Elotuzumab Plus Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Extended 4-Year Follow-Up and Analysis of Relative Progression-Free Survival From the Randomized ELOQUENT-2 Trial

Meletios A. Dimopoulos, MD; Sagar Lonial, MD; Keith A. Betts, PhD; Clara Chen, PhD; Miriam L. Zichlin, MPH; Alexander Brun, PharmD; James E. Signorovitch, PhD; Dinara Makenbaeva, MD; Sabeen Mekan, MD; Oumar Sy, PhD; Katja Weisel, MD; and Paul G. Richardson, MD

BACKGROUND: The randomized phase 3 ELOQUENT-2 study (NCT01239797) evaluated the efficacy and safety of elotuzumab plus lenalidomide and dexamethasone (ELd) versus lenalidomide and dexamethasone (Ld) in relapsed/refractory multiple myeloma (RRMM), and to date, has the longest follow-up of any monoclonal antibody in patients with RRMM. METHODS: In this extended 4-year follow-up of the ELOQUENT-2 trial, the coprimary endpoints of progression-free survival (PFS) and overall response rate as well as the secondary endpoint of overall survival were assessed. In the absence of head-to-head trials comparing Ld-based triplet regimens to guide treatment selection, 4 randomized controlled trials—ELOQUENT-2, ASPIRE, TOURMALINE-MM1, and POLLUX—were indirectly compared to provide insight into the relative efficacy of these regimens in RRMM. RESULTS: Data at 4 years were consistent with 2- and 3-year follow-up data: ELd reduced the risk of disease progression/death by 29% versus Ld (hazard ratio, 0.71) while maintaining safety. The greatest PFS benefit among the assessed subgroups was observed in patients at the median time or further from diagnosis (≥3.5 years) with 1 prior line of therapy, who had a 44% reduction in the risk of progression/death, and in patients in the high-risk category, who had a 36% reduction in favor of ELd. This regimen also showed a relative PFS benefit that was maintained beyond 50 months. CONCLUSIONS: The sustained PFS benefit and long-term safety of ELd at 4 years, similar to those observed at 2 and 3 years, support ELd as a valuable therapeutic option for the long-term treatment of patients with RRMM. Cancer 2018;124:4032–4043. © 2018 The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: ELOQUENT-2, elotuzumab, elotuzumab plus lenalidomide and dexamethasone (ELd), myeloma, progression-free survival.

INTRODUCTION
Multiple myeloma, a malignant clonal neoplasm of plasma cells of B-lymphocyte origin, accounted for approximately 18% of all new cases of hematologic malignancies in the United States in 2016. Advances in disease awareness and the use of proteasome inhibitors and immunomodulatory drugs have improved treatment outcomes and extended survival. Although multiple myeloma is associated with a 49% survival rate over 5 years, most patients eventually relapse or become refractory to treatment. Therefore, new treatment approaches are needed.

In the context of relapsed/refractory multiple myeloma (RRMM), therapeutic strategies combining agents with novel mechanisms of action, such as immuno-oncology (I-O) agents, with standard regimens may be key to overcoming drug resistance and providing durable responses that translate into long-term survival. Therefore, it is important to assess treatment outcomes with an immunotherapy-specific approach that captures the nuances particular to I-O therapy by the inclusion of long-term follow-up for survival endpoints as well as the analysis of landmark time points beyond the median and the hazard ratio (HR) over the study duration because it highlights the proportion of patients with durable responses and thus may provide evidence of a long-term survival benefit.
Elotuzumab is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody against signaling lymphocytic activation molecule F7 (SLAMF7), a glycoprotein expressed on myeloma cells and natural killer cells but not on normal nonlymphoid tissues. Elotuzumab exhibits a dual mode of antitumoral action that leads to targeted myeloma cell death by either directly activating natural killer cells or mediating antibody-dependent cellular cytotoxicity. The activation of natural killer cells and subsequent myeloma cell death are further enhanced by elotuzumab plus lenalidomide and dexamethasone (ELd) in comparison with either agent alone. ELd versus lenalidomide and dexamethasone (Ld) alone was assessed in the phase 3 ELOQUENT-2 study in patients with RRMM (NCT01239797). To date, ELd has the longest follow-up of any monoclonal antibody in patients with RRMM. In previous 2- and 3-year follow-up analyses, ELd reduced the relative risk of disease progression or death by 30% and 27%, respectively. Among patients receiving ELd versus Ld, progression-free survival (PFS) rates showed sustained relative improvements of 52% at 2 years (41% vs 27%) and 44% at 3 years (26% vs 18%). ELd treatment resulted in early, sustained separation of the Kaplan-Meier curves for both PFS and overall survival (OS). The greatest PFS benefit was demonstrated for patients with a time from the diagnosis of multiple myeloma longer than or equal to the median of 3.5 years and particularly for those patients 3.5 or more years from diagnosis who also had 1 prior line of therapy; this suggests that patients with slowly progressing disease may particularly benefit from the addition of elotuzumab to Ld.

Treatment selection and sequencing in RRMM are becoming increasingly complex, and clinicians have an increasing number of options when considering suitable treatment regimens for their patients. In addition to ELd, the current treatment landscape presents a myriad of combination therapies. The proteasome inhibitors carfilzomib and ixazomib and the anti-CD38 monoclonal antibody daratumumab are also approved for the treatment of RRMM in combination with Ld (ie, carfilzomib plus lenalidomide and dexamethasone [CLd], ixazomib plus lenalidomide and dexamethasone [ILd], and daratumumab plus lenalidomide and dexamethasone [DLd]). In separate randomized controlled phase 3 studies, these 4 regimens have shown varying magnitudes of PFS benefit in comparison with Ld. Although none of the reported trials included patients who progressed while on Ld, clinical judgment should be used to determine whether a patient may still be sensitive to treatment with an Ld-containing regimen. In the absence of head-to-head trials and because of the difficulties associated with assessing differing study designs, patient populations, and durations of follow-up, novel methodologies are necessary to evaluate the clinical benefit of different regimens. Guidelines developed by the United Kingdom’s National Institute for Health and Care Excellence, providing evidence-based guidance and advice for improving health and social care in England, support survival analysis methodologies such as those described by Guyot et al to reconstruct individual patient-level data, which allow indirect comparisons between clinical trial data. The use of such analyses, adopted by various bodies within health services research, may also help physicians to understand the relative durability of response of available treatments.

Given the survival benefits observed with elotuzumab with 2 and 3 years of follow-up, in this study, using extended 4-year follow-up data from ELOQUENT-2, we assessed the durability of response, including additional analyses of PFS and long-term safety, with ELd versus Ld. We also performed an indirect comparison using data from publicly available randomized controlled phase 3 clinical trials of patients with RRMM to describe time-specific effects on the relative PFS of triplet regimens with elotuzumab (ELd), carfilzomib (CLd), ixazomib (ILd), and daratumumab (DLd) in comparison with Ld to provide insight into the relative efficacy of these regimens in the RRMM setting.

**MATERIALS AND METHODS**

**ELOQUENT-2**

**Study design**

The study design for ELOQUENT-2 has been previously described (for additional details, see the supporting information). The protocol and its amendments received approval by the institutional review board or independent ethics committee at each study site prior to initiation.

**Patients**

Patients were 18 years old or older and had multiple myeloma, measurable disease, an Eastern Cooperative Oncology Group performance status ≤ 2, and a creatinine clearance ≥30 mL/min. Patients had received 1 to 3 prior lines of therapy and had documented disease progression after their most recent therapy. Patients were classified at the time of study entry according to International Myeloma Working Group risk categorization criteria.
as follows: high risk, which was defined as International Staging System stage II or III disease and a t(4;14) or del(17p) abnormality; low risk, which was defined as International Staging System stage I or II disease, an absence of t(4;14), del(17p), and 1q21 abnormalities, and an age younger than 55 years; or standard risk (when patients did not meet the definition of either high or low risk). All patients provided informed consent for participation in the study.

**Study endpoints**
The coprimary endpoints were PFS and overall response rate. OS was a secondary endpoint. Exploratory endpoints reported here include the duration of response and safety.

**Assessments**
Efficacy endpoints were centrally assessed on the basis of European Group for Blood and Marrow Transplantation criteria and a blinded review of tumor assessments by an independent review committee (see also the supporting information).

**Statistics**
The coprimary endpoint of PFS used the primary definition of PFS (see the supporting information) and an independent review committee assessment of tumor response, which was analyzed in all randomized patients. The calculation of the median PFS and its confidence intervals (CIs) is detailed in the supporting information. Post hoc analyses examined PFS stratified by the best overall response according to the International Myeloma Working Group risk criteria as well as the impact of the time from diagnosis and the number of prior lines of therapy on PFS. In the 4-year follow-up, an assessment of PFS was not prespecified, whereas an assessment of OS as an exploratory endpoint was predefined, but no statistical analysis was planned. All P values shown for 4-year data are descriptive and not adjusted for multiplicity; the P value for OS could not be provided to avoid interference with the final planned OS analysis (prespecified after the occurrence of 427 deaths). The cutoff date for all analyses was October 18, 2016.

**Relative PFS analysis**
Individual patient-level data were reconstructed from Kaplan-Meier PFS curves from ELOQUENT-2 (for ELd), ASPIRE (for CLd), TOURMALINE-MM1 (for ILd), and POLLUX (for DLd) with data available as of April 2017. Engauge Digitizer software was used by 2 independent researchers to trace and digitize the series of coordinates of each Kaplan-Meier PFS curve to ensure accuracy. The coordinates extracted from PFS curves, the reported numbers of events, and the numbers of patients at risk at various time points were used to generate individual patient-level data with the statistical program R (version 3.4.0) on the basis of the methods described by Guyot et al. With the reconstructed individual patient-level data, Kaplan-Meier PFS curves were created for each arm in each trial and were overlaid with the original available curves to validate the reconstructed individual patient-level data. The relative PFS benefit over time was calculated as the difference between the PFS estimate of each triplet regimen and the PFS estimate of Ld divided by the PFS estimate of Ld:

\[
\text{Relative PFS} (t) = \frac{S_{\text{ELd}} (t) - S_{\text{Ld}} (t)}{S_{\text{Ld}} (t)}
\]

where \( S(t) \) is the Kaplan-Meier PFS estimate at time \( t \) and \( X \) is elotuzumab, carfilzomib, ixazomib, or daratumumab. Relative PFS benefits at 6-, 12-, 24-, 36-, and 48-month time points are reported.

**RESULTS**

**ELOQUENT-2: 4-Year Follow-Up**

**Patient flow and recruitment**
A total of 646 patients were randomized in ELOQUENT-2; of the 635 who were treated, 319 received ELd, and 316 received Ld. In both treatment arms, the median time from diagnosis to randomization was 3.5 years. At 4 years, an analysis of PFS was performed after a minimum follow-up (last patient first visit until database lock) of 48 months. The median follow-up for patients without a PFS event (ie, progression or death) was 46 months (n = 132). The median number of completed cycles of treatment was 19 in the ELd arm and 14 in the Ld arm. Almost twice as many patients remained on treatment with ELd (n = 54 [17%]) in comparison with Ld (n = 28 [9%]). The main reason for discontinuation was disease progression, which was equally distributed in the 2 groups (n = 172 [54%]; Supporting Table 1).

**Baseline characteristics**
The baseline demographics and characteristics, which have been described elsewhere, were generally consistent between the treatment arms; they included the median age (67 years) and the disease stage at enrollment. The proportions of patients with high-risk (19% on ELd...
and 20% on Ld) and standard-risk disease (72% on ELd and 68% on Ld) were similar between the treatment arms. Identical proportions of patients in the 2 arms had del(17p): 32% of the patients if a definition of ≥1 cell positive for this cytogenetic deletion was used or 19% according to a post hoc analysis using a threshold of ≥60% of positive cells. The t(4;14) translocation was present in 9% of ELd patients and in 10% of Ld patients. The proportions of patients who had received prior bortezomib, thalidomide, or lenalidomide were also comparable between the arms.

**Efficacy**

**PFS**

A relative improvement of 50% was observed in the 4-year PFS rate among patients receiving ELd in comparison with Ld (21% vs 14%). The PFS HR at the 4-year follow-up was 0.71 (95% CI, 0.59-0.86; \( P = .0004 \)), which represents a 29% reduction in the risk of disease progression or death in favor of ELd (Fig. 1). Patients with a very good partial response or better in the ELd group showed a 35% reduction in the risk of progression or death in comparison with the Ld group (HR, 0.65; 95% CI, 0.46-0.94; \( P = .0208 \); Fig. 2).

PFS benefits in favor of ELd in the overall population were consistent across key patient subsets, including patients aged 75 years or older, patients at the median time or further from their diagnosis (≥3.5 years), and patients with high-risk cytogenetics (Fig. 3). In a post hoc analysis of the impact of the time from diagnosis and the number of prior lines of therapy on PFS, the greatest PFS benefit was observed in patients at the median time or further from diagnosis (≥3.5 years) with 1 prior line of therapy; this demonstrated a 44% reduction in the risk of progression or death in favor of ELd in patients with 1 prior line of therapy (HR, 0.56; 95% CI, 0.34-0.93; \( P = .0224 \); Fig. 4A). This was closely followed by a 41% risk reduction in patients with more than 1 prior line of therapy (HR, 0.59; 95% CI, 0.42-0.81; \( P = .0011 \); Fig. 4B). Patients less than the median time from diagnosis (<3.5 years) with 1 prior line of therapy had a 15% reduction in the risk of progression or death in favor of ELd (HR, 0.85; 95% CI, 0.61-1.16, \( P = .3030 \)), whereas those less than the median time from diagnosis (<3.5 years) with more than 1 prior line of therapy had a 10% risk reduction in favor of ELd (HR, 0.90; 95% CI, 0.60-1.36, \( P = .6198 \); Supporting Table 2).

Relative risk reductions for progression or death of 36% (HR, 0.64; 95% CI, 0.43-0.97; \( P = .0331 \)) and

![Figure 1. Kaplan-Meier curves of PFS for all randomized patients. CI indicates confidence interval; ELd, elotuzumab plus lenalidomide and dexamethasone; HR, hazard ratio; Ld, lenalidomide and dexamethasone; PFS, progression-free survival.](image-url)
23% (HR, 0.77; 95% CI, 0.62-0.95; P = .0159) were observed in favor of ELd in patients with high-risk and standard-risk disease, respectively (Supporting Fig. 1). High-risk patients treated with ELd had a median PFS that was 2 times longer than that of patients who received Ld (15 months with ELd [95% CI, 9.3-21.2 months] vs 7 months with Ld [95% CI, 5.7-12.0 months]; HR, 0.64; 95% CI, 0.43-0.97; P = .0331).

**Overall response rate**

The overall response rate was 79% with ELd and 66% with Ld, whereas the proportion of patients with a very good partial response or better was 35% in the ELd arm and 29% in the Ld arm (Supporting Table 3). The duration-of-response benefit was maintained over time (HR, 0.77; 95% CI, 0.62-0.95; P = .0176) with a median duration of response of 21 months (95% CI, 18-26 months) with ELd versus 17 months (95% CI, 15-19 months) with Ld (Supporting Table 3).

**OS**

The early separation of OS curves was maintained over time in favor of ELd with 4-year OS rates of 50% for ELd and 43% for Ld (HR, 0.78; 95% CI, 0.63-0.96; Fig. 5). The median OS was 48 months in the ELd arm and 40 months in the Ld arm (Fig. 5).

**Safety**

Extended safety data were similar between the treatment arms (Table 1). Adverse events (AEs) were reported in almost all patients (99%) in both treatment arms. Almost twice as many patients remained on therapy in the ELd arm (n = 54) in comparison with the Ld arm (n = 28). Fewer deaths occurred with ELd (n = 165) than Ld (n = 186), with the most common cause in both groups being disease progression (n = 109 in the ELd group and n = 120 in the Ld group). Death due to infection was numerically higher overall for the ELd group (n = 3) than the Ld group (n = 16), but the difference was not statistically significant (HR, 1.3; P = .4143). Deaths occurring within 60 days of the last dose as a result of infection were similarly distributed across the arms and were mainly due to sepsis (n = 3 in the ELd group and n = 3 in the Ld group) or pneumonia (n = 2 in the ELd group and n = 1 in the Ld group).

**Relative PFS Analysis**

Relative PFS was calculated at specific time points—6, 12, 24, 36, and 48 months—against the common Ld backbone used as the control treatment for all trials included in this analysis, and this allowed a time point–specific indirect comparison of relative PFS between these trials when data were available. Individual patient-level data...
from ELOQUENT-2 (for ELd), 6 ASPIRE (for CLd), 8 TOURMALINE-MM1 (for ILd), 9,15 and POLLUX (for DLD) 10,16 were reconstructed and validated (Supporting Fig. 2a-d). At least 12 months of PFS data were available for all 4 regimens; at the time of data lock for this analysis (April 2017), ELOQUENT-2 had the longest follow-up, with ELd PFS data available through 62 months, whereas PFS data were available through 12 months for DLd, through 30 months for ILd, and through 48 months for CLd. The relative PFS benefit over time is displayed in Figure 6, and the relative PFS benefits at the 6-, 12-, 24-, 36-, and 48-month time points are shown in Table 2. At 6 months of treatment, DLd and ELd had the numerically highest relative PFS benefit (18% and 15%, respectively), and they were followed by CLd (10%) and ILd (3%). At 12 months, DLd had the highest relative PFS benefit (43%), and it was followed by CLd (22%), ELd (20%), and ILd (10%). At 24 months, among the triplet regimens with available data, ELd had the numerically highest relative PFS benefit (46%), and it was followed by CLd (34%) and ILd (24%). ELd maintained its relative PFS benefit at 36 months (46%), but a decline was observed for CLd (19%). The relative PFS benefit for ELd was maintained beyond 50 months (Table 2 and Fig. 6).

**DISCUSSION**

The 4-year data reported here from ELOQUENT-2 represent the longest follow-up to date of any monoclonal

| Event                              | ELd (n = 318) | Ld (n = 317) |
|------------------------------------|--------------|--------------|
| Total                              | Any Grade    | Grade 3 or 4 | Any Grade    | Grade 3 or 4 |
| Common hematologic toxic effects, No. (%) a | 316 (99)     | 246 (77)     | 314 (99)     | 216 (68)     |
| Lymphocytopenia                    | 316 (99)     | 250 (79)     | 311 (98)     | 155 (49)     |
| Anemia                             | 309 (97)     | 64 (20)      | 301 (96)     | 66 (21)      |
| Thrombocytopenia                   | 268 (84)     | 67 (21)      | 248 (78)     | 65 (21)      |
| Neutropenia                        | 263 (83)     | 115 (36)     | 282 (89)     | 144 (45)     |
| Common nonhematologic adverse effects, No. (%) b |             |              |             |              |
| General disorders                  |              |              |             |              |
| Fatigue                            | 154 (48)     | 32 (10)      | 130 (41)     | 26 (8)       |
| Pyrexia                            | 128 (40)     | 9 (3)        | 80 (25)      | 10 (3)       |
| Gastrointestinal disorders         |              |              |             |              |
| Diarrhea                           | 157 (49)     | 18 (6)       | 120 (38)     | 15 (5)       |
| Constipation                       | 115 (36)     | 4 (1)        | 89 (26)      | 1 (<1)       |
| Musculoskeletal or connective-tissue disorders |            |              |             |              |
| Muscle spasm                       | 98 (31)      | 2 (1)        | 84 (26)      | 3 (1)        |
| Back pain                          | 100 (31)     | 18 (6)       | 93 (29)      | 15 (5)       |
| Other disorders                    |              |              |             |              |
| Cough                              | 108 (34)     | 1 (<1)       | 61 (19)      | 0            |
| Infections                         | 266 (84)     | 105 (33)     | 239 (75)     | 81 (26)      |
| Vascular disorders                 | 128 (40)     | 33 (10)      | 90 (28)      | 25 (8)       |
| Cardiac disorders                  | 70 (22)      | 15 (5)       | 59 (19)      | 24 (8)       |
| Pneumonia                          | 66 (21)      | 45 (14)      | 48 (15)      | 31 (10)      |
| SPMs c                             | 53 (17)      | 30 (9)       | 35 (11)      | 18 (6)       |
| Lymphopenia                        | 41 (13)      | 27 (8)       | 23 (7)       | 12 (4)       |
| Herpes zoster infection            | 22 (7)       | 5 (2)        | 8 (3)        | 2 (1)        |
| Sepsis                             | 6 (2)        | 4 (1)        | 9 (3)        | 3 (1)        |

Abbreviations: ELd, elotuzumab plus lenalidomide and dexamethasone; LD, lenalidomide and dexamethasone; SPM, second primary malignancy.

a Listed are adverse events reported in ≥30% of patients in the ELd or LD arm.

b SPMs included benign, malignant, and unspecified neoplasms (including cysts and polyps), including 1 case of malignant melanoma in situ (in the LD arm) and 1 case each of a melanocytic nevus and skin cancer (both in the ELd arm).

Cancer October 15, 2018 4037
Figure 3. Progression-free survival by predefined subgroups. *Patients were considered del(17p)-positive if any cell was positive. CI indicates confidence interval; ELd, elotuzumab plus lenalidomide and dexamethasone; HR, hazard ratio; ISS, International Staging System; Ld, lenalidomide and dexamethasone.

Table 2. Relative PFS Benefit at 6, 12, 24, 36, and 48 Months

| Triplet Regimen | Relative PFS Benefit, % |
|-----------------|-------------------------|
|                 | 6 mo | 12 mo | 24 mo | 36 mo | 48 mo |
| ELd             |      |       |       |       |       |
| CLd             |      |       |       |       |       |
| ILd             |      |       |       |       |       |
| DLd             |      |       |       |       |       |

Abbreviations: CLd, carfilzomib plus lenalidomide and dexamethasone; DLd, daratumumab plus lenalidomide and dexamethasone; ELd, elotuzumab plus lenalidomide and dexamethasone; ILd, ixazomib plus lenalidomide and dexamethasone; NA, not available for the specified time; PFS, progression-free survival.
Figure 4. Kaplan-Meier curves of PFS for patients at the median time or further from diagnosis (≥3.5 years) who had (A) 1 prior line of therapy or (B) more than 1 prior line of therapy. CI indicates confidence interval; ELd, elotuzumab plus lenalidomide and dexamethasone; HR, hazard ratio; Ld, lenalidomide and dexamethasone; NA, not available; PFS, progression-free survival.
Figure 5. Kaplan-Meier curves of OS. CI indicates confidence interval; ELd, elotuzumab plus lenalidomide and dexamethasone; HR, hazard ratio; Ld, lenalidomide and dexamethasone; OS, overall survival.

Figure 6. Relative PFS benefit over time. CLd indicates carfilzomib plus lenalidomide and dexamethasone; DLd, daratumumab plus lenalidomide and dexamethasone; ELd, elotuzumab plus lenalidomide and dexamethasone; ILd, ixazomib plus lenalidomide and dexamethasone; Ld, lenalidomide and dexamethasone; PFS, progression-free survival.
antibody in patients with RRMM. ELd showed a clinically relevant improvement in PFS, with a sustained 29% reduction in the risk of progression or death, consistent with 2- (30%) and 3-year follow-up data (27%). The sustained relative improvement in the PFS rate in favor of ELd in comparison with Ld was maintained throughout the 4-year follow-up (52% at 2 years, 44% at 3 years, and 50% at 4 years). To our knowledge, ELOQUENT-2 is the only randomized trial in the RRMM setting in which PFS data have been centrally assessed continuously after the median PFS was reached. In other large contemporary studies such as ASPIRE, TOURMALINE-MM1, and POLLUX, all subsequent reviews after the median PFS was reached were according to the treating physician. This unique feature of the ELOQUENT-2 trial provides a more accurate assessment of long-term PFS in comparison with local laboratory evaluations. Furthermore, the early and persistent separation of the PFS and OS curves demonstrates the durable long-term clinical benefit provided by ELd.

A post hoc analysis demonstrated that the PFS benefit of ELd was consistent across all key subgroups, including patients aged 75 years or older, patients at the median time or further from diagnosis (≥3.5 years), and patients with high-risk disease. The greatest benefit among the subgroups assessed was seen in patients at the median time or further from diagnosis with 1 prior line of therapy, who had a 44% reduction in the risk of progression or death. A better response to additional treatment has been seen with other I-O therapies in patients who have higher risk disease, as observed with nivolumab in other tumor types; however, the reasons for such an association between high risk and improved response are not clear. In ELOQUENT-2, almost all patients (98%) were assessed for risk on the basis of their cytogenetic profile; 19% of these patients tested positively in at least 60% of cells for del(17p), a genetic event associated with high-risk disease. Although the cytogenetic profile was unknown for a considerable number of patients in ELOQUENT-2, these results suggest that ELd continues to demonstrate long-term efficacy even in patients with a high cytogenetic risk.

Overall, the data presented here support the use of ELd in the context of providing a durable, clinically relevant survival benefit to patients with RRMM. Elotuzumab, in combination with Ld, is one of several regimens recommended by the National Comprehensive Cancer Network for the treatment of patients with RRMM. However, establishing efficacy with respect to Ld is insufficient to inform clinical treatment decisions, and the absence of head-to-head trials adds to the complexity of treatment selection among different regimens with a common Ld backbone. We used an innovative, descriptive approach based on methods described by Guyot et al and recognized by the National Institute for Health and Care Excellence to investigate the relative PFS benefit of the triplet regimens investigated in the ELOQUENT-2, ASPIRE (carfilzomib), TOURMALINE-MM1 (ixazomib), and POLLUX (daratumumab) trials.

ELd showed a relative PFS benefit that was maintained beyond 50 months, and this supports ELd as a feasible treatment regimen for extending survival in patients with RRMM. Although the potential of daratumumab in combination with Ld for long-term durability has yet to be supported by evidence because of the short follow-up, 2 recent network meta-analyses have suggested that DLd may be the best treatment option for patients with RRMM. Although one analysis compared HRs for PFS from all publicly available randomized controlled phase 3 trials, the other analysis described a Bayesian network meta-analysis that compared the clinical efficacy of Ld-containing regimens. In our study, instead of using a network meta-analysis to compare treatments, we applied a metric of relative PFS benefit. The approach used here allowed comparisons between triplet regimens at specific time points (6, 12, 24, 36, and 48 months) when data were available as opposed to the overall duration of each trial; this minimized the impact of different follow-up durations. Comparisons beyond 24 months excluded the TOURMALINE-MM1 and POLLUX trials because of insufficient follow-up duration.

The proteasome inhibitors carfilzomib and ixazomib, in combination with Ld, showed initial relative PFS benefits in comparison with Ld alone, which were diminished by the end of data availability. However, this may be explained, at least for the carfilzomib-based triplet regimen, by the fact that carfilzomib was discontinued after 18 cycles (approximately 18 months), and patients received only Ld from this cycle onward. Furthermore, data on the long-term safety of carfilzomib were not available at the start of the ASPIRE study, and this, therefore, limits the long-term analysis of carfilzomib treatment.

The relative PFS methodology is descriptive and not a statistical comparison and has several limitations. First, the relative PFS at the far right of each Kaplan-Meier curve should be interpreted with caution because there is high uncertainty due to the very few patients at risk at these time points. Second, the different lengths of
follow-up reported in each trial at the time of this analysis limit potential long-term comparisons; nonetheless, it is valid for each time point with data available. Indeed, the relative PFS analysis should be performed again when updated CLd, ILd, and DLd follow-up data are published. In light of ELd providing a survival advantage sustained over 4 years, this methodology could also be applied to OS when the final analyses for ELd, CLd, ILd, and DLd are published. In the case of ELOQUENT-2, this will occur after 427 deaths; this number has yet to be reached. Third, findings from this approach should also be interpreted with some caution because of differences in the study design, treatment duration, or patient populations. However, the baseline characteristics for all 4 trials, including age, median number of prior lines of therapy, and Ld dosing, were comparable. Fourth, we did not consider differences in the modes of administration. Both elotuzumab and daratumumab were given intravenously, whereas carfilzomib was administered as an infusion, and ixazomib was given orally. The differences in the modes of administration and their efficacy are beyond the scope of this study. Fifth, because our analysis focused on relative PFS, we did not account for the safety profile and AEs reported. Finally, we assessed only regimens with an Ld backbone and thus are unable to comment on the relative PFS of studies with non–Ld-based regimens.

The extended follow-up for ELd showed that, in addition to a durable clinical benefit, the safety and tolerability profile was also maintained. The safety profile over the extended (4-year) analysis remained relatively similar between the ELd and Ld arms and was consistent with the 2- and 3-year findings. Both the total number of AEs and the number of exposure-adjusted AEs were similar between the ELd and Ld groups. The higher rates of specific AEs in the ELd arm, most notably infections and second primary malignancies, were a reflection of the longer treatment duration, as indicated by the exposure-adjusted analysis. The efficacy of ELd is, therefore, retained over time without safety being compromised.

The proteasome inhibitors carfilzomib and ixazomib, in combination with Ld (CLd and ILd, respectively), are generally well tolerated, although carfilzomib has been associated with cardiac complications. Higher rates of neutropenia and infusion-related reactions have been reported with daratumumab in combination with Ld despite the short follow-up. Further follow-up is necessary to confirm whether the tolerability and efficacy of DLd will be maintained over time and with a longer exposure, as was seen for ELd.

Overall, the presented results demonstrate that the sustained efficacy of ELd observed in ELOQUENT-2 is further supported by findings from the relative PFS analysis. This, combined with the well-established long-term safety and tolerability profile, supports this regimen as a valuable treatment option offering long-term benefits to patients with RRMM. The favorable long-term risk-benefit profile of ELd at present distinguishes it from other Ld-based regimens.

FUNDING SUPPORT
This study was funded by Bristol-Myers Squibb in collaboration with AbbVie Biotherapeutics.

CONFLICT OF INTEREST DISCLOSURES
Meletios A. Dimopoulos has received honoraria from and served as a consultant for Amgen, Celgene, Janssen, Takeda, and Novartis. Sagar Lonial has served as a consultant or in an advisory role for Bristol-Myers Squibb, Celgene, Janssen Oncology, Millennium, Novartis, Onyx, and Sanofi and is a member of the editorial board for Cancer. Keith A. Betts, Miriam L. Zichlin, and James E. Signorovitch are employees of Analysis Group, Inc, which received consultancy fees from Bristol-Myers Squibb for this project. Clara Chen and Alexander Brun are employees of Bristol-Myers Squibb. Disana Makenbaeva, Saben Mekan, and Oumar Sy are employees of and own stock in Bristol-Myers Squibb. Katja Weisel has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Onyx, Novartis, and Takeda; has served as a consultant or in an advisory role for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Onyx, and Takeda; has received research funding from Amgen, Celgene, Janssen, and Sanofi; and has received travel/accommodation/expenses from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, and Takeda. Paul G. Richardson has served as a consultant or in an advisory role for Genmab and has received research funding from Celgene and Millennium.

AUTHOR CONTRIBUTIONS
Meletios A. Dimopoulos: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing—review and editing. Sagar Lonial: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing—review and editing. Keith A. Betts: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing—review and editing. Clara Chen: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing—review and editing. Miriam L. Zichlin: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing—review and editing. Alexander Brun: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing—review and editing. James E. Signorovitch: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources,
and writing–review and editing. **Dinara Makenbaeva**: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, and writing–review and editing. **Sabeen Mekan**: Conceptualization, investigation, methodology, formal analysis, and validation. **Oumar Sy**: Formal analysis, validation, software, and writing–review and editing. **Katja Weisel**: Conceptualization, investigation, methodology, formal analysis, validation, and writing–review and editing. **Paul G. Richardson**: Conceptualization, investigation, methodology, data curation, formal analysis, investigation, resources, validation, and writing–review and editing.

**REFERENCES**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7-30.
2. Hoering A, Durie B, Wang H, Crowley J. End points and statistical considerations in immuno-oncology trials: impact on multiple myeloma. *Future Oncol*. 2017;13:1181-1193.
3. Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res*. 2008;14:2775-2784.
4. Collins SM, Bakan CE, Swartzel GD, et al. Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. *Cancer Immunol Immunother*. 2013;62:1841-1849.
5. Balasa B, Yun R, Belmar NA, et al. Elotuzumab enhances natural killer cell activation and myeloma cell killing through interleukin-2 and TNF-alpha pathways. *Cancer Immunol Immunother*. 2015;64:61-73.
6. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621-631.
7. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. *Br J Haematol*. 2017;178:896-905.
8. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed myeloma. *N Engl J Med*. 2015;372:142-152.
9. Moreau P, Massi T, Grasso N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374:1621-1634.
10. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:1319-1331.
11. Guyot P, Ades AE, Ouweens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMJ Med Res Methodol*. 2012;12:9.
12. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trial—extrapolation with patient-level data. Report by the Decision Support Unit, March 2016. https://sheart.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/NICE-DSU-TSD-Survival-analysis.updat-ed-March-2013.v2.pdf. Accessed March 18, 2018.
13. Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;28:269-277.
14. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease resp presented at: 58th American oncology and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol*. 1998;102:1115-1123.
15. Center for Drug Evaluation and Research. Statistical review and evaluation: Ninlaro (208462Orig1s0000). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000StatR.pdf. Accessed October 13, 2017.
16. Usmani SZ, Dimopoulos MA, Belch A, et al. Efficacy of daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma patients with 1 to 3 prior lines of therapy: updated analysis of POLLUX. Oral presented at: 58th American Society of Hematology Annual Meeting & Exposition; December 3–6, 2016; San Diego, CA. Oral Presentation 1151.
17. Mitchell M, Mufakhadinov B, Winchen T, et al. Engauge Digitizer [software]. https://markummitchell.github.io/engauge-digitizer. Accessed September 5, 2017.
18. R-Core Team. R version 3.4.0 [software]. https://www.R-project.org/. Accessed November 15, 2017.
19. Kadid T, Kantarjian H, Jabbour E, et al. Nivolumab maintenance therapy for patients with high-risk acute myeloid leukemia (AML) in remission. Poster presented at: 22nd Congress of the European Hematology Association; June 22–25, 2017; Madrid, Spain. Poster P211.
20. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377:1824-1835.
21. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: multiple myeloma. Version 3.2016. https://www.nccn.orgprofessionals/physician_gls/f_guidelines.asp. Accessed February 2, 2016.
22. van Beurden-Tan CHY, Franken MG, Blommeestaet HM, Uyl-de Groot CA, Sonneveld P. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. *J Clin Oncol*. 2017;35:1312-1319.
23. Dimopoulos MA, Kaufman JL, White D, et al. A comparison of the efficacy of immunomodulatory-containing regimens in relapsed/refractory multiple myeloma: a network meta-analysis. *Clin Lymphoma Myeloma Leuk*. 2018;18:163-173.
24. Atrash S, Tulloss A, Panozzo S, et al. Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib. *Blood Cancer J*. 2015;5:e272.