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# 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

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## Summary

The randomized phase III ELOQUENT-2 study (NCT01239797) evaluated the efficacy and safety of elotuzumab + lenalidomide/dexamethasone (ELd) *versus* lenalidomide/dexamethasone (Ld) in relapsed/refractory multiple myeloma. ELd reduced the risk of disease progression/death by 30% *versus* Ld (hazard ratio [HR] 0·70). Median time from diagnosis was 3·5 years. We present extended 3-year follow-up data. Endpoints included progression-free survival (PFS), overall response rate (ORR) and interim overall survival (OS). Exploratory *post-hoc* analyses included impact of time from diagnosis and prior lines of therapy on PFS, and serum M-protein dynamic modelling. ORR was 79% (ELd) and 66% (Ld) ($P = 0{\cdot}0002$). ELd reduced the risk of disease progression/death by 27% *versus* Ld (HR 0·73; $P = 0{\cdot}0014$). Interim OS demonstrated a trend in favour of ELd ($P = 0{\cdot}0257$); 1-, 2- and 3-year rates with ELd *versus* Ld were: 91% *versus* 83%, 73% *versus* 69% and 60% *versus* 53%. In patients with ≥ median time from diagnosis and one prior therapy, ELd resulted in a 53% reduction in the risk of progression/death *versus* Ld (HR 0·47). Serum M-protein dynamic modelling showed slower tumour regrowth with ELd. Adverse events were comparable between arms. ELd provided a durable and clinically relevant improvement in efficacy, with minimal incremental toxicity.

**Keywords:** multiple myeloma, elotuzumab, monoclonal antibody, progression-free survival, overall survival.

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Next-generation proteasome inhibitors, including ixazomib and carfilzomib, and novel immuno-oncology agents, including daratumumab and elotuzumab, received US Food and Drug Administration (FDA) approval for multiple myeloma (MM) treatment between November 2015 and January 2016 (Amgen, 2016; Food and Drug Administration, 2016a,b,c), demonstrating the rapidly evolving treatment landscape. The introduction of immuno-oncology agents that target the immune system may lead to further improvements, as they have the potential to induce a sustained immune response translating into durable clinical benefit. Elotuzumab, an immunostimulatory monoclonal antibody, recognizes signalling lymphocytic activation molecule F7 (SLAMF7), a protein expressed by myeloma and natural killer cells. Elotuzumab elicits its effect via a dual mechanism of action, both by directly activating natural killer cells and by mediating antibody-dependent cell-mediated cytotoxicity via the CD16 pathway to cause targeted myeloma cell death (Hsi *et al*, 2008; Collins *et al*, 2013). ELOQUENT-2 (NCT01239797), a phase III study, compared elotuzumab + lenalidomide and dexamethasone (ELd) *versus* lenalidomide and dexamethasone (Ld) (Lonial *et al*, 2015). Previously, following a median follow-up of 24·5 months, it was reported that this trial met its primary endpoint, demonstrating that ELd resulted in a significant 30% reduction in the risk of disease progression or death *versus* Ld (hazard ratio [HR] 0·70; 95% confidence interval [CI], 0·57–0·85; $P < 0·001$). Multivariate Cox regression analysis adjusting progression-free survival (PFS) for baseline characteristics suggested that patients diagnosed with MM ≥3·5 years before entering the study (median time from diagnosis to randomization) had the greatest benefit in PFS (HR 0·55, 95% CI, 0·44–0·70; $P < 0·001$). Overall response rate (ORR) was 79% (95% CI, 74–83%) with ELd versus 66% (95% CI, 60–71%) with Ld ($P < 0·001$) (Lonial *et al*, 2015). The addition of elotuzumab to Ld was well tolerated, with minimal added toxicity. At the time of the analysis, 35% of patients were still on therapy in the ELd group *versus* 20% in the Ld group. Based on these findings, the FDA approved ELd for the treatment of patients with MM who have received one to three previous therapies (http://packageinserts.bms.com/pi/pi_empliciti.pdf; National Cancer Institute, 2015). More recently, ELd received approval for use in Europe in adult patients with MM who have received at least one prior therapy (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Produc

t_Information/human/003967/WC500206673.pdf). In ELOQUENT-2, 20% of patients were 75 years of age or older and the study included a high proportion of patients (30%) with a high-risk cytogenetic profile (Lonial *et al*, 2015). Herein, we describe extended 3-year follow-up efficacy and safety data from ELOQUENT-2, as well as exploratory *post-hoc* analyses on the effect of time from diagnosis and number of prior lines of therapy on PFS, and rates of tumour shrinkage and regrowth following ELd treatment.

## Methods

The study design for ELOQUENT-2 has been described (Lonial *et al*, 2015) (see Data S1). Institutional review board approval and written informed consent were obtained.

### *Patients*

Patients were aged 18 years or older and had MM, measurable disease and creatinine clearance of 30 ml/min or higher. Patients received one to three previous therapies and had documented disease progression after their most recent therapy.

### *Objectives*

Co-primary endpoints were PFS (provided progression/death occurred within 10 weeks of the last adequate tumour assessment; see Data S1 for primary definition of PFS) and ORR (partial response or better). Secondary endpoints included overall survival (OS; time from randomization to death from any cause). Exploratory *post-hoc* analyses assessed time to next treatment (TTNT; time from randomization to earliest start date of subsequent therapy; patients who did not receive subsequent therapy were censored at the date of their last follow-up visit; patients with no follow-up visits were censored at their last date of study medication; patients who received no treatment were censored at their randomization date), the impact of time from diagnosis and number of prior lines of therapy on PFS, and serum M-protein dynamic modelling.

### *Assessments*

Efficacy endpoints were assessed centrally per the European Group for Blood and Marrow Transplantation criteria and on a blinded review of tumour assessments by an independent review committee (see Data S1 for further assessment details).

### *Statistical and dynamic analysis*

The co-primary endpoint of PFS used the primary definition of PFS. A supportive PFS analysis was performed using the intent-to-treat (ITT) definition of PFS (see Data S1 for ITT definition). Impact of time from diagnosis and prior lines of therapy on PFS was assessed by Kaplan–Meier analysis; PFS data were based on independent review committee assessment (primary definition) and took into account all deaths, including those events that had occurred during the follow-up for survival. As supportive analysis, a stratified multivariate Cox regression model was used to assess the treatment effect after adjusting for possible imbalances in known or potential prognostic factors (primary definition of PFS); stratification factors were the same as those used for randomisation. Longitudinal serum M-protein data for both arms were assessed with the tumour dynamic model (Wang *et al*, 2009) using a non-linear mixed-effect (NLME) population method [i.e., tumour growth dynamic model, mathematically expressed as $A = A_0 \times exp^{-ks \times t} + k_g \times t$, where $A$ is serum M protein at time ($t$) in g/dl, $A_0$ is baseline serum M protein in g/l, $k_s$ (expressed per day) is an exponential tumour shrinkage rate constant, and $k_g$ is linear tumour regrowth rate in g/l/day]. The NLME analyses were conducted using Phoenix NLME 1.3 software (version 6.4.0.768; Certara, St Louis, MO, USA). The impact of time from diagnosis on tumour shrinkage and tumour regrowth was assessed using a serum M-protein dynamic method (Fig 1A) (Wang *et al*, 2009). Patients with serum M-protein values at baseline, including non-measurable values, were included in the analysis.

Extended 3-year follow-up was performed after 428 PFS events. A stratified log-rank test was used to compare treatment arms (see Data S1). Interim OS analysis was planned 1 year after the interim PFS analysis, assuming PFS statistical significance [significance threshold: 0·014 based on 295/427 (69%) events required for the final analysis]. TTNT was assessed using a stratified Cox regression model on the ITT population. Safety was analysed for all randomized patients who had received at least one dose of study medication.

Cut-off dates for analyses were August 2015 (ORR, PFS, safety and *post-hoc* analyses) and October 2015 (OS analyses).

## Results

Overall, 646 patients were randomized in ELOQUENT-2; 635 were treated (ELd, 319; Ld, 316). Across both treatment arms, the median time from diagnosis to randomization was 3·5 years. Minimum follow-up for PFS and ORR was 33 months (median for patients who did not progress was 32·4 months). As of August 2015, 126 patients were still on treatment (ELd, 26%; Ld, 14%; Table SI). The main reason for discontinuation was disease progression (ELd, 48%; Ld, 51%; see online Table SI for discontinuation reasons). Thirty patients (9%) in the ELd arm and 44 (14%) in the Ld arm discontinued from the study due to study drug toxicity. Subsequent systemic therapy in ≥5% of patients is shown in Table SII.

Baseline characteristics have been described (Lonial *et al*, 2015). Thirty-five percent of patients in each arm were refractory to their most recent therapy. The proportion of

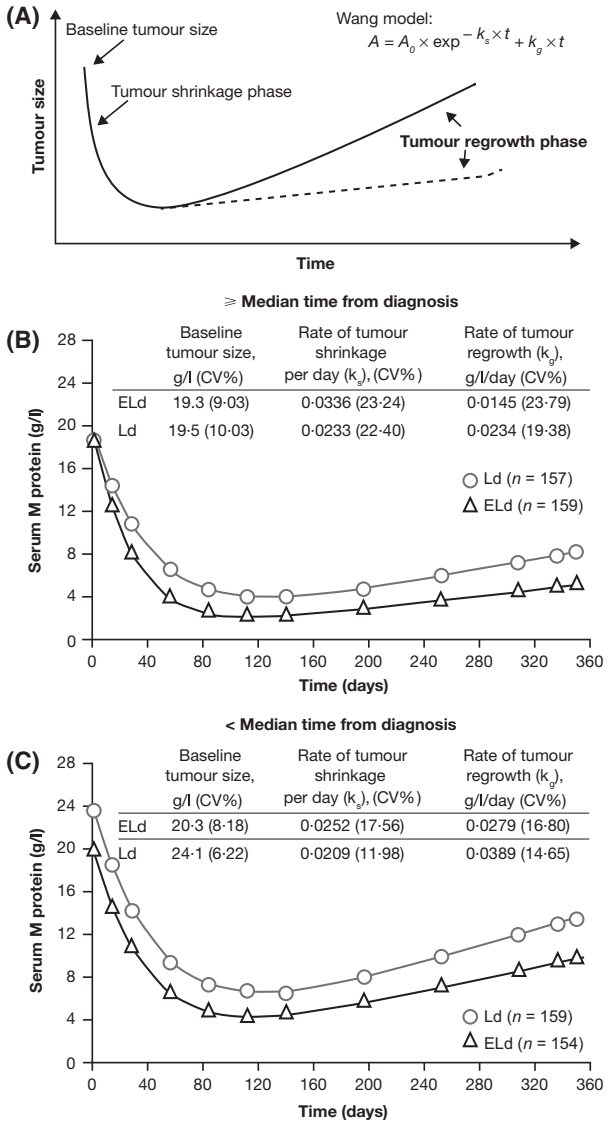



**Fig 1.** Serum M-protein dynamic modelling. (A) Tumour growth dynamic modelling concept, (B) simulated longitudinal M protein in patients with ≥ median time from diagnosis, (C) simulated longitudinal M protein in patients with < median time from diagnosis. A, tumour size at *t*; $A_0$, baseline tumour size; CV%, coefficient of variation (CV% = [std/mean] × 100); ELd, elotuzumab + lenalidomide/dexamethasone; $k_g$, rate of tumour regrowth; $k_s$, rate of tumour shrinkage; Ld, lenalidomide/dexamethasone; *t*, time.

patients who had received prior bortezomib, thalidomide or lenalidomide was comparable between treatment arms. Depending on the definition used, the del(17p) variant was present in 32% of patients in both arms [patients were considered del(17p) positive if any cell was positive], or in 19% of patients in both arms [patients were considered del(17p) positive if ≥60% of cells were positive]. Additionally, 9% and 10% of patients in the ELd and Ld arms, respectively, had the t(4;14) translocation.

ORR was 79% with ELd and 66% with Ld ($P = 0{\cdot}0002$; Table SIII). Three-year PFS was 26% and 18% in the ELd *versus* Ld arm, respectively, indicating a sustained relative improvement in PFS of 44% at 3 years. The PFS HR (primary definition) with extended follow-up was 0·73 (95% CI, 0·60–0·89; $P = 0{\cdot}0014$), representing a 27% reduction in the risk of disease progression or death (Fig 2), which was consistent with the primary analysis. PFS benefits were consistent across predefined subgroups, including patients refractory to their most recent treatment and those with the t(4;14) and del(17p) variants (Fig 3). In the supportive analysis, the PFS HR (ITT definition) was 0·72 (95% CI, 0·60–0·86; $P = 0{\cdot}0004$), indicating a 28% reduction in the risk of disease progression or death (Fig 4). Significant predictors of PFS (primary definition) were no prior stem cell transplant ($P = 0{\cdot}0046$; HR 0·69) and ≥ median time from diagnosis ($P < 0{\cdot}0001$; HR 0·57).

There were 295 deaths (136/321 in the ELd arm and 159/325 in the Ld arm), representing 69% of the 427 deaths that were prespecified for the final OS analysis. Minimum follow-up for OS was 36 months (median, 38·7 months). OS analysis demonstrated a trend in favour of ELd (Fig 5); median OS was 43·7 months (95% CI, 40·3–not evaluable [NE]) and 39·6 months (95% CI, 33·3–NE) with ELd and Ld, respectively ($P = 0{\cdot}0257$). OS rates in the ELd *versus* Ld arms were: 91% *versus* 83% at 1 year, 73% *versus* 69% at 2 years, and 60% *versus* 53% at 3 years, with a sustained separation over time observed in the Kaplan–Meier curves (Fig 5). ELd OS benefits were consistent across predefined subgroups (Fig 6), including in patients aged ≥75 years, refractory to their most recent therapy and with prior bortezomib exposure. Significant predictors of OS were Eastern Cooperative Oncology Group Performance Status score of 0–1 ($P < 0{\cdot}0001$; HR 0·44) and ≥ median time from diagnosis ($P < 0{\cdot}0001$; HR 0·49).

In the exploratory *post-hoc* TTNT analysis, ELd-treated patients had a 38% reduction in the risk of starting a subsequent therapy during follow-up (HR 0·62; 95% CI, 0·50–0·77; Fig 7). ELd-treated patients had a median delay of 1 year in TTNT *versus* Ld-treated patients (median [95% CI], 33·4 months [26·2–40·2] vs. 21·2 months [18·1–23·2]).

Progression-free survival was favourable for ELd *versus* Ld across patient subgroups according to time from diagnosis: patients with ≥ median time from diagnosis (3·5 years) had a 40% reduction in the risk of disease progression or death in the ELd arm *versus* the Ld arm (median PFS, 26·0 vs. 17·3 months; $P = 0{\cdot}0004$; Fig 3A). Among those with < median time from diagnosis, patients in the ELd arm had a 13% reduction in the risk of disease progression or death *versus* the Ld arm (median PFS, 15·8 vs. 12·9 months; $P = 0{\cdot}2963$; Fig 3A).

When stratified by median time from diagnosis and number of prior lines of therapy, PFS HR consistently favoured the ELd arm (Fig 3B). In patients with ≥ median time from diagnosis and one prior line of therapy, the risk of disease progression or death was mostly reduced, by 53% in the ELd arm *versus* the Ld arm (HR 0·47).

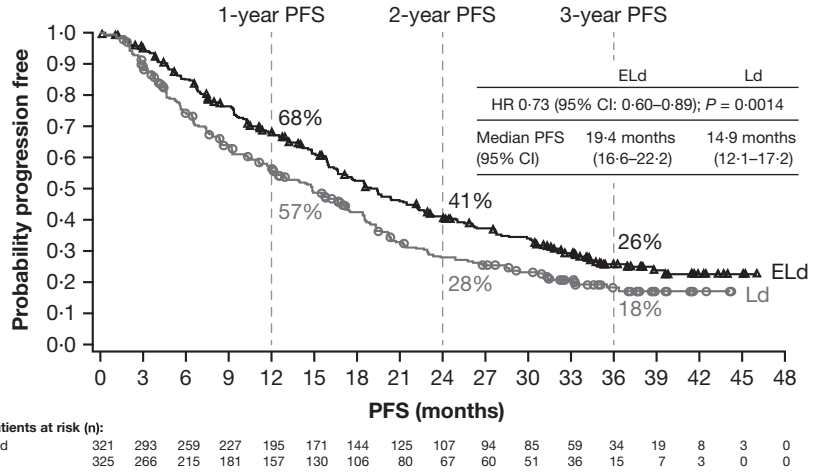



**Fig 2.** Kaplan–Meier curves of PFS (primary definition). CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; Ld, lenalidomide/dexamethasone; PFS, progression-free survival.

Serum M-protein dynamic modelling (an indicator of tumour shrinkage or regrowth), using quantitative serum protein electrophoresis, showed that the ELd arm had an increased rate of tumour shrinkage and a decreased rate of tumour regrowth *versus* the Ld arm, with a larger effect seen on the rate of tumour regrowth. When assessing the potential impact of time from diagnosis, tumour regrowth was slower for patients in the ELd arm *versus* the Ld arm regardless of whether patients had ≥ or < median time from diagnosis (Fig 1B, C). In patients with ≥ median time from diagnosis, the tumour regrowth rates were 0·0145 g/l/day in the ELd arm and 0·0234 g/l/day in the Ld arm (Fig 1B). In patients with < median time from diagnosis, the rates of tumour regrowth were 0·0279 g/l/day and 0·0389 g/l/day in the ELd and Ld arm, respectively (Fig 1C).

Extended safety data were consistent with earlier findings (Lonial *et al*, 2015), demonstrating minimal incremental toxicity with the addition of elotuzumab to Ld despite longer follow-up. Adverse events (AEs) occurred in almost all patients (99%) in both treatment arms. AEs reported in ≥30% of patients are listed in Table I. Although the absolute incidence of infections (ELd, 1165 events; Ld, 885 events) and second primary malignancies (ELd, 36; Ld, 20) was greater in the ELd arm, the exposure-adjusted incidence rates per 100 patient-years for infection were 198 and 192; and for second primary malignancies, 5 and 3 for ELd and Ld, respectively. Clinically important MM-related AEs are listed in Table SIV. Infusion reactions were reported in 10% (33/318) of ELd-treated patients, mostly occurring during the first cycle, and most were grade 1–2 (grade 1, 5%; grade 2, 4%; grade 3, 1%). No grade 4–5 infusion reactions were reported.

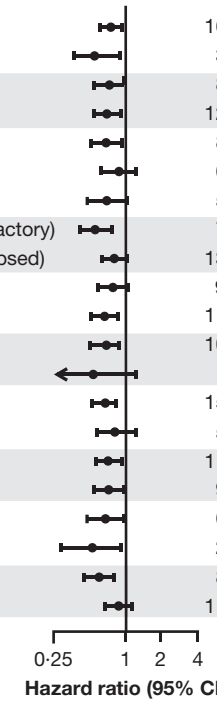
## Discussion

With extended follow-up, ELd continued to provide durable and clinically meaningful benefit in ORR and PFS in patients with relapsed/refractory multiple myeloma (RRMM), with PFS demonstrating a 27% reduction in risk of disease progression or death *versus* Ld. The results reported here support published data (Lonial *et al*, 2015) on the durable and clinically relevant improvement in PFS, as well as demonstrate a trend in OS, in favour of ELd. To the best of our knowledge, these data represent the longest follow-up of any recently approved therapeutic agent for MM, and continue to demonstrate a significant reduction in the risk of disease progression in the overall patient population. The benefit of ELd across predefined subgroups was consistent with the primary analysis. Patients who benefited from ELd treatment included those refractory to their most recent treatment and those with the t(4;14) and del(17p) variants. The greatest benefit in PFS occurred among patients with ≥ median time from diagnosis (HR 0·60; compared with HR 0·87 in patients with < median time from diagnosis), with a median survival of 26·0 months with ELd *versus* 17·3 months with Ld. These data are consistent with those from the primary analysis, which reported an HR of 0·55 in patients diagnosed with MM ≥3·5 years prior to study entry (Lonial *et al*, 2015). *Post-hoc* analyses of the effects of time from diagnosis and number of prior lines of therapy on PFS indicate that, while benefit favoured the ELd arm *versus* the Ld arm across subgroups, PFS was particularly favourable for ELd in patients with ≥ median time from diagnosis and one prior therapy. Additionally, our analysis suggests that median time from diagnosis is a significant predictor of both PFS (primary definition) and OS. A number of questions still remain unanswered in the field of MM treatment, including when a particular drug should be utilized, especially in the RRMM setting. The exploratory analyses described demonstrate the role of elotuzumab in slowing tumour regrowth in the overall population, which may be a contributor to the long-term durability of ELd therapy seen in ELOQUENT-2.

Interim OS analysis demonstrated a trend in favour of ELd, with an HR for OS of 0·77 ($P = 0·0257$). The survival benefit of adding elotuzumab to Ld was observed across predefined subgroups and was consistent with the trend seen in

**(A)**

| | Events, *n* (Patients, *n*) ELd | Events, *n* (Patients, *n*) Ld | Hazard ratio (95% CI) | Interaction *P*-value |
|---|---|---|---|---|
| Age (<75 years) | 169 (253) | 178 (264) | 0·76 (0·62–0·94) | 0·3875 |
| Age (≥75 years) | 39 (68) | 42 (61) | 0·59 (0·38–0·91) | |
| Age (<65 years) | 86 (134) | 96 (142) | 0·74 (0·55–0·99) | 0·9315 |
| Age (≥65 years) | 122 (187) | 124 (183) | 0·72 (0·56–0·92) | |
| ISS stage at enrolment (I) | 83 (141) | 86 (138) | 0·70 (0·52–0·95) | |
| ISS stage at enrolment (II) | 69 (102) | 72 (105) | 0·90 (0·64–1·25) | 0·5401 |
| ISS stage at enrolment (III) | 52 (66) | 51 (68) | 0·72 (0·49–1·06) | |
| Response to most recent line of therapy (refractory) | 76 (113) | 83 (114) | 0·57 (0·41–0·78) | 0·0463 |
| Response to most recent line of therapy (relapsed) | 131 (206) | 137 (211) | 0·82 (0·65–1·05) | |
| Number of lines of prior therapy (1) | 98 (151) | 107 (159) | 0·79 (0·60–1·05) | 0·4189 |
| Number of lines of prior therapy (2 or 3) | 110 (170) | 113 (166) | 0·68 (0·52–0·88) | |
| Prior IMiD therapy (prior thalidomide only) | 100 (150) | 108 (153) | 0·68 (0·52–0·90) | 0·4507 |
| Prior IMiD therapy (other) | 10 (16) | 14 (21) | 0·55 (0·24–1·25) | |
| Prior bortezomib (yes) | 151 (219) | 163 (231) | 0·68 (0·55–0·85) | 0·3754 |
| Prior bortezomib (no) | 57 (102) | 57 (94) | 0·83 (0·58–1·21) | |
| Prior stem cell transplant (yes) | 112 (167) | 129 (185) | 0·73 (0·57–0·94) | 0·9258 |
| Prior stem cell transplant (no) | 96 (154) | 91 (140) | 0·74 (0·55–0·98) | |
| del(17p) (yes)[a] | 61 (102) | 67 (104) | 0·70 (0·49–0·99) | 0·9091* |
| t(4;14) (yes) | 24 (30) | 26 (31) | 0·52 (0·29–0·93) | 0·2793† |
| ⩾ median time from diagnosis | 89 (160) | 108 (163) | 0·60 (0·45–0·79) | 0·0623 |
| < median time from diagnosis | 119 (161) | 112 (162) | 0·87 (0·67–1·13) | |




**(B)**

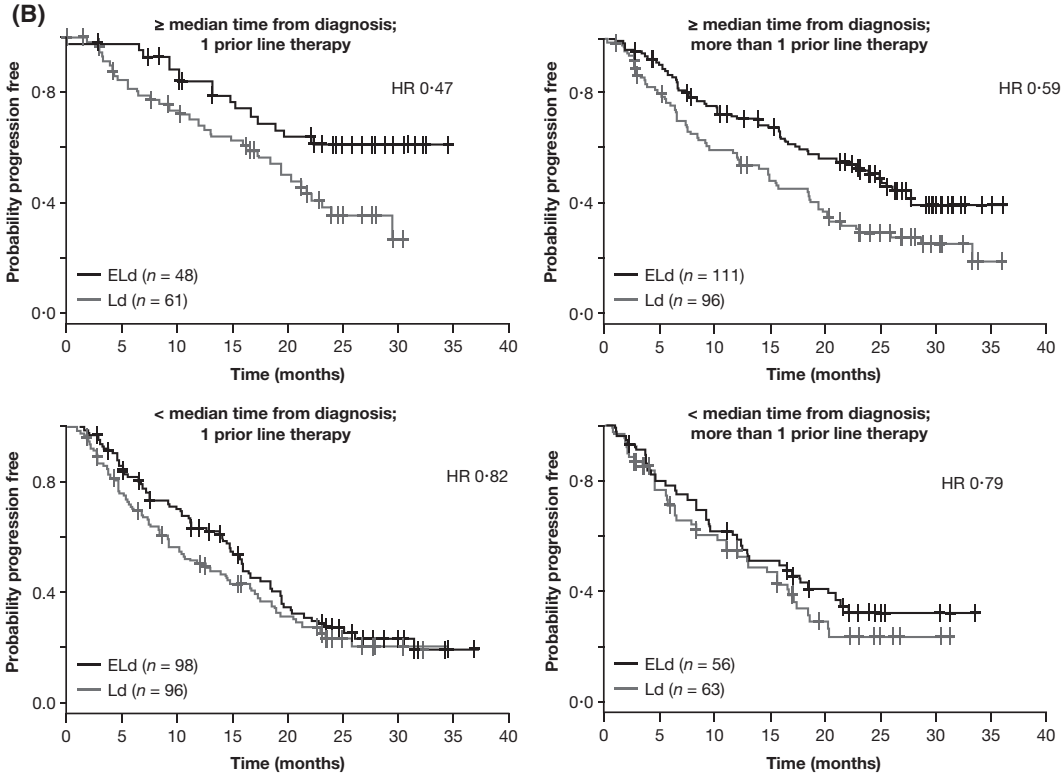



**Fig 3.** (A) PFS by predefined subgroups and (B) Kaplan–Meier curves of PFS (primary definition), stratified by median time from diagnosis and number of prior lines of therapy. [a]Patients were considered del(17p) positive if any cell was positive. *Interaction *P*-value corresponds to del(17p) (yes) *versus* del(17p) (no); †Interaction *P*-value corresponds to t(4:14) (yes) *versus* t(4:14) (no). CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; Ld, lenalidomide/dexamethasone; PFS, progression-free survival.

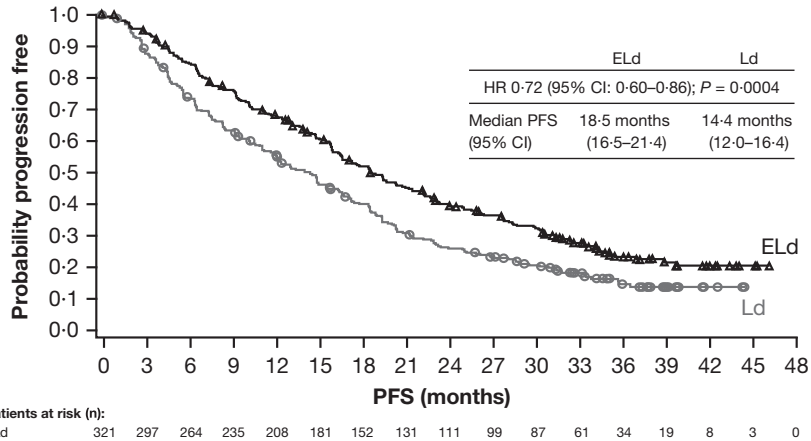



**Fig 4.** Kaplan–Meier curves of PFS (intent-to-treat definition). CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; Ld, lenalidomide/dexamethasone; PFS, progression-free survival.

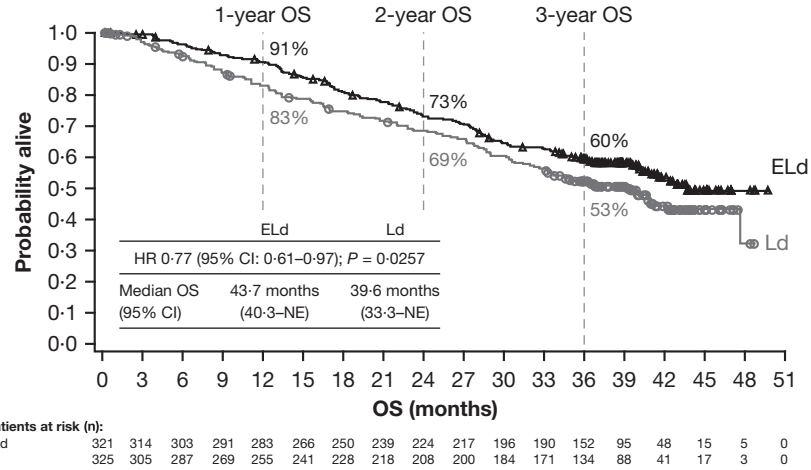



**Fig 5.** Kaplan–Meier curves of OS. CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; Ld, lenalidomide/dexamethasone; NE, not evaluable; OS, overall survival.

the predefined PFS subgroup analyses. Importantly, there was a clear separation towards the tail end of the Kaplan–Meier curves for ELd *versus* Ld, potentially indicating sustained clinical benefit of elotuzumab. OS is a keenly awaited outcome in myeloma studies; however, final OS analysis typically requires an extensive period of follow-up. The interim OS analysis reported herein was assessed after 3 years of follow-up, suggesting that the benefit seen in favour of ELd is likely to be maintained. Cross-trial comparisons are challenging owing to differing patient populations; however, the median OS following Ld treatment was 38·0 months in a pooled study of two phase III, long-term follow-up studies (Dimopoulos *et al*, 2009), indicating that the ELOQUENT-2 control arm is comparable with historical Ld trials.

As elotuzumab is an immunomodulating therapeutic monoclonal antibody with a unique mechanism of action, the stronger PFS and OS trend in favour of ELd could be due to long-term effects of elotuzumab on the immune system, resulting in a delay in symptom development, as seen with other immune-based regimens (Wolchok *et al*, 2009). This is further supported by the serum M-protein dynamic modelling results reported herein, which suggests that the survival may be due to not only faster tumour shrinkage, but, more importantly, from slower tumour regrowth with ELd, which is consistent with the clinical potential of long-term disease control based on the immunostimulatory mechanism of action of elotuzumab.

Progression-free survival was assessed centrally according to the European Group for Blood and Marrow Transplantation criteria, which require specific reductions in M-protein levels for each category of response. However, such criteria do not specify the minimum level of M protein required to allow accurate response assessment; this allows for substantial investigator discretion, leading to inconsistency in estimated response rates (Durie *et al*, 2006). Serum M-protein modelling was assessed using quantitative serum protein electrophoresis, which may provide a more accurate tool to assess response. Therefore, PFS and Serum M-protein modelling provide different parameters by which to assess tumour response to ELd treatment.

It is important to acknowledge some limitations of the current study. First, further follow-up to confirm the OS benefit of ELd *versus* Ld is required and, indeed, is underway. Second, further studies are needed on clinical and biological characteristics to better identify patients with RRMM who may optimally benefit from treatment with ELd. Third, initiation of

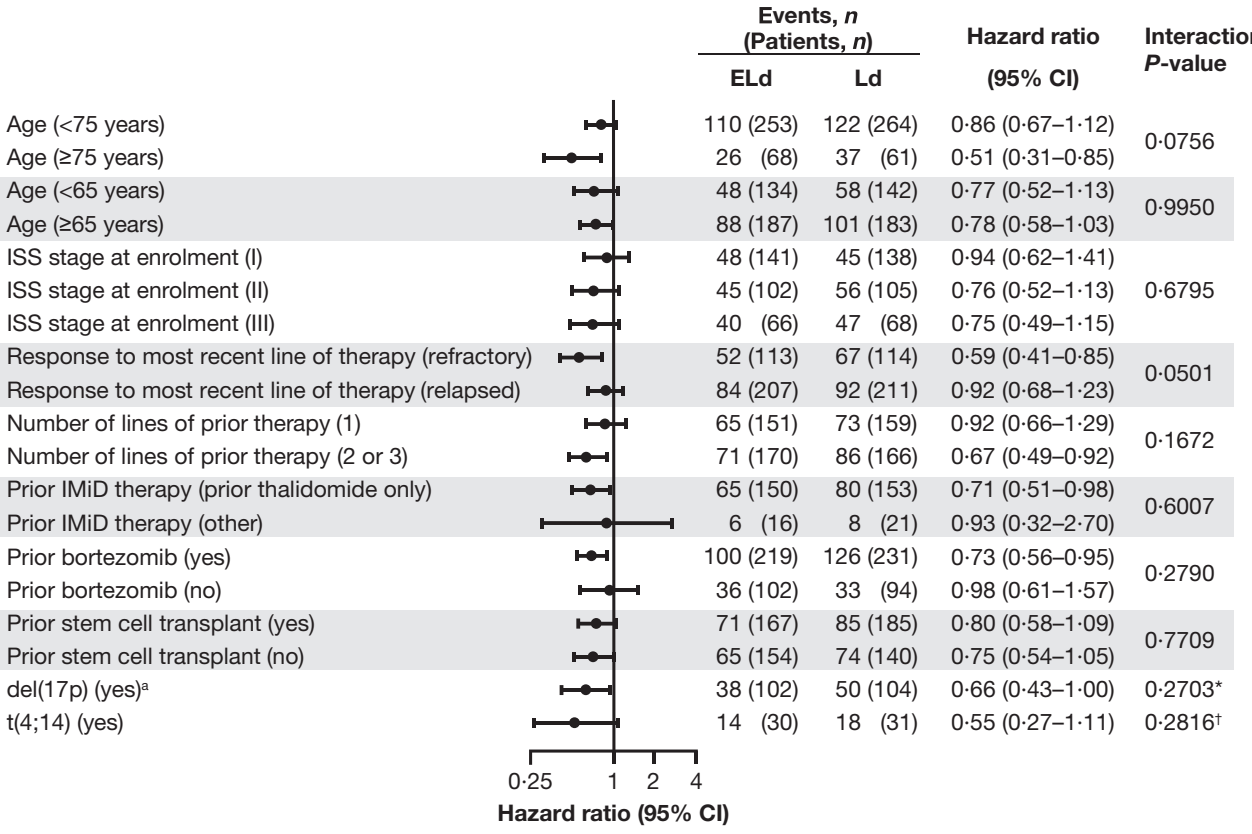



**Fig 6.** OS by predefined subgroups. [a]Patients were considered del(17p) positive if any cell was positive; *Interaction *P*-value corresponds to del(17p) (yes) *versus* del(17p) (no); †Interaction *P*-value corresponds to t(4:14) (yes) *versus* t(4:14) (no). CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; Ld, lenalidomide/dexamethasone; OS, overall survival.

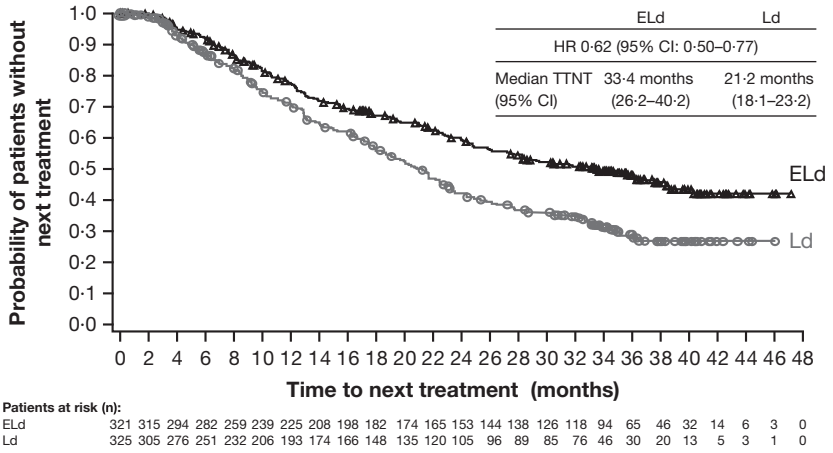



**Fig 7.** Kaplan–Meier curves of TTNT. CI, confidence interval; ELd, elotuzumab + lenalidomide/dexamethasone; HR, hazard ratio; Ld, lenalidomide/dexamethasone; TTNT, time to next treatment.

subsequent therapy was at the investigators' discretion; therefore, it was not initiated consistently between patients.

In addition to ELOQUENT-2, a number of clinical trials have been performed using an Ld backbone. For example, carfilzomib (the ASPIRE study) and daratumumab (the POLLUX study) have been assessed in combination with Ld (Stewart *et al*, 2015; Dimopoulos *et al*, 2016). However, it is difficult to make cross-trial comparisons with ELOQUENT-2 due to differing follow-up periods and patient populations.

In conclusion, the extended follow-up of ELOQUENT-2 provides long-term efficacy data for the use of ELd in RRMM, demonstrating an improvement in PFS and ORR *versus* Ld alone, and a trend toward improved survival. *Post-hoc* analyses suggest that PFS is favourable for ELd *versus* Ld across patient subgroups stratified by median time from diagnosis and number of prior therapies, with a greater benefit seen in patients with ≥ median time from diagnosis and one prior line of therapy. Additionally, serum M-protein

**Table I.** AEs reported in ≥30% of patients in the ELd or Ld arm.

| | ELd ($n$ = 318) | | Ld ($n$ = 317) | |
|---|---|---|---|---|
| AE | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| All AEs regardless of relationship | 316 (99·4) | 248 (78·0) | 314 (99·1) | 212 (66·9) |
| Non-haematological | | | | |
| Fatigue | 154 (48·4) | 29 (9·1) | 128 (40·4) | 26 (8·2) |
| Diarrhoea | 152 (47·8) | 17 (5·3) | 118 (37·2) | 15 (4·7) |
| Pyrexia | 122 (38·4) | 9 (2·8) | 79 (24·9) | 9 (2·8) |
| Constipation | 114 (35·8) | 4 (1·3) | 88 (27·8) | 1 (0·3) |
| Cough | 105 (33·0) | 1 (0·3) | 60 (18·9) | 0 |
| Muscle spasms | 96 (30·2) | 2 (0·6) | 84 (26·5) | 3 (0·9) |
| Haematological | | | | |
| Anaemia | 309 (97·2) | 62 (19·5) | 301 (95·3) | 67 (21·1) |
| Neutropenia | 261 (82·1) | 113 (35·5) | 282 (89·2) | 141 (44·5) |

AE, adverse event; ELd, elotuzumab + lenalidomide/dexamethasone; Ld, lenalidomide/dexamethasone.
Data shown as $n$ (%) of patients.

dynamic modelling demonstrated a slower tumour regrowth rate with ELd *versus* Ld.

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## Author contributions

MAD, SL, PM, JSM, OSh, KA, SG, IS, M-VM, DR, MB, EB, VP, JK, AS and PR participated in study design. MAD, SL, DW, PM, AP, JSM, OSh, KA, SG, IS, M-VM, AB, DR, MB, EB, VP, JS, JK, AS and PR participated in data analysis. MAD, DW and JS prepared the manuscript. SL, DW, PM, JSM, OSh, KA, SG, IS, AW-C, HM, M-VM, AB, DR, MB and PR participated in patient enrolment. SL, DW, PM, JSM, OSh, KA, SG, IS, AW-C, HM, M-VM, DR, MB, EB, VP, JK, AS and PR participated in interpretation of the data. OSy performed statistical data analyses and interpretation. All authors critically reviewed the manuscript and approved the final version of the manuscript for submission.

## Conflict of interest statement

MAD has received consultancy fees and honoraria from Amgen, Bristol-Myers Squibb, Janssen-Cilag, Celgene and Novartis. SL has received consultancy fees and research funding from Millennium, Celgene, Novartis, Bristol-Myers Squibb, Janssen and Onyx. DW has received consultancy fees and honoraria from, and served on a Board of Directors or advisory committee for, Celgene; and received consultancy fees and honoraria from Janssen-Cilag, Amgen, Novartis and Millennium. PM has received honoraria from, and served on a Board of Directors or advisory committee for, Bristol-Myers Squibb, Celgene, Novartis, Millennium and Janssen-Cilag. AP is an employee of Takeda, and has received honoraria from, and served as a consultant for, Amgen, Novartis, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis and Merck; received research funding from Amgen, Novartis, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis, Merck and Binding Site; and participated in a speakers bureau for Bristol-Myers Squibb. JSM has received honoraria from Bristol-Myers Squibb, Celgene, Janssen-Cilag, Millennium, Novartis, Sanofi-Aventis and Onyx. OSh has acted in a consultancy/advisory role for Millennium, Takeda and Gilead. KA has acted in a consultancy/advisory role for Celgene, Millennium, Gilead, Sanofi-Aventis and Bristol-Myers Squibb; and served as Scientific Founder of Oncopep and Acetylon. IS has acted in a consultancy/advisory role for Celgene, Janssen-Cilag, Bristol-Myers Squibb, Amgen, Millennium and Onyx; and has received research funding from Celgene. HM has acted in a consultancy/advisory role for Millennium, Takeda, Bristol-Myers Squibb, Celgene, Janssen-Cilag and Onyx. M-VM has acted in a consulting/advisory role for Takeda, Janssen-Cilag, Onyx and Celgene; and received honoraria from Janssen-Cilag and Celgene. AB has received consulting fees from Amgen, Celgene and Janssen-Cilag. DR has acted in a consulting/advisory role for Celgene, Janssen-Cilag and Onyx; received honoraria from Celgene, Janssen-Cilag, Amgen, Novartis and Lundbeck; and received research funding from Celgene, Janssen-Cilag, Merck, Bristol-Myers Squibb, Otsuka, Millennium Takeda and Novartis. MB has received honoraria from Takeda and Amgen; received consulting fees from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Takeda and Novartis; and participated in a speakers bureau for Amgen, Janssen-Cilag and Celgene. EB, VP, JS, OSy and JK are employees of Bristol-Myers Squibb and hold stock options in the company. AS is an employee of AbbVie. PR has been a member of an advisory committee for Bristol-Myers Squibb and Celgene; and is an Associate Editor for *British Journal of Haematology*. SG and AW-C declare no competing financial interests.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Methods.

**Table SI.** Reasons for discontinuation (all randomized patients).

**Table SII.** Subsequent systemic therapy in ≥5% of patients in the ELd or Ld arm.


 

**Table SIII.** Treatment responses (all randomized patients).
**Table SIV.** AEs of special interest (any grade).

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