Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry

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Received 8 May 2013; received in revised form 30 October 2013; accepted 3 November 2013. Published online 06 December 2013.

Abstract
This 5-year, prospective registry enrolled 600 lower-risk MDS patients (pts) with transfusional iron overload. Clinical outcomes were compared between chelated and nonchelated pts. At baseline, cardiovascular comorbidities were more common in non-chelated pts, and MDS therapy was more common in chelated pts. At 24 months, chelation was associated with longer median overall survival (52.2 months vs. 104.4 months; \( p < .0001 \)) and a trend toward longer leukemia-free survival and fewer cardiac events. No differences in safety were apparent between groups. Limitations of this analysis included varying time from diagnosis and duration of chelation, and the fact that the decision to chelate may have been influenced by pt clinical status.

Keywords: Myelodysplastic syndrome, Iron overload, Chelation, Survival, Ferritin, Leukemia

1. Introduction
Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by impaired hematopoiesis and increased risk of acute myeloid leukemia (AML). Approximately half of patients with MDS will develop severe anemia (hemoglobin level less than 10 mg/dL) and will require periodic or regular red blood cell transfusions \[1, 2\]. Transfusion requirement may lead to iron overload and has been associated with increased risk of death and shorter leukemia-free survival \[3, 4\]. Retrospective and observational studies have shown that iron overload is associated with an increased risk of cardiac, hepatic, and endocrine damage \[5\]. Malcovati et al. have shown a stepwise increase in risk of death associated with increased serum ferritin in patients with MDS. Each 500 ng/mL increase in serum ferritin above 1000 ng/mL was associated with a 40% increased risk of death \[3\]. Similarly, a multicenter, observational study by Groupe Francophone des Myélodysplasies (GFM) sought independent prognostic factors for survival in patients who are iron-overloaded with lower-risk MDS \[6\]. Multivariate analysis showed that...
transfusion requirement of more than 3 units/month and increased International Prognostic Scoring System (IPSS) risk status were associated with increased risk of death, whereas adequate iron chelation (40 mg/kg/day deferoxamine 3 or more times/week) was associated with 70% lower risk of death. Adequate chelation was the strongest predictor of overall survival in the French study, in which patients had a mean of 1.7 comorbidities.

Recently, prospective evidence for the benefits of iron chelation on hematologic parameters has been published for the oral iron chelator deferasirox. The large evaluation of patients’ iron chelation with Exjade® trial assessed iron-overload parameters in transfusion-dependent patients with MDS and showed reductions in serum ferritin, labile plasma iron, and alanine aminotransferase (ALT) levels after 1 year of chelation therapy [7]. List et al. showed similar results over 3 years of follow-up in heavily transfused, lower-risk patients with MDS [8]. At study end, serum ferritin was reduced by 37%, labile plasma iron was normalized in patients with elevated baseline levels, and transferrin saturation was reduced to 67% from a baseline of 91%. Improved ALT levels were significantly correlated with reduced serum ferritin in the study by List et al.

However, prospective data on the relationship between chelation, morbidity, and mortality are lacking. The goal of this registry is to evaluate the association between chelation and clinical outcomes in lower-risk MDS patients. We report 24-month data from an ongoing, 5-year registry of lower-risk patients with MDS in the United States. This registry provides prospectively collected data on clinical and safety parameters in chelated versus non-chelated, iron-overloaded, transfusion-dependent, lower-risk patients with MDS.

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2. Patients and methods

This study is a prospective, 5-year, observational registry of 600 lower-risk patients with MDS and iron overload from 118 centers in the United States (9 academic sites; 109 community cancer centers) that enrolled patients over a 2-year period. The first patient first visit was completed on December 20, 2010. The current analysis presents 24-month data from the registry; this represents a composite of data from patients who have completed up to 24 months on the registry. Patient baseline characteristics and study outcomes were analyzed according to their chelation status (non-chelated, chelated, and chelated ≥6 months cumulatively). Chelated patients were defined as those patients who received chelation at any point. In addition, a planned subanalysis was performed for patients who received ≥6 months of cumulative chelation because this duration was thought to provide an adequate treatment period. The chelated ≥6 months group was included in the overall chelated group. Follow-up occurred every 6 months for up to 60 months or death. Assessments included demographics, survival, causes of death, leukemic transformation, serum ferritin, concomitant illnesses, MDS therapy, ongoing transfusion requirements, and safety.

Patients were aged 18 years or older with transfusional iron overload (serum ferritin more than 1000 ng/mL, 20 or more packed red blood cell units, or ongoing transfusion requirement of 6 or more units every 12 weeks) and lower-risk MDS by IPSS, World Health Organization (WHO), and/or French-American-British (FAB) criteria. Approved and experimental MDS therapies were permitted. Adverse events were documented occurring on study and during the 4 weeks after stopping chelation therapy. This study was conducted in accordance with the declaration of Helsinki. All enrolled patients gave written informed consent.

Data are summarized according to demographic and baseline characteristics, safety observations, and outcome measurements. Summary statistics were calculated for continuous variables, and descriptive statistics were calculated for discrete variables and laboratory tests.

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3. Results

3.1. Baseline characteristics

Median age was similar across patient groups (non-chelated, 77 years [range, 47–99]; chelated, 75 years [range, 21–94]; chelated ≥6 months, 74 years [range, 21–94]; Table 1). All groups had a larger percentage of men than of women, although the difference was noted less in the chelated groups. Overall, 86.7% of patients were Caucasian, 6.2% were Hispanic, 5.5% were African American, 1.0% were Asian, and 0.3% each were Native American or other. In all, 82% of patients were enrolled at community cancer centers.

Table 1. Baseline demographics and MDS risk status.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-chelated n = 337</th>
<th>Chelated n = 263</th>
<th>Chelated ≥6 months n = 191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>77 (47–99)</td>
<td>75 (21–94)</td>
<td>74 (21–94)</td>
</tr>
<tr>
<td>Male: female ratio</td>
<td>1.42:1</td>
<td>1.31:1</td>
<td>1.20:1</td>
</tr>
<tr>
<td>MDS risk status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>World Health Organization</td>
<td>112 (33.2)</td>
<td>78 (29.7)</td>
<td>57 (29.8)</td>
</tr>
<tr>
<td>Refractory anemia</td>
<td>38 (33.9)</td>
<td>13 (16.7)</td>
<td>8 (14.0)</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts</td>
<td>34 (30.4)</td>
<td>40 (51.3)</td>
<td>32 (56.1)</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>20 (17.9)</td>
<td>12 (15.4)</td>
<td>8 (14.0)</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ring sideroblasts</td>
<td>8 (7.1)</td>
<td>7 (9.0)</td>
<td>5 (8.8)</td>
</tr>
</tbody>
</table>
Approximately half of patients were classified lower-risk MDS by IPSS criteria, approximately 30% were classified lower-risk by WHO, and approximately 20% were classified lower-risk by FAB. The MDS risk status profiles were similar across groups except that a larger percentage of non-chelated patients were classified as intermediate-1 risk by IPSS criteria (non-chelated, 66.3%; chelated, 55.9%; and chelated ≥ 6 months, 60.0%), having refractory anemia by WHO criteria (non-chelated, 33.9%; chelated, 16.7%; and chelated ≥ 6 months, 14.0%), and having refractory anemia with excess blasts by FAB criteria (non-chelated, 32.2%; chelated, 13.8%; and chelated ≥ 6 months, 12.8%).

Baseline cardiac and vascular comorbidities were more common in the non-chelated group (Table 2). Cardiac conditions included coronary artery disease, cardiomyopathy, rhythm abnormalities, structural abnormalities, and infectious/inflammatory conditions. Use of MDS therapies was more common in chelated patients. Overall, 287 (85.2%), 243 (92.4%), and 175 patients (91.6%) in the non-chelated, chelated, and chelated ≥ 6 months groups, respectively, had received MDS therapy prior to or at enrollment. Growth factor use trended higher among chelated patients. Erythropoietin was used by 65.3% of non-chelated, 76.8% of chelated, and 80.1% of chelated ≥ 6 months groups; granulocyte colony-stimulating factor (GCSF) was used by 18.1% of non-chelated, 24.0% of chelated, and 25.7% of chelated ≥ 6 months groups. Low-dose chemotherapy/immunomodulator use, with the exception of hydroxyurea, trended higher in chelated patients. Azacitidine use in non-chelated, chelated, and chelated ≥ 6 months groups was 40.1%, 51.7%, and 55.0%; decitabine use was 26.1%, 31.2%, and 30.9%; lenalidomide use was 16.3%, 36.5%, and 39.8%; thalidomide use was 3.6%, 7.2%, and 7.9%; and hydroxyurea use was 3.6%, 2.3%, and 2.6%, respectively. Units transfused trended higher in the chelated group. Median (range) lifetime units transfused before the study were 20 (0–250), 39 (0–620), and 44 (0–620) in the non-chelated, chelated, and chelated ≥ 6 months groups, respectively.

Table 2. Baseline concomitant conditions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-chelated n = 337</th>
<th>Chelated n = 263</th>
<th>Chelated ≥ 6 months n = 191</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>173 (51.3)</td>
<td>92 (35.0)</td>
<td>59 (30.9)</td>
</tr>
<tr>
<td>Vascular</td>
<td>201 (59.6)</td>
<td>125 (47.5)</td>
<td>88 (46.1)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>146 (43.3)</td>
<td>100 (38.0)</td>
<td>66 (34.6)</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>10 (3.0)</td>
<td>10 (3.8)</td>
<td>9 (4.7)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>127 (37.7)</td>
<td>92 (35.0)</td>
<td>64 (33.5)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>114 (33.8)</td>
<td>70 (26.6)</td>
<td>45 (23.6)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>42 (12.5)</td>
<td>31 (11.8)</td>
<td>23 (12.0)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>42 (12.5)</td>
<td>27 (10.3)</td>
<td>15 (7.9)</td>
</tr>
<tr>
<td>Neurologic/psychiatric</td>
<td>36 (10.7)</td>
<td>38 (14.4)</td>
<td>28 (14.7)</td>
</tr>
<tr>
<td>Renal</td>
<td>7 (2.1)</td>
<td>3 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>53 (15.7)</td>
<td>27 (10.3)</td>
<td>17 (8.9)</td>
</tr>
<tr>
<td>Audiologic</td>
<td>30 (8.9)</td>
<td>27 (10.3)</td>
<td>17 (8.9)</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>23 (6.8)</td>
<td>18 (6.8)</td>
<td>13 (6.8)</td>
</tr>
</tbody>
</table>

*A patient is counted once at system organ class or condition level if one or more conditions are reported.
3.2. Interim analysis of patients completing 24 months on the registry

At follow-up, 249 patients (41.5%) remained on study and 351 (58.5%) discontinued due to death (278 [46.3%]), lost to follow-up (51 [8.5%]), and other (22 [3.7%]).

Overall survival in each patient group was calculated from the date of MDS diagnosis. Kaplan–Meier analysis showed that median (25th, 75th percentile) time to death from MDS diagnosis was significantly longer in the chelated groups (Fig. 1). Patients in the non-chelated, chelated, and chelated ≥ 6 months groups survived a median of 52.2 (24.0, 136.2), 99.3 (54.1, not attained [NA]), and 104.4 months (63.4, NA), respectively ($p < .0001$ for non-chelated vs. chelated groups). In the IPSS low-risk group, median (range) overall survival was 53.6 (4.1, 66.3) months for non-chelated patients and 98.7 (12.8, 103.8) months for chelated ≥ 6 months patients ($p = .028$). In the IPSS intermediate-1 group, overall survival was 44.7 (5.5, 151.6) months for non-chelated patients and 70.0 (12.5, 83.4) months for chelated ≥ 6 months patients ($p = .013$).

There were 171 (50.7%), 107 (40.7%), and 70 deaths (36.6%) in non-chelated, chelated, and chelated ≥ 6 months groups ($p = .0018$ for non-chelated vs. chelated ≥ 6 months groups), respectively. More than half of the deaths in the study could be attributed to MDS/AML (43.9%) and cardiac causes (15.5%; Fig. 2). For combined MDS/AML deaths, approximately 66% were attributed to MDS and 34% were attributed to AML. Given the substantial overlap in disease features and the absence of bone marrow biopsies near demise in most patients, it was often difficult to distinguish MDS progression from progression to AML as the final cause of death. An increased number and percentage of deaths secondary to non-myeloid malignancy among non-chelated patients was the only significant difference in causes of death among treatment groups ($p = .023$).

The percentage of patients who progressed to AML trended higher in non-chelated patients. In all, 30 (8.9%), 12 (4.6%), and 10 patients (5.2%) progressed to AML in the non-chelated, chelated, and chelated ≥ 6 months groups, respectively. Time from MDS diagnosis to progression to AML trended longer in both chelated groups (Fig. 3). Mean (standard deviation) time to progression was 27.3 (20.3), 40.6 (25.3), and 40.8 months (27.0) in the non-chelated, chelated, and chelated ≥ 6 months groups, respectively.

Baseline ferritin levels trended higher in chelated versus non-chelated patients (Table 3). There was no clear trend in ferritin levels among patient groups over the course of the 24 months studied.

### Table 3. Serum ferritin

<table>
<thead>
<tr>
<th>Serum ferritin (ng/mL)</th>
<th>Non-chelated $n = 337$</th>
<th>Chelated $n = 263$</th>
<th>Chelated ≥ 6 months $n = 191$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>258</td>
<td>232</td>
<td>169</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1353 (3–7379)</td>
<td>1513 (81–16,422)</td>
<td>1500 (81–16,422)</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>82</td>
<td>149</td>
<td>117</td>
</tr>
</tbody>
</table>
Serum ferritin (ng/mL) Non-chelated *n* = 337 Chelated *n* = 263 Chelated ≥ 6 months *n* = 191

<table>
<thead>
<tr>
<th></th>
<th>Non-chelated</th>
<th>Chelated</th>
<th>Chelated ≥ 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>1380 (22–6250)</td>
<td>1562 (30–10,646)</td>
<td>1505 (30–10,646)</td>
</tr>
</tbody>
</table>

12 months

*n* 61 140 111

Median (range) 1437 (5–11,647) 1962 (188–20,966) 1740 (188–20,966)

18 months

*n* 40 88 72

Median (range) 2000 (3–6901) 1610 (184–26,097) 1609 (184–26,097)

24 months

*n* 15 52 45

Median (range) 1540 (39–16,458) 1538 (363–8768) 1501 (363–8768)

No consistent trend was observed in serum ferritin levels.

Newly diagnosed or progressive cardiac conditions after study entry trended higher in the non-chelated group (155, 46.0%) versus the chelated (113, 43.0%) and chelated ≥ 6 months groups (76, 39.8%) (*p* = .167, non-chelated vs. chelated ≥ 6 months group). The frequency of other conditions appearing on study was similar among groups, including endocrine and hepatic conditions; renal, ocular, and auditory dysfunction; and new cytopenias.

The percentage of patients who received MDS therapies on study was similar across groups. In the entire registry population, erythropoietin and GCSF were used by 46.0% and 12.3% of patients, respectively. Azacitidine, decitabine, lenalidomide, thalidomide, and hydroxyurea were used by 28.3%, 17.5%, 11.2%, 0.3%, and 1.7% of patients, respectively. Cumulative duration of MDS therapy on study trended longer in chelated (median, 15 months [range, 0.1–39]) versus non-chelated patients (median, 9.9 months [range, 0.03–37]). Patients had received a median of 26 units (range, 0–620) transfused prior to enrollment and 1.85 units (range, 0–10.18) during any 4-week period on study.

In all, 29.1% of patients were receiving the following iron chelation therapy at baseline: 25.2% received deferasirox and 7.3% received deferoxamine. The percentage of chelated patients increased to 37% on study, in which 32.2% received deferasirox and 7.2% received deferoxamine. Some patients received different chelation therapies during the course of their treatment.

Median (range) duration of treatment in all patients who received chelation therapy was 17.4 (0.03, 146.53) months in chelated patients vs. 21.9 (6.18, 146.53) months in patients chelated ≥ 6 months (*p* < .0001).

3.3. Safety

Laboratory assessments for renal and hepatic function were performed at baseline and every 6 months thereafter. Baseline median serum creatinine levels (mg/dL) were in the normal range (1.1, 1.0, and 1.0 in non-chelated, chelated, and chelated ≥ 6 months patients, respectively) and were not different from baseline at any assessment (*p* > .3, all comparisons). Similarly, baseline liver transaminase levels were in the normal range. Median aspartate aminotransferase levels were 22.0 IU/L across all patient groups, and median ALT levels (IU/L) were 24.0, 29.5, and 30.0 in non-chelated, chelated, and chelated ≥ 6 months patients, respectively. Liver transaminase values did not increase from baseline at any assessment (*p* > .1, all comparisons). Safety assessments did not reveal any new concerns.

4. Discussion

Survival and clinical outcomes in chelated patients with MDS have not been evaluated prospectively in large, randomized trials. Nevertheless, National Comprehensive Cancer Network guidelines recommend the use of chelation therapy in iron-overloaded, lower-risk patients with MDS because of their longer predicted survival and the potential for developing organ damage secondary to iron overload [9]. However, it is difficult to determine the contribution of iron toxicity to morbidity and mortality in these patients because of their advanced age and the high prevalence of comorbidities driving non-leukemic mortality [10], [11]. This registry provides prospective information on the relationship between chelation therapy and survival and clinical outcomes in lower-risk, transfusion-dependent patients with MDS. Patients in the registry were treated predominantly in community cancer centers. Therefore, the study reflects care received by the majority of patients with MDS in the United States.

Median overall survival was statistically longer in chelated vs. non-chelated patients. Median time to death from MDS diagnosis was approximately half as long in non-chelated compared with chelated and chelated ≥ 6 months patients (52.2, 99.3, and 104.4 months, respectively; *p* < .0001). This pattern was also observed when patients were stratified by IPSS risk status, which suggests a survival benefit from chelation therapy can be realized across IPSS lower-risk patient groups. In low-risk patients, median overall survival in the chelated ≥ 6 months group vs. the non-chelated group was 98.7 vs. 53.6 months (*p* = .028). Similarly in Intermediate-1-risk patients, median survival in the chelated ≥ 6 months group vs. the non-chelated group was 70.0...
Comparison of 24-month outcomes in chelated and non-chelated lower-risk MDS patients

An observational study in patients with MDS by Rose et al. showed similar results with median time to death from diagnosis of 53 and 124 months in non-chelated and chelated patients, respectively (p ≤ .0003) [6]. It must be kept in mind interpreting these results, that the decision to chelate may have been influenced by the patient’s clinical status. Thus, the improved overall survival in chelated vs. non-chelated patients may have reflected a better initial clinical status as well as a potential benefit of chelation.

The rate of death from malignancies other than AML in this registry was only 4.3%. In comparing the chelated ≥6 months vs. non-chelated groups, there was a statistically significant difference in the rate of deaths due to non-myeloid malignancy (p = .023). While there were no other statistically significant differences in causes of deaths, between chelated ≥6 months and non-chelated patients, the percentage of patients dying from cardiac events, infection, and MDS/AML was higher in the non-chelated group. In the study by Rose et al., no differences in causes of death were seen [6]. Cardiac events, infections, and MDS/AML were the most common causes of death in this registry and the study by Rose et al. [6]. The lack of multivariate analysis to account for the contribution of comorbid conditions to mortality in either study may confound cause of death analysis.

There was a trend toward shorter AML-free survival in non-chelated patients over the 2-year analysis period. In all, 8.9%, 4.6%, and 5.2% of non-chelated, chelated, and chelated ≥6 months patients progressed to AML, respectively. The observational study by Rose et al. also showed a nonsignificant trend toward shorter AML-free survival in non-chelated patients. At 2.5 years, 34% of non-chelated and 17% of chelated patients had progressed to AML [6]. Kaplan–Meier analysis in the present study suggested that time to AML transformation may have been longer in chelated versus non-chelated patients (41 vs. 27 months, respectively).

In comparing baseline characteristics between the chelated and non-chelated patients, median age and risk stratification were similar; however, prevalence of cardiovascular disease at baseline was higher in the non-chelated group. Patients were classified lower-risk MDS by either IPSS, WHO, or FAB criteria, but some differences in subtype of anemia were observed among groups. The choice of risk classification criteria was determined by accepted practice at the time of initial diagnosis. Baseline serum ferritin levels trended higher in chelated versus non-chelated patients and remained higher in the chelated group over the course of the study. This trend may reflect the higher transfusion burden in chelated patients and thus their selection for chelation therapy. No clear pattern in serum ferritin levels was observed over the course of the study. These results are consistent with retrospective observations, in which mean serum ferritin levels did not predictably decrease after the initiation of chelation therapy [12]. However, significant reductions in serum ferritin levels were seen in interventional trials [7]. This disparity may reflect the different intensities and duration of chelation in a registry compared with a clinical trial.

Cardiac and vascular conditions were more common in non-chelated patients at baseline. The same trend was observed for cardiac conditions emerging while on study, in which 46%, 43%, and 40% of non-chelated, chelated, and chelated ≥6 months patients developed cardiac conditions, respectively (p = .167). The emergence of endocrine, hepatic, and renal conditions over the 2-year study was similar between chelated and non-chelated patients. The emergence of ocular and auditory dysfunction and new cytopenias was also similar between the chelated and non-chelated groups. There was a trend toward higher use of MDS-specific therapies in chelated patients compared with non-chelated patients. This trend toward higher use of MDS therapies in chelated patients may have contributed to their improved overall survival.

No specific safety concerns related to the use of chelation therapy were observed over the 24-month study period.

Limitations of these data include the fact that assessments were optional; therefore, some data points were not captured for every patient. In addition, there may have been some clinical bias in selecting patients for chelation. Patients with better overall performance status and predicted longer survival may be more likely to receive chelation. Potentially, this may have impacted clinical outcomes. It is unclear whether MDS therapy used in these patients affected clinical outcomes. Another question is whether the differences in baseline characteristics among the groups contributed to longer overall survival or the trend toward longer AML-free survival. Study strengths include the large number of patients enrolled in the registry along with the large number of participating study sites, which is likely to represent the heterogeneity of clinical practice.

The results of this registry are consistent with previous retrospective studies that show an association between chelation and increased overall survival in patients with MDS. Ongoing follow-up for the 5-year duration of the registry will provide further data on differences in outcomes between chelated and non-chelated patients.

Funding
This study was sponsored by Novartis Pharmaceuticals Corporation. Under the direction of the authors and funded by Novartis, Clay Isbell, MA, and Susan M Kaup, PhD, of Evidence Scientific Solutions provided medical writing assistance on the manuscript.

Conflict of interest
RML has received research funding from Novartis and Telik, and consultancy and research funding from Amgen and Incyte. GGM has received research funding from Novartis. CP and JE are employees of Novartis. BJM, LG, and ND declare no competing financial interests.

Acknowledgments
The authors would like to express their gratitude to the patients and their families, and the investigators and trial site personnel for participating in this study.

Contributions: RML collected and analyzed data, critically revised drafts, and approved final manuscript. BJM collected data, critically revised drafts, and approved final manuscript. CP designed study with steering committee input, analyzed data, critically revised drafts, and approved final manuscript. JE designed study with steering committee input, analyzed data, critically revised drafts, and approved final manuscript. LG collected data, critically revised drafts, and approved final
manuscript. ND collected data, critically revised drafts, and approved final manuscript. GGM participated in study design steering committee, collected and analyzed data, critically revised drafts, and approved final manuscript.

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