected)</th>
<th>Absolute difference between medians</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.6 (9.1-14.4)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>9.56 (5.6-12.99)</td>
<td>11.52 (5.92-23.16)</td>
<td>+1.96</td>
<td>0.0002</td>
</tr>
<tr>
<td>Neutrophils (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>6.65 (3.75-9.51)</td>
<td>7.69 (3.55-17.61)</td>
<td>+1.04</td>
<td>0.0032</td>
</tr>
<tr>
<td>Lymphocytes (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>1.99 (1.29-4.81)</td>
<td>2.54 (1.42-5.07)</td>
<td>+0.55</td>
<td>0.0020</td>
</tr>
<tr>
<td>Platelets (10&lt;sup&gt;3&lt;/sup&gt;/μL)</td>
<td>233 (98-324)</td>
<td>179 (73-728)</td>
<td>−54</td>
<td>0.1992</td>
</tr>
</tbody>
</table>

<sup>a</sup> White blood cell and platelet counts in blood from the placental intervillous space were corrected for the amount of dilution by the EDTA anticoagulant solution, based on the relative hemoglobin concentrations in the peripheral blood and placental intervillous space blood. The median correction ratio for all 40 placental blood samples (peripheral hemoglobin/placental hemoglobin) was 1.9 (range, 0.69-4.31).

<sup>b</sup> P values were obtained from the Wilcoxon signed-rank test.

<sup>c</sup> The median fetal blood contamination of the placental intervillous blood samples was 13.5%. To determine the effect of fetal blood contamination on white blood cell and platelet counts, data for the 20 placental blood samples with ≤ 13.5% contamination by fetal blood are presented.

Blood circulation through the placenta is similar to blood circulation through the spleen. In the spleen, some blood flows directly from arterioles to venules, without intervening capillaries, whereas other blood is shunted into the low pressure pools in the sinusoids. Plasma preferentially flows directly to the venules, described as “plasma skimming”, while the blood cells are sequestered in the sinusoids. Platelet counts in splenic blood are 7-fold greater than platelet counts in peripheral blood. In normal adults, one-third of all circulating platelets

FIGURE 1  Placental morphology and immunohistochemical staining of sections of a placenta obtained at delivery and included in this study. Placental sections were stained with hematoxylin and eosin (H&E) to demonstrate the structure of the villi and perivillous fibrinoid, and also with a rabbit anti-CD61 (platelet membrane glycoprotein IIIa) monoclonal antibody by ProPath referral pathology service, Dallas, TX, A. Low magnification view of the placental parenchyma illustrating mature terminal villi. Perivillous fibrinoid filling gaps in the syncytiotrophoblast surface of the villi are identified by the homogeneous pink stain. Representative examples of the perivillous fibrinoid are indicated by the arrows. (H&E, 10× objective) B. An adjacent location in the same placental section stained with anti-CD61 (brown color) demonstrating platelets within the perivillous fibrinoid, in a linear pattern along the villous surfaces throughout this section. Representative examples of platelet staining are indicated by the arrows (CD61 immunostaining, 10× objective) C, high magnification of the placental parenchyma illustrates a mature terminal villus. The arrow indicates perivillous fibrinoid sealing a gap in the syncytiotrophoblast surface. (H&E, 100× objective) D, An adjacent location stained with antiCD61 (brown color) demonstrating platelets within the perivillous fibrinoid, indicated by the arrow. (CD61 immunostaining, 100× objective)
are transiently sequestered within the splenic sinusoids. Increased spleen size results in greater splenic sequestration of platelets and lower peripheral blood platelet counts.1

In the placentas some blood also flows directly from arterioles to venules, without intervening capillaries, while other blood is shunted into the low pressure pools in the intervillous spaces. These similar patterns of circulation suggest that there may be increased sequestration of blood cells in the placental intervillous spaces, similar to the splenic sinusoids. Although platelets sequestered within splenic sinusoids return to the circulation,3 platelets sequestered within the intervillous spaces may be consumed by incorporation into the perivillous fibrinoid. Perivillous fibrinoid is present in all term placentas. It is a product of coagulation that fills gaps in the syncytiotrophoblast cells lining the surface of mature villi and maintains the integrity of the villous surface.4,5

Platelet counts of women with twin pregnancies are lower than platelet counts of women with singleton pregnancies at each trimester and at delivery.6 Women with twin pregnancies have larger placentas, or may have 2 placentas. This suggests that larger placentas in women with twin pregnancies may contribute to their greater platelet count decrease.

Based on these observations, we postulated that blood cells are sequestered within the intervillous spaces of the placenta and that platelets are then consumed by incorporation into perivillous fibrinoid. To test this hypothesis, we compared blood cell counts in maternal peripheral blood to blood obtained from the placental intervillous space.

We collected placentas from 40 women with uncomplicated singleton pregnancies who had a scheduled cesarean delivery for routine indications at the Oklahoma University Medical Center. The mother’s complete blood count (CBC) from the day of delivery was recorded. At delivery, placentas were immediately immersed in a solution of 4.5 mmol ethylenediaminetetraacetic acid (EDTA) in 0.85% sodium chloride to prevent blood coagulation within the intervillous space. Maternal placental blood was collected from the intervillous space6 and placental tissue samples for microscopy were also collected at the same time. Contamination of maternal blood with fetal blood was determined by the percent of fetal red blood cells in each sample. Then a CBC was performed on the placental blood sample with the lowest percentage of fetal blood. A stained smear of the placental blood was examined for platelet clumping; if clumping occurred, the sample was not used. To correct for dilution of placental blood by the EDTA solution, we used the ratio of hemoglobin concentration in the peripheral blood to placental blood to adjust the placental white blood cell and platelet counts. To determine if contamination of maternal blood from the intervillous space by fetal blood influenced the blood counts, we separately analyzed blood counts on the 20 women with placental blood samples that had fetal blood contamination less than the median value. This study was approved by the University of Oklahoma Institutional Review Board (approval #4156).

The median time between delivery and placental blood sample collection was 18 minutes (range, 13-82 minutes). The placental weight (median 501 g, range 364-938) was more than 2-fold the weight of a normal adult spleen (150-200 g). The median total white blood cell count, neutrophil count, and lymphocyte count, corrected for dilution by the EDTA solution, were all higher in placental blood than in the peripheral venous blood. These differences were significant when the placental blood of the 20 women with less fetal blood contamination was analyzed (Table 1). The median corrected platelet count in placental blood of all 40 women was lower than the platelet count in peripheral venous blood. The median corrected platelet count in placental blood of the 20 women with less fetal blood contamination was also lower than the platelet count in peripheral venous blood; however, the difference was not significant, possibly due to the smaller sample size and the variation among the platelet counts.

Microscopic examination of all 40 placentas documented that they were normal. None of the placentas had excessive subchorionic or perivillous fibrinoid, intervillosus or subchorionic thrombi, or inflammatory infiltrates. Immunohistochemical stains using a rabbit monoclonal antibody to the platelet membrane glycoprotein IIa (CD61) identified platelets within the perivillous fibrinoid (Figure 1). These images suggest that platelets are consumed in the process of blood coagulation and fibrinoid generation to seal the gaps in the syncytiotrophoblastic surface of the terminal villi.

The higher white blood cell counts in placental blood compared to peripheral venous blood are consistent with the sequestration of blood cells within the intervillous space, similar to the sequestration of blood cells in splenic sinusoids.3 The lower or equivalent platelet counts in placental blood compared to peripheral venous blood and the immunohistochemistry identification of platelets within the perivillous fibrinoid are consistent with the hypothesis that platelets are not only sequestered within the placental intervillous space but also consumed by incorporation into the perivillous fibrinoid, which maintains integrity of the syncytiotrophoblastic surface. These data support the hypothesis that the sequestration and consumption of maternal platelets within the placental intervillous space contribute to lower platelet counts during pregnancy.

ACKNOWLEDGMENT
This project was supported in part by 1K01HL135466-01 from the National Heart, Lung and Blood Institute (Terrell).

ETHICS STATEMENT
This study was approved by the University of Oklahoma Health Sciences Center Institutional Review Board (approval #4156).

CONFLICT OF INTEREST
Nothing to report.

ORCID
Deirdra R. Terrell https://orcid.org/0000-0003-0794-5851
James N. George https://orcid.org/0000-0002-4243-2691

Jessica A. Reese1,2
Jennifer D. Peck1
Zhongxin Yu3
Teresa A. Scordino3
David R. Deschamps4
Jennifer J. McIntosh4
Incorporation of novel agents (i.e., proteasome inhibitors, bortezomib and carfilzomib, and immunomodulatory drugs, thalidomide and lenalidomide) in the first line treatment of patients suffering from multiple myeloma (MM) has led to an unprecedented improvement in clinical outcomes. Nonetheless, a substantial proportion of patients still dies early in the course of treatment, mostly due to infections. Male gender, hypercalcemia, increased LDH serum level, decreased albumin serum level, renal failure, low body mass index, high Charlson comorbidity index, thrombocytopenia and plasma cell leukemia have been identified as predictors of an increased risk of early death (ED). It is worth noting, that some of these risk factors exclude patients from enrollment in clinical trials, thus making it difficult to extrapolate their results to daily practice. In reality, if regulatory Agencies make novel agents available outside of clinical trials, more and more elderly and/or fragile patients are likely to receive them. Whether these patients also benefit from programs containing one or more novel agents has not been clearly established yet. We hereby analyzed the clinical outcomes of 991 unselected newly diagnosed MM patients, consecutively treated before and after the introduction of novel agents-containing programs. We focused on their risk of ED, defined as the death occurring within 90 days from diagnosis of symptomatic MM.

Details on source of data, treatments of MM and statistical analysis are reported in Supplemental Material. The consort diagram of MM patients diagnosed between 1997 and 2015 is shown in Supporting Information Figure S1. The main demographic data of the patients who started their medical treatment at our Institution is shown in Supplemental Table. During the 18 years of analysis, 708 patients (71.4%) died. Of them, 92 patients died ≤90 days (ED cohort) (9.3% of the entire patients’ population and 13% of all deaths) from starting treatment (Supporting Information Figure S1). By univariate and multivariate analysis, older age, lambda light chain, stage B, and plasma cell leukemia were significantly more common in the ED group patients, whereas incorporation of at least a novel agent in the first line treatment resulted in a significant reduction of ED (Table 1). This beneficial effect was only seen in patients not enrolled in high-dose treatment with autotransplantation (ASCT) programs, in whom the incorporation of novel drugs reduced the prevalence of ED from 22% to 9% (adjusted odds ratio 0.09, 95% CI 0.03-0.22, P < .0001). Conversely, the prevalence of ED of patients enrolled in ASCT programs was 7% irrespective of inclusion of novel agents in induction. Information about the cause of ED was available in 65 (71%) patients: progression of MM (n = 34), infections (n = 16), cardio-vascular complications (n = 13), hepatotoxicity (n = 1), other cause while in partial remission (n = 1).

ED has been defined quite differently in the studies. We set its cutoff at 90 days from starting treatment, in order to focus on the role of the first line treatment and to avoid the confounding effect of further therapies on this clinical outcome. Indeed, among the ED cohort only one patient received a second line treatment. The prevalence of ED in our cohort closely resembles that reported by a tertiary care Korean Institution. These Authors found pneumonia to be the leading cause of ED of a large group of newly diagnosed MM patients. Bacterial and viral infections show a bimodal incidence in patients with MM, the first peak occurring during the induction phase and the second one at the time of relapse/recurrence. This coincides with moments in which MM requires treatment and is not yet under proper control. Although we were unable to analyze in detail the role of infections as cause of ED in our cohort, their contributing role is highly likely, since infections were documented in approximately one quarter of our MM patients at the time of death.