Original Study

Heterogeneity of Second-Line Treatment for Patients With Multiple Myeloma in the Connect MM Registry (2010-2016)

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Abstract

Connect MM is a large prospective observational US-based disease registry that was used to evaluate second-line treatment patterns in patients with relapsed or refractory multiple myeloma during a 5-year period, from 2010 to 2016. Treatment uptake was found to coincide with clinical milestones (ie, regulatory approvals, clinical study results), with growing preference for newer agents and triplet combinations over time.

Background: The treatment landscape for multiple myeloma (MM) has undergone recent changes with the regulatory approval of several new therapies indicated for second- and later-line disease. Using data from Connect MM, the largest multisite, primarily community-based, prospective, observational registry of MM patients in the United States, selection of second-line treatments was evaluated during a 5-year period from 2010 to 2016. **Patients and Methods:** Eligible patients were aged $\geq$ 18 years, had newly diagnosed MM $\leq$ 2 months before study entry, and were followed for up to 8 years. Patients who received $\geq$ 2 lines of therapy were analyzed. "Tepee" plots of stacked area graphs differentiated treatments by color to allow visualization of second-line treatment trends in MM patients. **Results:** As of February 2017, 855 of 2897 treated patients had progressed to second-line treatment. Treatment selection was heterogeneous; shifting patterns of treatment choices coincided with the approval status of newer agents. The most common treatment regimens in the early part of the decade were lenalidomide and/or bortezomib, with or without dexamethasone, with increasing use of newer agents (carfilzomib, pomalidomide, daratumumab, and elotuzumab) and triplet combinations over time. The influence of the baseline patient characteristics of age, history of diabetes, peripheral neuropathy, and renal function on treatment choice was also examined. **Conclusion:** These findings indicate that community physicians are current in their MM management practices, with uptake of new drugs and acquaintance with results of randomized clinical trials using combinations almost concurrent with their regulatory approval and publication.

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Introduction

Recent entry of new therapies into the multiple myeloma (MM) treatment landscape has been driven by evidence-based medicine, with continued impact from clinical trials. Although current treatment guidelines provide a list of preferred antimyeloma agents,[1] specific recommendations are lacking, resulting in wide variability in therapeutic approaches.

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Connect MM (NCT01081028) is the largest multisite, prospective, observational cohort study in the United States, with 3011 newly diagnosed MM (NDMM) patients enrolled from September 2009 through April 2016. Because a high proportion (84%) of patients are enrolled from community sites, Connect MM is a valuable resource for characterizing treatment uptake in daily practice. Connect MM has previously been used to describe the demographic and disease characteristics of NDMM patients in clinical practice[2] and how these differ compared to patients enrolled onto clinical trials,[3] to establish the low incidence of second primary malignancies associated with lenalidomide in this community-based population,[4] and to construct a matrix to predict individual patient risk of early mortality.[5]

The objective of this study was to describe second-line treatment patterns over time for patients with relapsed or refractory MM. The long-term prospective design of the Connect MM registry makes it a useful tool for describing salvage treatment options in MM. Patients were enrolled over the course of 7 years, allowing for longitudinal analyses of treatment patterns, captured both during the induction phase and throughout each patient's journey (for up to 8 years of follow-up).

Methods

Study Design

Connect MM was designed to characterize treatment and outcomes for patients with NDMM. Patients were enrolled onto 2 cohorts from September 2009 to April 2016 and were from community, academic, and government centers across the United States. Cohort 1 enrolled patients from September 2009 through December 2011; Cohort 2 enrolled patients from December 2012 through April 2016. Eligible patients were aged $\geq$ 18 years and must have been newly diagnosed with MM within 2 months before study entry. Patients were followed for up to 8 years. This analysis was conducted for the population of treated patients who received $\geq$ 2 lines of therapy. Data, including treatment choice, were captured at baseline and quarterly thereafter until death or discontinuation. To visualize trends in second-line treatment regimens used during the 5-year period (quarter 3-4, 2010, to quarter 1-2, 2016), we used a novel "Tepee" plot approach, consisting of a stacked area graph that differentiates treatments by color, with band width representing frequency of use at a given time interval; colors with wider bands signify more frequently used regimens.[6] Horizontal lines denote each sequential 6-month interval and represent 100% of patients initiating therapy during that time period.

Results

Disposition and Patient Characteristics

A total of 3011 patients were enrolled into 2 cohorts. As of the data cutoff date (July 7 2016), 2908 patients had initiated first-line treatment. Of those, 1095 continued to receive first-line treatment, 856 progressed and initiated second-line treatment, 491 died before second-line treatment, 366 discontinued before second-line treatment, and 100 progressed and stopped first-line treatment without initiating second-line treatment by the data cutoff date. At baseline, median age was 66 years (range, 32-93 years), with 37% of patients aged $\geq$ 70 years; 58% were men, and 84% were white. Patients had International Staging System stage I (17%), II (28%), or III (29%) MM (unspecified, 26%). A total of 84% of patients were enrolled in community centers, 15% in academic centers, and 1% in government centers.

Second-Line Treatment Patterns

The initial analysis showed heterogeneity in the use of various drugs and combinations for treatment in the second-line setting (Figure 1A). The most common treatment regimens used in late 2010 and early 2011 were bortezomib and dexamethasone; lenalidomide and dexamethasone; lenalidomide, bortezomib, and dexamethasone; bortezomib alone; lenalidomide alone; and cyclophosphamide, bortezomib, and dexamethasone. Regimens shifted over time, including increased use of carfilzomib and pomalidomide from 2012, coinciding with regulatory approval of these agents and availability through expanded access programs around the time of drug approval (Figure 1B). A smaller proportion (approximately 30%) of patients were categorized as having received "other" regimens, including multiple combination regimens, with no overriding trend (Figure 1B, Supplemental Table 1 in the online version).

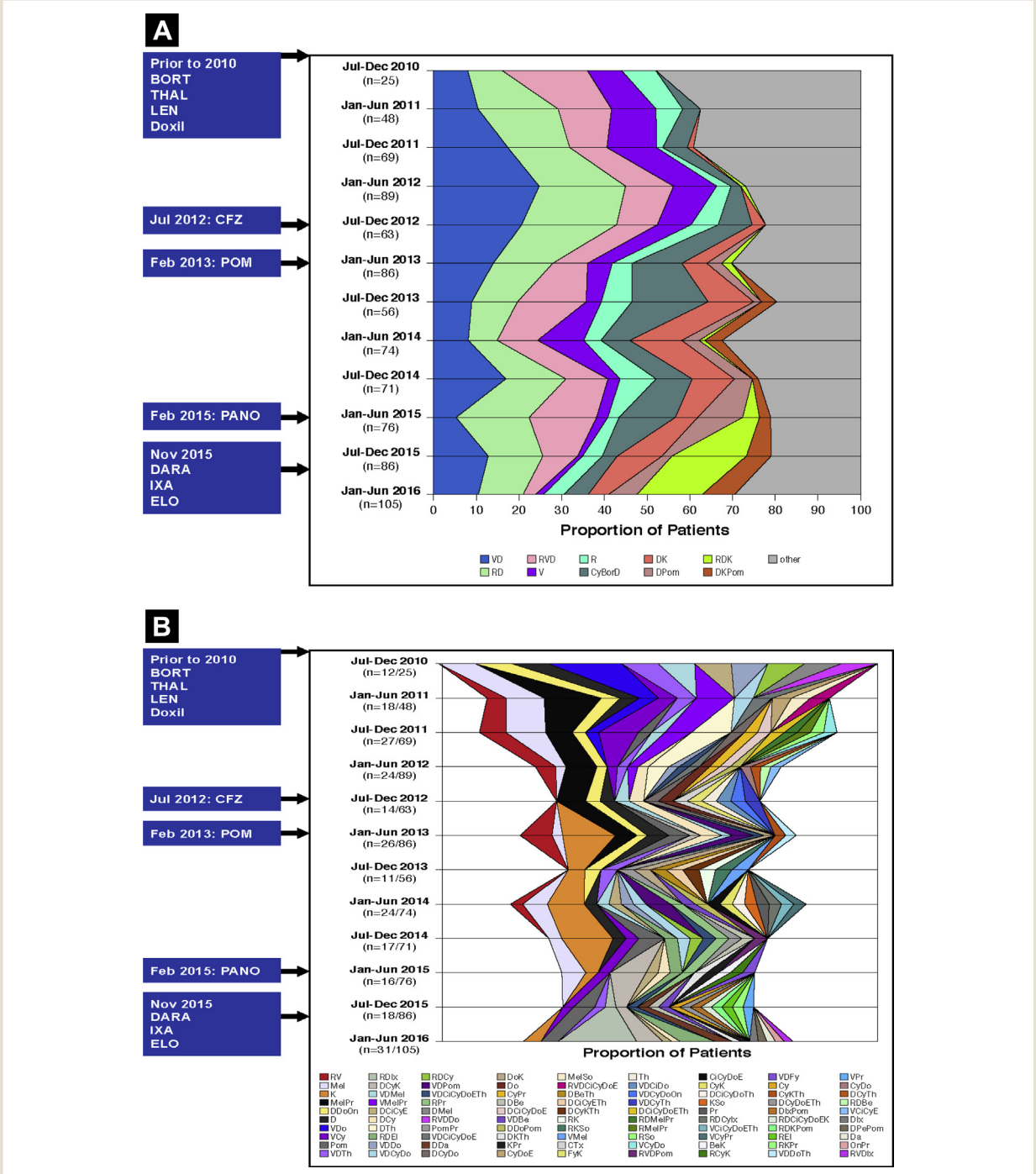
We also examined the use of therapies based on number of agents in a regimen and drug class. Triplet use, including combinations of chemotherapeutic agents, increased over time (Figure 2A). Use of alkylating agents and combinations such as dexamethasone, cyclophosphamide, etoposide, and cisplatin decreased after approval of pomalidomide and carfilzomib, whereas use of monoclonal antibodies increased after approval of daratumumab and elotuzumab (Figure 2B). At the most recent time point, immunomodulatory drugs and proteasome inhibitors, alone or in combination, comprised 80% of all treatments used (Figure 2B).

Factors Influencing Second-Line Treatment Choice

Treatment choices in second-line therapy were then characterized based on the presence or absence of potentially influential baseline characteristics. Age is an important factor for MM treatment decision by clinicians, because of its association with frailty, increased comorbidities, poor tolerability, and higher risk of complications.[7] Age was significantly associated with the number of drugs used ($P < .001$). Seventy-two percent (270/374) of patients aged $\geq$ 70 years received monotherapy or doublets versus 55% (264/481) of patients aged $<$ 70 years. Triplets or quadruplets (which included combinations of chemotherapeutic agents) were used more frequently in patients aged $<$ 70 years (45%, 217/481) than $\geq$ 70 years (28%, 104/374). Carfilzomib use was less frequent in patients aged $\geq$ 70 versus $<$ 70 years. Of the 148 patients who received carfilzomib, 95 (64%) were aged $<$ 70 years and 53 (36%) were aged $\geq$ 70 years. Use of novel therapy (immunomodulatory agents, proteasome inhibitors, and/or monoclonal antibodies) was similar in patients aged $<$ 70 and $\geq$ 70 years (Figure 2C and D) with approximately 80% of patients in either age group receiving these treatments. Age did not affect the use of steroids: 80% of patients aged $<$ 70 years (386/481) of patients aged $\geq$ 70 years (294/374) received steroids (Figure 2C and D). History of diabetes also did not affect the use of steroids: 79% (119/151) and 80% (554/694) of patients with and without a history of diabetes received steroids, respectively.

Peripheral neuropathy (PN) is a common complication in patients with MM and is frequently associated with certain anti-MM

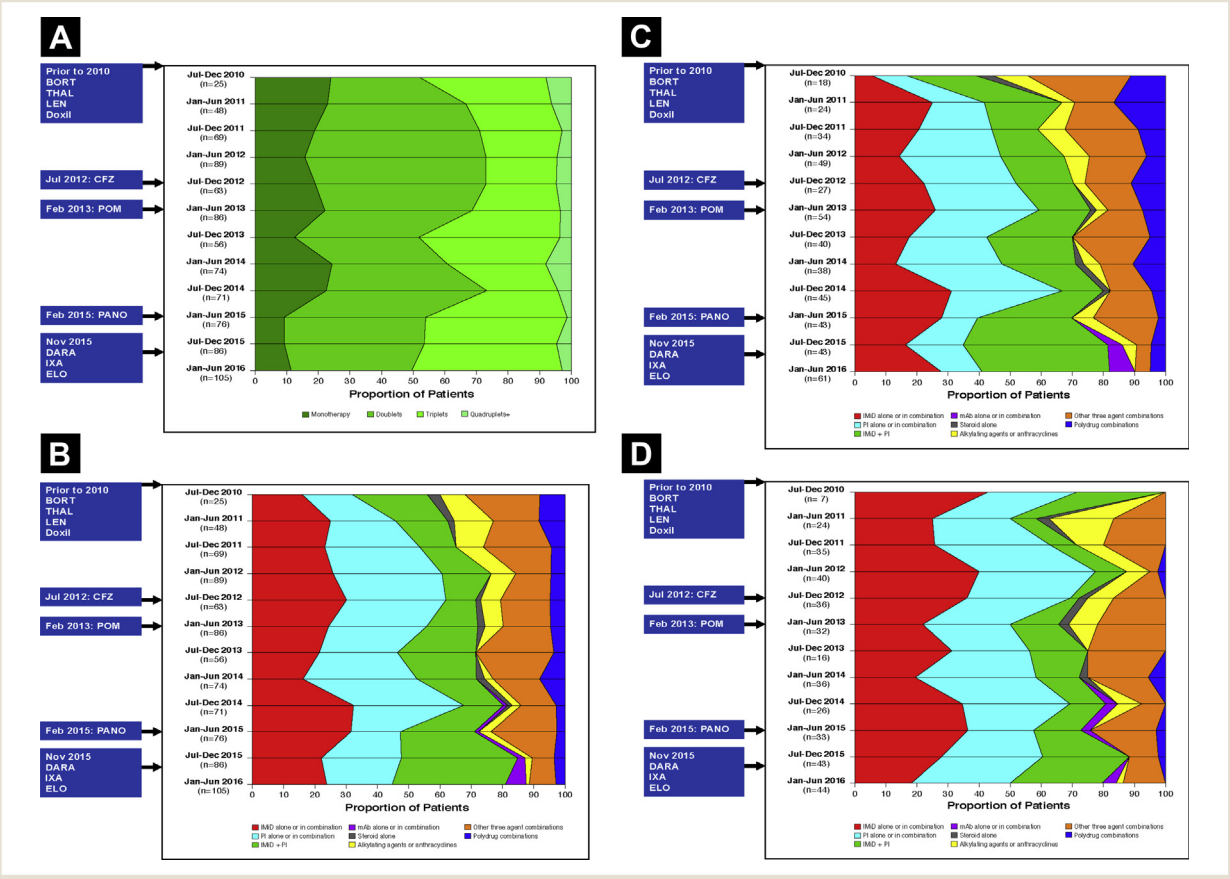
Figure 1 Second-Line Treatment Patterns, 2010-2016, Connect MM Registry. (A) Most Common Second-Line Treatments in 855 Patients. Gray Area at Right is Further Broken Down in (B). (B) Other Second-Line Treatments. Numbers Along *y*-axis are Total Number of Patients Initiating Therapy at Each Biannual Period



Abbreviations: Be = bendamustine; Bor = bortezomib; C = carboplatin; Ci = cisplatin; Cy = cyclophosphamide; D = dexamethasone; Da = daratumumab; Do = doxorubicin; E = etoposide; El = elotuzumab; Fy = panobinostat; Ix = ixazomib; K = carfilzomib; Mel = melphalan; On = vincristine; Pe = pembrolizumab; Pom = pomalidomide; Pr = prednisone; R = lenalidomide; So = methylprednisolone sodium succinate; Th = thalidomide; Tx = paclitaxel; V = bortezomib.

therapies, most notably thalidomide and bortezomib.[8-12] History of PN was significantly associated with number of drugs used ($P = .018$). Among patients with a history of PN, 77% of patients (51/66) received monotherapy or a doublet compared to 23% of patients (15/66) who received triplets or quadruplets. For patients without history of PN, monotherapy or doublets were administered to 60%

Figure 2 Second-Line Treatment Patterns by Agent and Patient Criteria. (A) Number of Agents (Single/Combination Regimens). (B) Agent Class. (C) Patient Age < 70 Years. (D) Patient Age ≥ 70 Years. Triplet and Quadruplet Regimens Include Patients Who Received Combinations of Chemotherapeutic Agents. Numbers Along *y*-axis are Total Number of Patients Initiating Therapy at Each Biannual Period



Abbreviations: IMiD = immunomodulatory agent; mAb = monoclonal antibody; PI = proteasome inhibitor.

(435/727) versus 40% (292/727) of patients who received triplets or quadruplets. Patients with a history of PN were less likely to receive bortezomib than those without (38%, 25/66, vs. 46%, 331/727).

Reduced renal function is a common comorbidity for patients with MM and an established marker of poor prognosis.[13,14] Renal impairment (RI) was not significantly associated with number of drugs used. Among patients with RI (defined as creatinine clearance ≤ 50 mL/min), 71% (155/218) used monotherapy or doublets compared to 29% (63/218) who used triplets or quadruplets. Among patients with normal renal function, monotherapy and doublet use was reported in 59% of patients (379/637) compared to 41% (258/637) who used triplets or quadruplets. The impact of renal function on lenalidomide use was minimal; it was administered in 35% of patients with RI (77/218) and 40% of patients without RI (255/637).

Impact of Novel Agent Use on Overall Survival

A total of 643 patients received novel agent therapy (immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies) and 212 patients received non–novel agent therapy in the second line. Baseline characteristics were generally similar for the 2 subgroups. The median overall survival from the start of second-line treatment was significantly longer for those who received novel agent therapy versus non–novel agent therapy (29.0 vs. 20.6 months; hazard ratio = 1.29; 95% confidence interval, 1.04; 1.60; $P = .022$).

Discussion

This analysis of the Connect MM registry indicates that, over a 5-year period, community physicians chose a wide range of second-line treatments for the management of patients with MM in first relapse. Regimens outside the 9 most frequently used were reported in up to 50% of patients and were diverse, illustrating personalization of treatments and combinations by physicians. Analyses of treatments based on patient characteristics led to some notable observations. Patients with a history of PN were less likely to receive bortezomib, presumably because of bortezomib-associated neurotoxic effects including worsening PN.[8,11,12] Use of lenalidomide appeared to be independent of renal function, whereas patients with

renal impairment were more likely to receive monotherapy or doublets as opposed to triplets or quadruplets. Older patients were less likely than younger patients to receive carfilzomib-containing regimens or the more aggressive triplet/quadruplet combinations.

The variability observed in second-line regimens for patients with relapsed or refractory MM reflects the ability of physicians to personalize treatments and combinations to optimize outcomes. Diverse treatment options allow a physician to select treatments based on an array of factors, including: (1) patient characteristics, such as age, frailty, and comorbidities (eg, renal impairment or PN); (2) disease biology, including disease risk, presence of plasmacytomas, and tumor burden among others; (3) prior therapies (progression on therapy, prior response duration); and (4) patient access and socioeconomics/healthcare coverage.

Until recently, novel agents have been approved either alone or in combination with steroids in the treatment of relapsed or refractory MM. Occasionally, when single-agent activity is limited, drugs are developed in combination (eg, bortezomib + panobinostat; elotuzumab + lenalidomide and dexamethasone). Clinical trials that lead to drug approvals are commonly designed with strict eligibility criteria that limit the enrollment of patients with significant comorbidities. Early or accelerated approval opportunities at regulatory agencies are made available for indications with urgent unmet needs, including relapsed or refractory MM, but uptake and utilization of new treatments depend largely on clinicians. Concerns arise when drug use is limited to single-agent use based on a narrow scope of approval (ie, dependent on evidence-based medicine). As a consequence, patients may not receive the full benefit of the drug due to compromised efficacy. Moreover, consensus guidelines from experts tend to adhere to the level of evidence, therefore providing little guidance on decision-making to clinicians. Ultimately, as more treatments enter the clinic, salvage therapy options are expected to grow. Registries such as Connect MM provide extensive databases that will be critical for informing clinicians of the impact of various treatment regimens in routine practice outside of a clinical trial setting. However, limitations of registries should be acknowledged, including the nonrandomized nature of the study, the lack of mandate for specific treatments (investigator selection) or response assessments, and the variations in treatment duration and intensity. As in any observational study, there is also potential for missing and erroneous data. However, a strength of this registry is the ability to query sites for more information on questionable data. Furthermore, by applying multiple imputation methods in the analyses, the impact of missingness should be substantially mitigated. Uptake of newer therapies is critical to improve the outcomes for patients. Our survival analysis showed that use of novel therapies (immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies) has increased the survival from the start of second line. These results are in alignment with another large population study from the Mayo Clinic showing improvement in survival for patients who receive novel agents.[15]

Conclusion

In conclusion, these results suggest that community physicians are current in their management practices, with uptake of new drugs and acquaintance with results of randomized clinical trials using combinations almost concurrent with their approval and publication, respectively. This is reflected by Surveillance, Epidemiology, and End Results data showing continued improvement in the 5-year relative survival ratio from 2009 through 2015.[16]

Clinical Practice Points

- The treatment landscape for MM has undergone recent changes with the regulatory approval of several new therapies indicated for second and later line disease.
- Using Connect MM, the largest multi-site, heavily community-based, prospective, observational registry of MM patients in the United States, selection of second-line treatments was evaluated over a 5-year period from 2010 to 2016.
- Shifting patterns of treatment choices coincided with the approval status of newer agents, with lenalidomide and/or bortezomib, with or without dexamethasone, representing the most common treatment regimens in the early part of the decade, and increasing use of newer agents (carfilzomib, pomalidomide, daratumumab, and elotuzumab) and triplet combinations over time.
- These findings show that community physicians are current in their MM management practices, with uptake of new drugs and acquaintance with results of randomized clinical trials using combinations almost concurrent with their regulatory approval and publication, respectively.

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Disclosure

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Supplemental Data

A supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2018.04.007.

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Supplemental Table 1 Percentages of Patients Receiving Other Second-Line Treatments, 2010-2016, Connect MM Registry

Treatment	Jul-Dec 2010 (N = 12/25)	Jan-Jun 2011 (N = 18/48)	Jul-Dec 2011 (N = 27/69)	Jan-Jun 2012 (N = 24/89)	Jul-Dec 2012 (N = 14/63)	Jan-Jun 2013 (N = 26/86)	Jul-Dec 2013 (N = 11/56)	Jan-Jun 2014 (N = 24/74)	Jul-Dec 2014 (N = 17/71)	Jan-Jun 2015 (N = 16/76)	Jul-Dec 2015 (N = 18/86)	Jan-Jun 2016 (N = 31/105)
RV	0	2.08	2.9	2.25	0	3.49	0	1.35	0	0	0	0
Mel	4	4.17	4.35	1.12	0	1.16	0	2.7	1.41	2.63	0	0
K	0	0	0	0	0	5.81	1.79	4.05	5.63	1.32	0	1.9
MelPr	0	6.25	2.9	3.37	3.17	2.33	0	0	0	0	0	0
DDoOn	4	2.08	1.45	1.12	1.59	1.16	1.79	0	0	0	0	0
D	4	2.08	0	0	1.59	2.33	0	1.35	1.41	0	0	0
VDo	8	2.08	1.45	0	0	0	0	0	0	0	0	0
VCy	0	2.08	4.35	1.12	0	0	0	0	1.41	1.32	1.16	0
Pom	0	0	1.45	0	0	2.33	0	0	2.82	0	2.33	1.9
VDTh	4	2.08	0	1.12	0	0	1.79	0	0	0	1.16	0
RDIx	0	0	0	0	0	0	0	0	0	0	1.16	8.57
DCyK	0	0	0	0	0	1.16	0	0	0	3.95	1.16	2.86
VDMel	4	0	1.45	0	1.59	0	0	1.35	0	0	0	0
VMelPr	0	4.17	2.9	1.12	0	0	0	0	0	0	0	0
DCiCyE	4	0	0	0	0	0	0	1.35	0	1.32	0	0.95
DCy	0	0	0	1.12	1.59	2.33	0	0	0	1.32	0	0.95
DTh	0	0	4.35	2.25	0	0	0	0	0	0	0	0
RDEl	0	0	0	0	0	0	0	0	1.41	1.32	0	3.81
VDDo	4	0	0	1.12	0	0	0	1.35	0	0	0	0
VDCyDo	0	2.08	0	0	0	1.16	0	1.35	1.41	0	0	0
RDCy	4	0	0	0	0	0	0	0	1.41	0	0	0
VDPom	0	0	0	0	0	2.33	0	2.7	0	0	0	0
VDCiCyDoETh	0	0	0	1.12	0	1.16	0	0	1.41	0	1.16	0
RPr	0	0	0	0	0	0	0	1.35	1.41	1.32	0	0
DMel	4	0	0	0	0	0	0	0	0	0	0	0
RVDDo	4	0	0	0	0	0	0	0	0	0	0	0
PomPr	0	0	0	0	0	0	1.79	0	1.41	0	0	0
VDCiCyDoE	0	2.08	0	1.12	0	0	0	0	0	0	0	0
DDa	0	0	0	0	0	0	0	0	0	0	1.16	1.9
DCyDo	0	0	1.45	0	1.59	0	0	0	0	0	0	0
DoK	0	0	0	0	0	1.16	1.79	0	0	0	0	0
Do	0	0	0	1.12	1.59	0	0	0	0	0	0	0
CyPr	0	0	1.45	1.12	0	0	0	0	0	0	0	0
DBe	0	0	0	0	0	0	0	0	1.41	0	1.16	0
DCiCyDoE	0	0	1.45	1.12	0	0	0	0	0	0	0	0
VDBe	0	0	0	0	0	0	0	1.35	0	0	1.16	0

Supplemental Table 1 Continued

Treatment	Jul-Dec 2010 (N = 12/25)	Jan-Jun 2011 (N = 18/48)	Jul-Dec 2011 (N = 27/69)	Jan-Jun 2012 (N = 24/89)	Jul-Dec 2012 (N = 14/63)	Jan-Jun 2013 (N = 26/86)	Jul-Dec 2013 (N = 11/56)	Jan-Jun 2014 (N = 24/74)	Jul-Dec 2014 (N = 17/71)	Jan-Jun 2015 (N = 16/76)	Jul-Dec 2015 (N = 18/86)	Jan-Jun 2016 (N = 31/105)
DDoPom	0	0	0	1.12	0	0	0	1.35	0	0	0	0
DKTh	0	0	0	0	0	0	0	0	0	1.32	0	0.95
KPr	0	0	0	0	0	0	0	0	0	1.32	0	0.95
CyDoE	0	2.08	0	0	0	0	0	0	0	0	0	0
MelSo	0	2.08	0	0	0	0	0	0	0	0	0	0
RVDCiCyDoE	0	2.08	0	0	0	0	0	0	0	0	0	0
DBeTh	0	0	0	0	0	0	1.79	0	0	0	0	0
DCiCyETh	0	0	0	0	0	0	1.79	0	0	0	0	0
DCyKTh	0	0	0	0	0	0	1.79	0	0	0	0	0
RK	0	0	0	0	0	0	1.79	0	0	0	0	0
RKSo	0	0	0	0	0	0	1.79	0	0	0	0	0
VMel	0	0	0	0	0	0	1.79	0	0	0	0	0
CTx	0	0	0	0	1.59	0	0	0	0	0	0	0
FyK	0	0	0	0	1.59	0	0	0	0	0	0	0
Th	0	0	0	0	1.59	0	0	0	0	0	0	0
VDCiDo	0	0	0	0	1.59	0	0	0	0	0	0	0
VDCyDoOn	0	0	0	0	1.59	0	0	0	0	0	0	0
VDCyTh	0	0	0	0	1.59	0	0	0	0	0	0	0
DCiCyDoETh	0	0	1.45	0	0	0	0	0	0	0	0	0
RDMelPr	0	0	1.45	0	0	0	0	0	0	0	0	0
RMelPr	0	0	1.45	0	0	0	0	0	0	0	0	0
RSo	0	0	1.45	0	0	0	0	0	0	0	0	0
VCyDo	0	0	1.45	0	0	0	0	0	0	0	0	0
RVDPom	0	0	0	0	0	0	0	0	1.41	0	0	0
CiCyDoE	0	0	0	0	0	0	0	1.35	0	0	0	0
CyK	0	0	0	0	0	0	0	1.35	0	0	0	0
DCiCyDoTh	0	0	0	0	0	0	0	1.35	0	0	0	0
KSo	0	0	0	0	0	0	0	1.35	0	0	0	0
Pr	0	0	0	0	0	0	0	1.35	0	0	0	0
RDCyIx	0	0	0	0	0	0	0	1.35	0	0	0	0
VCiCyDoETh	0	0	0	0	0	0	0	1.35	0	0	0	0
VCyPr	0	0	0	0	0	0	0	1.35	0	0	0	0
BeK	0	0	0	0	0	0	0	0	0	1.32	0	0
RCyK	0	0	0	0	0	0	0	0	0	1.32	0	0
VDFy	0	0	0	0	0	0	0	0	0	1.32	0	0

Supplemental Table 1 Continued

Treatment	Jul-Dec 2010 (N = 12/25)	Jan-Jun 2011 (N = 18/48)	Jul-Dec 2011 (N = 27/69)	Jan-Jun 2012 (N = 24/89)	Jul-Dec 2012 (N = 14/63)	Jan-Jun 2013 (N = 26/86)	Jul-Dec 2013 (N = 11/56)	Jan-Jun 2014 (N = 24/74)	Jul-Dec 2014 (N = 17/71)	Jan-Jun 2015 (N = 16/76)	Jul-Dec 2015 (N = 18/86)	Jan-Jun 2016 (N = 31/105)
Cy	0	0	0	0	0	0	0	0	0	0	1.16	0
CyKTh	0	0	0	0	0	1.16	0	0	0	0	0	0
DCyDoETh	0	0	0	0	0	0	0	0	0	0	1.16	0
DIxPom	0	0	0	0	0	0	0	0	0	0	1.16	0
RDCiCyDoEK	0	0	0	0	0	0	0	0	0	0	1.16	0
RDKPom	0	0	0	0	0	0	0	0	0	0	1.16	0
REl	0	0	0	0	0	0	0	0	0	0	1.16	0
RKPr	0	0	0	0	0	0	0	0	0	0	1.16	0
VDDoTh	0	0	0	0	0	1.16	0	0	0	0	0	0
VPr	0	0	0	0	0	0	0	0	0	0	1.16	0
CyDo	0	0	0	1.12	0	0	0	0	0	0	0	0
DCyTh	0	0	0	1.12	0	0	0	0	0	0	0	0
RDBe	0	0	0	1.12	0	0	0	0	0	0	0	0
VCiCyE	0	0	0	1.12	0	0	0	0	0	0	0	0
DIx	0	0	0	0	0	0	0	0	0	0	0	0.95
DPePom	0	0	0	0	0	0	0	0	0	0	0	0.95
Da	0	0	0	0	0	0	0	0	0	0	0	0.95
OnPr	0	0	0	0	0	0	0	0	0	0	0	0.95
RVDIx	0	0	0	0	0	0	0	0	0	0	0	0.95

Abbreviations: Be = bendamustine; C = carboplatin; Ci = cisplatin; Cy = cyclophosphamide; D = dexamethasone; Da = daratumumab; Do = doxorubicin; E = etoposide; El = elotuzumab; Fy = panobinostat; Ix = ixazomib; K = carfilzomib; Mel = melphalan; On = vincristine; Pe = pembrolizumab; Pom = pomalidomide; Pr = prednisone; R = lenalidomide; So = methylprednisolone sodium succinate; Th = thalidomide; Tx = paclitaxel; V = bortezomib.