Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation ineligible multiple myeloma (ELOQUENT-1): an open-label, multicentre, randomised, phase 3 trial

Elotuzumab, lenalidomide, and dexamethasone for patients with newly diagnosed, transplant ineligible multiple myeloma: results from the randomised, open-label, phase 3 ELOQUENT-1 trial

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Summary

Background Elotuzumab plus lenalidomide and dexamethasone (ERd) has improved progression-free and overall survival versus lenalidomide and dexamethasone (Rd) in relapsed/refractory multiple myeloma. We assessed ERd in patients with newly diagnosed multiple myeloma ineligible for stem-cell transplantation (SCT).

Methods This multicentre, randomised, controlled, open-label, phase 3 trial (ELOQUENT-1) recruited patients from 185 hospitals, oncology practices, or research centres from 19 countries. Eligible patients were aged ≥18 years with newly diagnosed, untreated, symptomatic myeloma and not candidates for high-dose therapy plus SCT. Patients were randomised (1:1) to ERd or Rd stratified by ISS stage, age, and ECOG performance status. Patients in the ERd group received intravenous elotuzumab 10 mg/kg weekly in cycles 1–2, every two weeks in cycles 3–18, and 20 mg/kg every four weeks thereafter. Patients in both groups received 25 mg oral lenalidomide on days 1–21 of each cycle and 40 mg oral equivalent dexamethasone weekly. The primary endpoint was progression-free survival (per protocol) per independent review committee according to European Society for Blood and Marrow Transplantation (EBMT) criteria. The trial is registered with ClinicalTrials.gov, NCT01335399. Recruitment is complete.

Findings Between August 4, 2011, and June 19, 2014, 965 patients were enrolled and 748 randomised to ERd (n=374) or Rd (n=374). At a minimum follow-up of 65·3 months, median progression-free survival was 31·4 months (95% CI 26·2–36·8) with ERd and 29·5 months (23·5–34·3) with Rd (hazard ratio 0·93, 95·71% CI 0·77–1·12; p=0·44). The most common grade 3–4 treatment-related adverse event was neutropenia (64 [17%] of 371 patients with ERd *vs* 79 [21%] of 371 with Rd). Treatment-related deaths occurred in five patients (1%) with ERd and four (1%) with Rd.

Interpretation ERd did not significantly improve progression-free survival versus Rd in patients with newly diagnosed multiple myeloma ineligible for SCT. While these data contribute to the treatment landscape, further research is needed to find optimal treatments.

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Research in context

Evidence before this study We searched for articles on PubMed and abstracts from major oncology congresses for studies relevant to newly diagnosed multiple myeloma in patients ineligible for stem cell transplantation and patients with relapsed/refractory multiple myeloma, with a focus primarily on phase 3 trials. Search terms included, but were not limited to, "newly diagnosed multiple myeloma", "relapsed/refractory multiple myeloma", "immunotherapy", "proteasome inhibitors", "immunomodulatory", "elotuzumab", "lenalidomide", and "dexamethasone", and relevant articles published from database inception to March 17, 2021 were identified. In the relapsed/refractory multiple myeloma setting, on the basis of results from ELOQUENT-2 and ELOQUENT-3, elotuzumab demonstrated a 30% and 46% reduction in the risk of disease progression or death in combination with lenalidomide/dexamethasone (ERd) and pomalidomide/dexamethasone (EPd), respectively. At the time of the ELOQUENT-1 study design (2011), regimens commonly used for newly diagnosed multiple myeloma included melphalan-based regimens with bortezomib, or immunomodulatory drugs including thalidomide, or lenalidomide-based regimens. The phase 3 FIRST study demonstrated that treatment with lenalidomide and dexamethasone (Rd) significantly improved survival outcomes versus melphalan, prednisone, and thalidomide in transplant-ineligible patients with newly diagnosed multiple myeloma, and Rd is now one of the standards of care. Phase 3 trials have evaluated several agents in combination with Rd in this setting: bortezomib (VRd), daratumumab (DRd), carfilzomib (KRd), and ixazomib (IRd); however, only VRd and DRd have demonstrated statistically significant benefits in progression-free survival compared with Rd. Thus, front-line treatments that significantly improve outcomes over existing standards of care are still needed.

Added value of this study Here we present results from the phase 3, international, randomised ELOQUENT-1 study, which assessed ERd compared with Rd for the treatment of patients with newly diagnosed, previously untreated multiple myeloma who were ineligible for stem cell transplantation. ERd did not demonstrate a statistically significant improvement in progression-free survival compared with Rd; however, these data contribute to the evolving treatment landscape for newly diagnosed multiple myeloma. Overall response rates were similar between treatment groups. Treatment with ERd was well tolerated and no new safety signals were identified beyond those reported in other studies of ERd or EPd.

Implications of all the available evidence Data from ELOQUENT-1 demonstrate that ERd did not meet the primary endpoint of improved progression-free survival versus Rd for the treatment of patients with newly diagnosed multiple myeloma ineligible for stem cell transplantation. Although effective in the relapsed/refractory multiple myeloma setting, the negative results of ERd, and also KRd and IRd, may reflect the challenge of improving treatment outcomes in the newly diagnosed setting. The reasons for this are currently unknown and further research is required to investigate the difference in treatment responses between patients in the newly diagnosed and relapsed/refractory settings. A search for triplet regimens with improved outcomes is ongoing.

Introduction

Effective first-line treatments for patients with multiple myeloma who are ineligible for stem cell transplantation are critical. Durability of response is limited once patients have relapsed/refractory disease and decreases with an increased number of prior lines of therapy.[1-5] The introduction of novel therapeutic agents in the first-line setting, including immunomodulatory drugs and proteasome inhibitors, has improved outcomes and reduced mortality, especially in elderly patients.[6] The large phase 3 FIRST study demonstrated that the combination of the immunomodulatory drug lenalidomide and dexamethasone (Rd) as an all-oral doublet significantly prolonged progression-free survival and overall survival compared with melphalan, prednisone, and thalidomide in transplant-ineligible patients with newly diagnosed multiple myeloma, and established Rd as a standard of care in this setting.[7,8] Since then, triplet regimens combining a proteasome inhibitor or a monoclonal antibody with Rd have also become standard treatments.[9-12]

Elotuzumab is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody that targets signalling lymphocytic activation molecule family member 7, a glycoprotein highly expressed on myeloma cells, natural killer (NK) cells, and some immune cells, but not on other normal tissues.[13] Elotuzumab exerts its effect via multiple mechanisms, including NK cell activation, NK cell-mediated antibody-dependent cellular cytotoxicity, and macrophage-mediated antibody-dependent cellular phagocytosis.[13-16]

The benefit of elotuzumab plus Rd (ERd) has been demonstrated in the relapsed/refractory multiple myeloma setting in the phase 3 ELOQUENT-2 study.[17] At the primary analysis, ERd reduced the risk of disease progression or death by 30%, with acceptable toxicity.[17] These results led to the approval of ERd for the treatment of patients with relapsed/refractory multiple myeloma who had received ≥1 prior therapy. The progression-free survival benefit with ERd was sustained through the 5-year follow-up and at the final overall survival analysis, ERd reduced the risk of death by 18% compared with Rd.[18-20]

Here, we report the findings from ELOQUENT-1, a large, international study, which assessed whether ERd improved progression-free survival compared with Rd for the treatment of patients with newly diagnosed multiple myeloma who were ineligible for stem cell transplantation.

Methods

Study design and participants

ELOQUENT-1 is a phase 3, open-label, multicentre, randomised, controlled study carried out at 185 hospitals, oncology practices or research centres in 19 countries (appendix pp 2–10).

Eligible patients were aged ≥18 years with newly diagnosed, untreated, symptomatic myeloma per European Society for Blood and Marrow Transplantation (EBMT) criteria who were not candidates for high-dose therapy plus stem cell transplantation due to age (≥65 years) or comorbidities. Patients (<65 years) without comorbidities who refused to undergo high-dose therapy with stem cell transplantation were not eligible for

study entry. Patients had measurable disease (serum immunoglobulin G, A, or M, M-protein ≥0·5 g/dL, serum immunoglobulin D ≥0·05 g/dL, or urine M-protein ≥200 mg/24 h), an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, creatinine clearance ≥30 mL/min, and a life expectancy >3 months. Key exclusion criteria were non-secretory, oligo-secretory, or serum free light chain only myeloma; smouldering multiple myeloma and monoclonal gammopathy of undetermined significance; Waldenström's disease; plasma cell leukaemia; significant cardiac disease; prior cerebrovascular event with persistent neurological effect; prior or concurrent malignancy (except treated basal cell carcinoma, squamous skin cell cancer, or any other disease-free cancer for >5 years); and uncontrolled diabetes. Prior systemic chemotherapy, immunotherapy, or investigational agents for multiple myeloma were not permitted. The full exclusion criteria are shown in the appendix (pp 11–12).

This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation and the Declaration of Helsinki. The protocol, amendments, patient consent forms, and patient recruitment materials received approval by the institutional review boards and independent ethics committees at each study site prior to initiation of the study. All patients provided written informed consent.

The study was overseen by an independent data monitoring committee. Results for the final analysis of the primary endpoint are presented here. This study is registered at ClinicalTrials.gov (NCT01335399). The full study protocol is available online at https://clinicaltrials.gov/ProvidedDocs/99/NCT01335399/Prot_001.pdf.

Randomisation and masking

The study design and treatment regimens are shown in the appendix (p 41; supplementary figure 1). Enrolment was done by study centre staff who were trained on study eligibility requirements. Eligible patients were randomised 1:1 to receive ERd or Rd via an interactive voice response system. Randomisation was stratified by International Staging System (ISS) stage (I–II *vs* III), age (<75 *vs* ≥75 years), and ECOG performance status (0 *vs* 1–2), and was done using permuted blocks of size 4 within each stratum. Patients and investigators were not masked to treatment assignment.

Procedures

Treatment was administered in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Patients in the ERd group received elotuzumab (Bristol Myers Squibb, Princeton, USA) administered intravenously at a dose of 10 mg/kg on days 1, 8, 15, and 22 during cycles 1 and 2, days 1 and 15 for cycles 3–18, and then at a dose of 20 mg/kg on day 1 for subsequent cycles (appendix p 41). In both treatment groups, patients received lenalidomide (Bristol Myers Squibb, Princeton, USA) 25 mg orally on days 1–21 of each cycle, and 40 mg dexamethasone (Merck & Co, Kenilworth, USA) on days 1, 8, 15, and 22 of each cycle (split 28 mg oral and 8 mg intravenous dose on weeks of elotuzumab administration in the ERd group). Further information on elotuzumab infusion and premedication is in the appendix (p 12). The lenalidomide starting dose was to be adjusted based on the severity of renal impairment, while the dexamethasone starting dose was not adjusted for age. Further information regarding dose interruption or

reduction can be found in the appendix (p 13). Patients were followed every 4 weeks for tumour response until confirmed disease progression, then every 16 weeks (or more frequently) for survival, subsequent myeloma therapy, and development of second primary malignancy. Tumour assessments were based on the European Society for Blood and Bone Marrow Transplantation criteria (evaluation of stringent complete response and very good partial response was per the uniform response criteria of the International Myeloma Working Group[21,22]). Details regarding further assessments, including the frequency and types of laboratory and adverse event monitoring, are outlined in the appendix (pp 14–15).

Outcomes

The primary endpoint was progression-free survival per EBMT criteria based on independent review committee assessment using the primary definition of progression-free survival. Secondary endpoints were overall response rate per independent review committee, progression-free survival rates at 1 to 5 years, overall survival, and change from baseline in the mean scores of pain severity and pain interference in the Brief Pain Inventory–Short Form. Exploratory endpoints included time to and duration of response, time to next treatment, progression-free survival after the next line of treatment, and safety (appendix p 15).

Progression-free survival was defined, per protocol, as the time from randomisation to the date of first documented tumour progression or death, whichever occurred first. For the primary definition of progression-free survival used for the primary endpoint, censoring rules were applied for patients who received subsequent therapy prior to disease progression, those with a progression-free survival event more than 10 weeks after the last prior tumour assessment (missed two or more assessments), and those who did not progress or die. Clinical deterioration was not considered progression (see appendix p 16 for additional details). Progression-free survival under the intent-to-treat definition and relative censoring rules are described in the appendix (p 16). Overall response rate was defined as the proportion of randomised patients who achieved partial response or better. Overall survival was defined as the time from randomisation to the date of death. Additional outcomes are defined in the appendix (p 16).

Safety evaluations included assessments of adverse events and serious adverse events, clinical laboratory tests, vital signs, and physical examination with assessment of ECOG performance status. Adverse events were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3·0, and were counted according to their worst grade.

Statistical analysis

Approximately 750 patients were planned to be randomised to obtain at least 482 progression events (disease progression or death). It was estimated that 482 events would provide 90·5% power to detect a hazard ratio (HR) of 0·74 for disease progression or death with a two-sided type I error rate of 5% and one planned interim analysis. Additional interim analysis details are described in the appendix (p 16). The independent data monitoring committee's recommendation at this interim analysis was to continue the trial to final analysis. Accounting for an alpha of 0·0244 (2-sided) at interim analysis, the remaining alpha for the final analysis of progression-free survival was 0·0429 (2-sided) and an observed p-value smaller than the

threshold (or, equivalently, the 95·71% confidence interval [CI] for HR excluding 1) would indicate statistical significance. A hierarchical testing procedure was used to preserve a family-wise type 1 error rate of 5% for the primary endpoint and the two secondary endpoints of overall response rate and overall survival. Overall response rate was formally tested only if the primary endpoint was met, and overall survival was formally tested only if the overall response rate was statistically significant.

Analyses of baseline characteristics and efficacy outcomes were conducted in all randomised patients. Extent-of-exposure and safety analyses were performed in the treated population, which consisted of all patients who received ≥1 dose of study medication. The distribution and median of each censored time-to-event endpoint was estimated using the Kaplan–Meier product limit method. The Brookmeyer and Crowley method was used to calculate the 95% CI for the median of each time-to-event endpoint. A two-sided stratified log-rank test was used to compare progression-free survival (and overall survival if appropriate) between groups using the same stratification factors used in randomisation. A stratified Cox proportional hazards model was used to estimate the HR and corresponding CI of the ERd group to the Rd group for progression-free survival and overall survival. Overall response rates between treatment groups were compared using the Cochran–Mantel–Haenszel method stratified by the same factors used in randomisation. An estimate of the treatment odds ratio and corresponding two-sided 95% CI was presented. Statistical analyses were performed using the Statistical Analysis System, version 9·2.

Role of the funding source

The study was designed by the sponsors (Bristol Myers Squibb and AbbVie Biotherapeutics). Bristol Myers Squibb oversaw data collection and contributed to data analysis and interpretation in collaboration with the authors. All authors attest that the trial was conducted in accordance with the protocol (https://clinicaltrials.gov/ProvidedDocs/99/NCT01335399/Prot_001.pdf) and vouch for the accuracy and completeness of the data and analyses and approved the manuscript for submission. All authors had full access to the data reported from the study. The corresponding author had final responsibility for the decision to submit for publication. The manuscript was prepared with professional medical writing assistance funded by Bristol Myers Squibb.

Results

Of the 965 patients enrolled between August 4, 2011, and June 19, 2014, 748 were randomised (ERd, n=374; Rd, n=374) and 742 were treated (ERd, n=371; Rd, n=371; figure 1). Baseline demographics and disease characteristics were generally balanced between the two treatment groups (table 1). The median age of the overall study population was 73·0 years (interquartile range [IQR] 69·0–78·0); 294 (39%) patients were ≥75 years. The proportions of patients with high-risk disease, defined as ISS stage II or III and t(4;14) or del(17p) abnormality per International Myeloma Working Group criteria,[23] were similar between treatment groups (ERd, n=31 [8%]; Rd, n=35 [9%]). Renal impairment (creatinine clearance <60 mL/min) was present in 146 (39%) and 173 (46%) patients in the ERd and Rd groups, respectively.

At database lock (December 3, 2019), after a minimum follow-up of 65·3 months, 38 (10%) patients in the ERd group versus 32 (9%) patients in the Rd group remained on therapy. In total, 333 (90%) and 339 (91%) patients, respectively, discontinued treatment, mainly due to disease progression (n=114 [31%] *vs* n=141 [38%]) or to adverse events (unrelated to study drug, n=105 [28%] *vs* n=65 [18%]; study drug toxicity, n=51 [14%] *vs* n=64 [17]%; figure 1). The median number of treatment cycles was 26 (IQR 9–53) in the ERd group and 21 (IQR 8–46) in the Rd group. In the ERd group, median duration of treatment was 23·0 months (IQR 6·5–49·5) for elotuzumab, 23·7 months (IQR 6·7–46·7) for lenalidomide, and 23·7 months (IQR 7·4–49·0) for dexamethasone. In the Rd group, median duration of treatment was 18·9 months (IQR 7·1–41·6) for lenalidomide and 16·1 months (IQR 6·9–35·4) for dexamethasone. Details on dose intensity for each agent are in the appendix (p 17, supplementary table 1).

At the final analysis, the study did not meet the primary endpoint of progression-free survival. At this time, 586 patients had experienced disease progression or died (ERd, 291/374 [78%]; Rd, 295/374 [79%]). The median progression-free survival was 31·4 months (95% CI 26·2–36·8) in the ERd group versus 29·5 months (95% CI 23·5–34·3) in the Rd group (figure 2A). The HR for progression-free survival was 0·93 (95·71% CI 0·77–1·12; stratified log-rank p=0·44). The progression-free survival rates at 5 years were 26% (95% CI 21–32) with ERd and 25% (95% CI 20–30) with Rd; rates at 1 to 4 years were similar between treatment groups (figure 2A). A total of 130 (35%) of 374 patients in the ERd group and 134 (36%) of 374 in the Rd group were censored in the progression-free survival analysis; 32 (9%) and 43 (11%) patients, respectively, were censored due to initiating subsequent systemic therapy prior to disease progression. The actual time to accumulation of events required for progression-free survival analysis was 65 months versus the estimated time of 29 months. Progression-free survival results with ERd and Rd were consistent across key patient subgroups (figure 2B). The median progression-free survival per the intent-to-treat definition was 29·5 months (95% CI 25·3–33·2) in the ERd group versus 26·7 months (95% CI 22·1–30·5) in the Rd group with an HR of 0·92 (95·71% CI 0·77–1·09) (appendix p 42, supplementary figure 2).

As the primary endpoint of this study was not met, overall response rate and overall survival analyses were descriptive. The overall response rate was 83% (95% CI 79–87) in the ERd group and 79% (95% CI 75–83) in the Rd group, with an odds ratio of 1·26 (95% CI 0·87–1·82; table 2). The proportion of patients who achieved very good partial response or better was 53% and 49% in the ERd and Rd groups, respectively. Among responders, the median time to response was 1·1 months (IQR 1·0–2·3) in the ERd group and 1·9 months (IQR 1·0–2·8) in the Rd group. The median time to best response was also similar between treatment groups (ERd, 5·6 months [IQR 1·9–15·3]; Rd, 4·7 months [IQR 2·0–12·5]). The median duration of response was approximately 33 months for both ERd (33.2 months [95% CI 28.2–38.2]) and Rd (33.1 months [95% CI 28.4–38.0]; appendix p 43, supplementary figure 3).

At database lock, there were 436 deaths (ERd, 221/371; Rd, 215/371). The median overall survival was 60·4 months (95% CI 52·8–67·4) in the ERd group versus 57·6 months (95% CI 49·0–66·6) in the Rd group, with a HR of 0·99 (95% CI 0·82–1·19; appendix p 44, supplementary figure 4).

The time to disease progression, time to next treatment, and progression-free survival after next line of treatment showed no significant differences between treatment groups. Median time to disease progression was 42·0 months (95% CI 33·2–51·4) in the ERd group and 36·0 months (95% CI 31·3–45·4) in the Rd group (HR 0·85 [95% CI 0·69–1·05]; appendix p 45, supplementary figure 5). The median time to next treatment was 34·3 months (95% CI 29·8–39·6) in the ERd group and 29·2 months (95% CI 25·5–32·9) in the Rd group (HR 0·85 [95% CI 0·72–1·01]; appendix p 46, supplementary figure 6). The median progression-free survival after next line of treatment was 51·7 months (95% CI 45·5–57·1) in the ERd group and 43·5 months (95% CI 38·0–48·0) in the Rd group (HR 0·88 [95% CI 0·73–1·05]; appendix p 47, supplementary figure 7).

All 742 patients who received ≥1 dose of study therapy were included in the safety analysis. The most frequent adverse events and those of special interest are shown in table 3. All additional adverse events of grade 3, 4, or 5 severity are listed in the appendix (pp 18–38, supplementary table 2).

The most common any-grade non-haematological adverse events included diarrhoea (195 [53%] of 371 patients in the ERd group *vs* 181 [49%] of 371 patients in the Rd group), fatigue (182 [49%] *vs* 187 [50%]) and peripheral oedema (162 [44%] *vs* 181 [49%]). Any-grade hyperglycaemia occurred in 121 (33%) of patients in the ERd group and 69 (19%) in the Rd group; grade 3–4 hyperglycaemia was reported in 58 (16%) *vs* 37 (10%) patients, respectively. Grade 3–4 cardiac disorders were reported in 45 (12%) patients in the ERd group *vs* 31 (8%) in the Rd group. The most common any-grade haematological adverse events were anaemia (ERd, 152 [41%] *vs* Rd, 163 [44%]) and neutropenia (94 [25%] *vs* 118 [32%]). In the ERd group, 64 (17%) patients had grade 3–4 neutropenia, compared with 79 (21%) patients in the Rd group. Additionally, grade 3–4 lymphopenia was reported in 15 (4%) and 5 (1%) patients in the ERd and Rd groups, respectively.

Infections were reported in 294 (79%) patients in the ERd group versus 272 (73%) in the Rd group; rates were similar after adjustment for drug exposure (129·6 and 128·9 events per 100 patient-years for ERd and Rd, respectively). Median (range) time to onset of first infection was 4·0 (0·0–75·3) months in the ERd group (n=294) and 3·6 (0·0–85·2) months in the Rd group (n=272).

Infusion reactions occurred in 57 (15%) of all treated patients in the ERd group and were predominantly grade 1 (24 [6%]) or grade 2 (30 [8%]); three patients (1%) receiving elotuzumab had a grade 3 reaction and no grade 4–5 reactions were reported. The majority of infusion reactions (47 [82%]) occurred with the first elotuzumab dose. Second primary malignancies were reported in 42 (11%) patients in the ERd group versus 36 (10%) in the Rd group; these were predominantly basal cell carcinomas (ERd, 12 [3%] patients vs Rd, 10 [3%] patients).

Adverse events leading to discontinuation occurred in 199 (54%) patients in the ERd group and 172 (46%) in the Rd group. The most common any-grade adverse events leading to discontinuation of any study drug were pneumonia (14 [4%] patients in the ERd group *vs* 8 [2%] in the Rd group), sepsis (9 [2%] *vs* 1 [<1%]), fatigue (14 [4%] *vs* 12 [3%]), acute kidney injury (7 [2%] *vs* 7 [2%]), diarrhoea (6 [2%] *vs* 4 [1%]), and dyspnoea (6 [2%] *vs* 1 [<1%]).

Serious adverse events (any grade) were reported in 292 (79%) patients receiving ERd and 277 (75%) receiving Rd, most frequently pneumonia in both groups (60 [16%] and 48 [13%] patients, respectively; appendix p 39, supplementary table 3). In total, 221 (60%) patients from the ERd group and 215 (58%) from the Rd group died, most commonly due to disease progression (n= 80 [22%] *vs* n=106 [29%], respectively; appendix p 40, supplementary table 4). Study drug toxicity was the reported cause of death in five (1%) patients treated with ERd and four (1%) treated with Rd.

In both ERd and Rd groups, there were no noticeable changes in the mean pain severity and pain interference scores from baseline throughout treatment (appendix p 48, supplementary figure 8).

Discussion

In this randomised, controlled, open-label, phase 3 study, ERd did not demonstrate a statistically significant improvement in progression-free survival compared with Rd for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation. Overall response rates were similar between treatment groups and approximately half of all patients in both groups achieved a very good partial response or better. There were no differences in overall survival. The safety profile of ERd was consistent with the known profile of elotuzumab in combination with immunomodulatory drugs.[17-20]

The median duration of treatment was longer in the ERd group versus the Rd group; however, this difference did not translate into a progression-free survival advantage for patients in the ERd group. Nonetheless, in ELOQUENT-1, median progression-free survival for Rd (29·5 months) was similar to that from the MAIA (31·9 months) and SWOG S0777 (30·0 months) trials in similar disease settings, although cross-study comparisons should be interpreted with caution.[8,11,12] Further, while disease progression was the main factor for treatment discontinuation in patients treated with Rd compared to ERd (38% *vs* 31%, respectively), adverse events were reported as a reason for treatment discontinuation at a higher rate with ERd versus Rd (42% *vs* 35%, respectively), despite ERd being a well-tolerated regimen. The exploratory endpoints of time to progression, time to next treatment, and progression-free survival after next line of treatment were numerically higher in patients treated with ERd versus Rd, but the differences between groups were not statistically significant.

Treatment with ERd was well tolerated and no new safety signals were identified beyond those reported in other studies of ERd or in ELOQUENT-3 in patients with relapsed or refractory multiple myeloma, where elotuzumab was combined with pomalidomide and dexamethasone (EPd).[17,24] The higher rates of hyperglycaemia and lower rates of neutropenia in the ERd versus Rd group may reflect the oral dexamethasone dose given up to 24 h prior to elotuzumab infusion.

The clinical benefit of elotuzumab combined with an immunomodulatory drug was demonstrated in the relapsed/refractory setting on the basis of results from ELOQUENT-2 and ELOQUENT-3, in which ERd and EPd showed a 30% and 46% reduction in the risk of disease progression or death, respectively, versus control.[17,24] The efficacy of ERd in newly diagnosed, transplant ineligible multiple myeloma has previously

been shown in a randomised study of 82 patients in Japan, in which the observed investigator-assessed overall response rate based on International Myeloma Working Group criteria was 88% with a minimum follow-up of 6 months[25] and 93% with a minimum follow-up of 2·5 years[26] in the ERd group, and the observed overall response rate was 74% in the Rd group. The progression-free survival data in the Japanese study are not available. It is unclear why the efficacy of elotuzumab was not replicated in the newly diagnosed setting in ELOQUENT-1, but this has been previously observed with other regimens with activity in the relapsed/refractory setting. Carfilzomib plus Rd (KRd) is approved to treat relapsed/refractory disease; however, in ENDURANCE, the co-primary endpoint of improved progression-free survival with KRd versus bortezomib plus Rd (VRd) was not met and, in CLARION, carfilzomib plus melphalan and prednisone did not significantly improve progression-free survival compared with bortezomib plus melphalan and prednisone.[27,28] Similarly, ixazomib plus Rd (IRd) significantly improved progression-free survival versus placebo plus Rd in the relapsed/refractory setting,[29] but not in newly diagnosed patients in TOURMALINE-MM2.[30] However, results from TOURMALINE-MM2 may be explained by the lower doses of ixazomib and lenalidomide that were received after 18 cycles and reflected by the median progression-free survival in the control arm.[31] The negative results from first-line trials of ERd, carfilzomib-based studies (including KRd), and IRd studies may reflect the broader difficulty of demonstrating treatment superiority in the newly diagnosed setting, possibly due to differences in disease biology, likely higher clinical burden of disease, and the larger differences in outcomes needed to demonstrate a treatment effect. Conversely, both the SWOG S0777 and MAIA studies have demonstrated significantly improved progression-free survival with VRd and DRd, respectively, versus Rd.[11,12] Differences in the mechanism of action of these agents may account for the enhanced efficacy and/or synergy of these regimens compared with other Rd combinations.

This study has some limitations. First, the dosing regimen/study schedule, including the frequency of safety assessments and follow-up may have been burdensome and inconvenient to patients, particularly to those in the Rd arm. Continuous treatment with Rd was a standard of care for this patient population; therefore, the commercial availability of Rd may have enabled patients in the Rd group to discontinue treatment before confirmed progression and may have contributed to the shorter treatment duration of Rd versus ERd. Second, as dexamethasone dose adjustment by age was not established when ELOQUENT-1 was designed, dexamethasone was given at the same dose (40 mg weekly) regardless of age. Lack of dexamethasone dose adjustment by age may also have contributed to the high discontinuation rate due to adverse events in both treatment groups. Third, due to the high rate of treatment discontinuation before confirmed progression, the follow-up time for assessment of progression-free survival was twice as long as planned. Fourth, at the time of the study setup, the central laboratory contracted to perform fluorescence in situ hybridization cytogenetic analyses did not have capabilities to perform enrichment for CD38+ plasma cells. Therefore, the frequencies of the various cytogenetic abnormalities reported in the study are likely diluted, and this may be reflected in the lower rates of International Myeloma Working Group high-risk category. Finally, a high percentage of patients were censored for the primary progression-free survival analysis; however, additional sensitivity analyses with different censoring approaches did not seem to affect the progression-free survival comparison.

Although effective in the relapsed/refractory multiple myeloma setting, data from ELOQUENT-1 did not demonstrate a similar progression-free survival benefit in the newly diagnosed setting. The reasons for this are unknown and likely multifactorial.

Contributors

MAD, PGR, SL, and KW contributed to the conception and design of the study.

MAD, PGR, NJB, SG, MC, MB, WL, AML, HG, AB, HM, AL, JPL, MTP, DR, DW, M-VM, IS, ML, JB, JLK, SL, and KW contributed to data acquisition, including enrolling and treating patients. MAD, PGR, Y-MJ, AG, MPM, SL, and KW analysed the data. All authors interpreted the data, contributed to the development of the manuscript, and approved the final version for publication.

Declaration of interests

MAD has received personal fees (honoria) from Amgen, Bristol Myers Squibb, BeiGene, Janssen, and Takeda (served on advisory boards for all), all outside the submitted work.

PGR has received personal fees from AstraZeneca, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, Protocol Intelligence, Regeneron, Sanofi, Secura Bio, and Takeda; and grant funding from Bristol Myers Squibb, Celgene, Karyopharm, Oncopeptides, and Takeda, all outside the submitted work.

NJB has received personal fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Janssen, Karyopharm, Pfizer, and Sanofi; and grant funding from Celgene, all outside the submitted work.

SG has no conflicts of interest to declare.

MC has received personal fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; and speaker's bureau from Celgene and Janssen, all outside the submitted work.

MB has served on speaker's bureau for Amgen, Celgene, Janssen, Oncopeptides, Sanofi, and Takeda; and on advisory boards for Amgen, Celgene, Janssen, Sanofi, and Takeda, all outside the submitted work.

WL has no conflicts of interest to declare.

AML has received grant funding, personal fees, and non-financial support from Bristol Myers Squibb, all for the work under consideration for publication. In addition, she has received grant funding from AbbVie, Archigen, BeiGene, Celgene, FibroGen, GlaxoSmithKline, Janssen, Karyopharm, Novartis, MorphoSys, Onconova, Oncopeptides, Pfizer, Roche, Sanofi, Servier, Takeda, and Verastem; personal fees from AbbVie, Celgene, Incyte, Janssen, Novartis, and Servier; and non-financial support from AbbVie, Janssen, Novartis, Roche, Sanofi, Takeda, and Verastem, all outside the submitted work.

HG has received grant funding and/or provision of investigational medicinal products from Amgen, Bristol Myers Squibb, Celgene, Chugai, the Dietmar Hopp Foundation, Janssen, Johns Hopkins University, and Sanofi; research support from Amgen, BMS, Celgene, Chugai, Janssen, Incyte, Molecular Partners, Merck Sharp & Dohme, Mundipharma GmbH, Novartis, Sanofi, and Takeda; has served on advisory boards for Adaptive Biotechnology, Amgen, Bristol Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; and received honoraria from Amgen, Bristol Myers Squibb, Celgene, Chugai, GlaxoSmithKline, Janssen, Novartis, and Sanofi, all outside the submitted work.

AB has no conflicts of interest to declare.

HM has no conflicts of interest to declare.

AL has received personal fees (honoria) from Amgen, Bristol Myers Squibb, Celgene, Janssen, and GlaxoSmithKline; and personal fees for serving on advisory boards from Bristol Myers Squibb, Celgene, Janssen, and Takeda, all outside the submitted work.

JPL has no conflicts of interest to declare.

MTP has received personal fees (for both honoria and advisory boards) from Amgen, Bristol Myers Squibb, Janssen-Cilag, Celgene, GlaxoSmithKline, Karyopharm (advisory board only), Roche (advisory board only), Sanofi and Takeda; and travel support from Amgen, Bristol Myers Squibb, Janssen-Cilag, Celgene, Sanofi and Takeda, all outside the submitted work.

DR has no conflicts of interest to declare.

DW has received personal fees (honoria) from Amgen, Antengene, Bristol Myers Squibb, Janssen, Karyopharm, Sanofi, and Takeda, all outside the submitted work.

M-VM has received personal fees (for both honoria and advisory boards) from AbbVie, Adaptive, Amgen, bluebird bio, Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi, Seagen, and Takeda, all outside the submitted work.

IS has received personal fees from Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, and Takeda; and non-financial support from Amgen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Novartis, Sanofi, and Takeda, all outside the submitted work.

ML has no conflicts of interest to declare.

JB has received research funding from AbbVie, Acetylon, Amgen, bluebird bio, Bristol Myers Squibb, Celgene, Celularity, CRISPR Therapeutics, EMD Serono, Genentech, GlaxoSmithKline, Ichnos Sciences, Incyte, Janssen, Lilly, Novartis, Poseida, Sanofi, Takeda, and Teva; and consultancy fees from bluebird bio, Bristol Myers Squibb, Celgene, CRISPR Therapeutics, Janssen, Kite Pharma, Legend Biotech, Secura Bio, Takeda, all outside the submitted work.

JLK has received grant funding from Bristol Myers Squibb, all for the work under consideration for publication. In addition, he has received grant funding from AbbVie, Bristol Myers Squibb, Celgene, Fortis

Therapeutics, Genentech, Janssen, Sanofi Genzyme, and Sutro Biopharma; and personal fees from AbbVie, Bristol Myers Squibb, Celgene, Genentech, Incyte, Janssen, Pharmacyclics, Sanofi Genzyme, Tecnofarma, and TG Therapeutics, all outside the submitted work.

AG is employee of Bristol Myers Squibb.

MPM is employee of Bristol Myers Squibb.

SL has received research support from Bristol Myers Squibb, Celgene, Janssen, and Takeda; served on advisory boards for AbbVie, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Novartis, and Takeda; and served as a member of the board of directors for TG therapeutics, all outside the submitted work.

KW has received grant funding from Celgene, all for the work under consideration for publication. In addition, she has received grant funding from Amgen, Celgene, Janssen, and Sanofi; and personal fees from AbbVie, Amgen, Adaptive Biotech, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, Roche, Sanofi, and Takeda; and non-financial support from Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Sanofi, and Takeda, all outside the submitted work.

Data sharing

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

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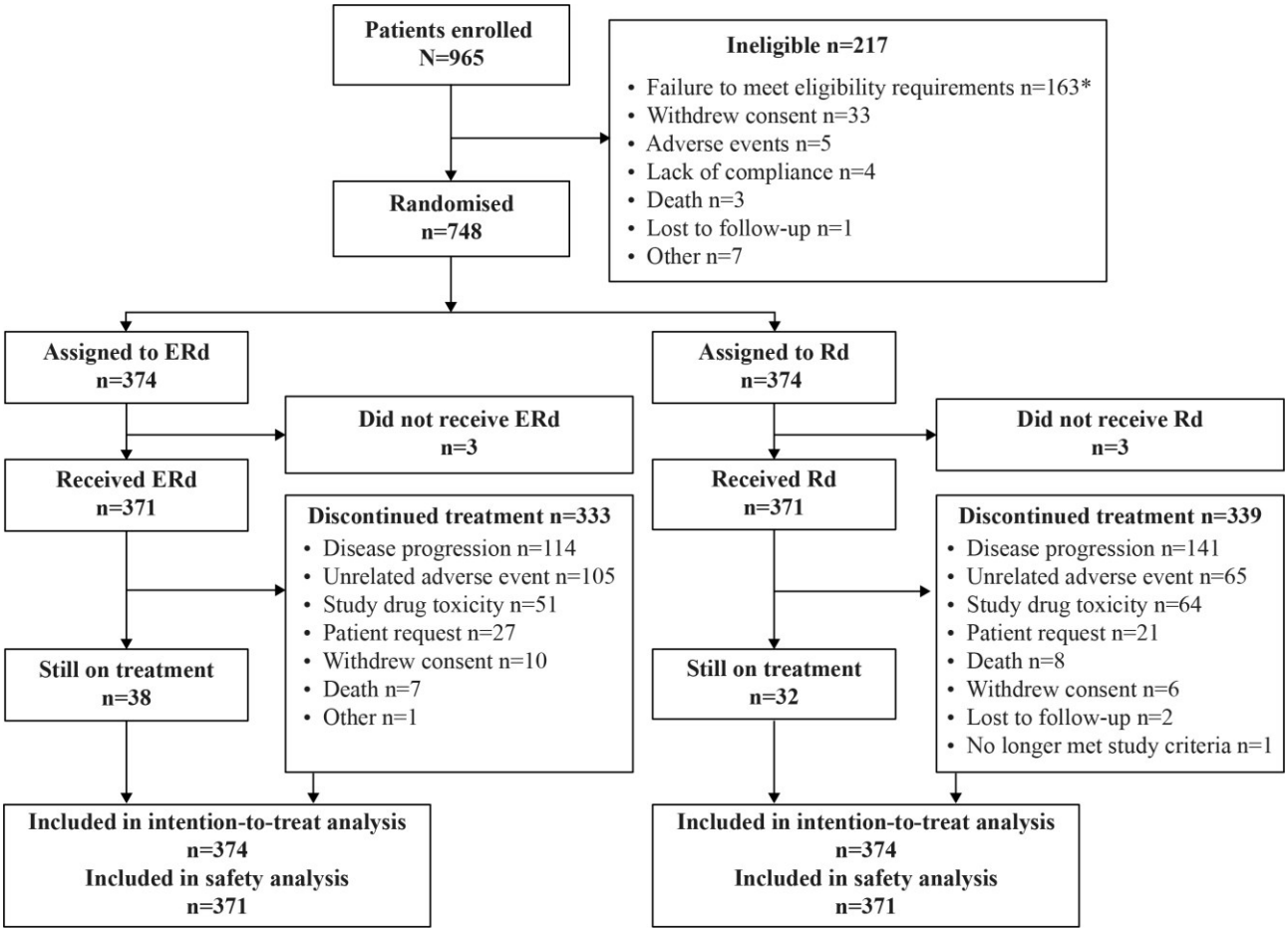
diagnosed multiple myeloma (NDMM). 62nd American Society of Hematology (ASH) Annual Meeting and Exposition; December 5–8, 2020. 2020.

Tables

See accompanying file for Tables.

Figure 1: **Trial profile**

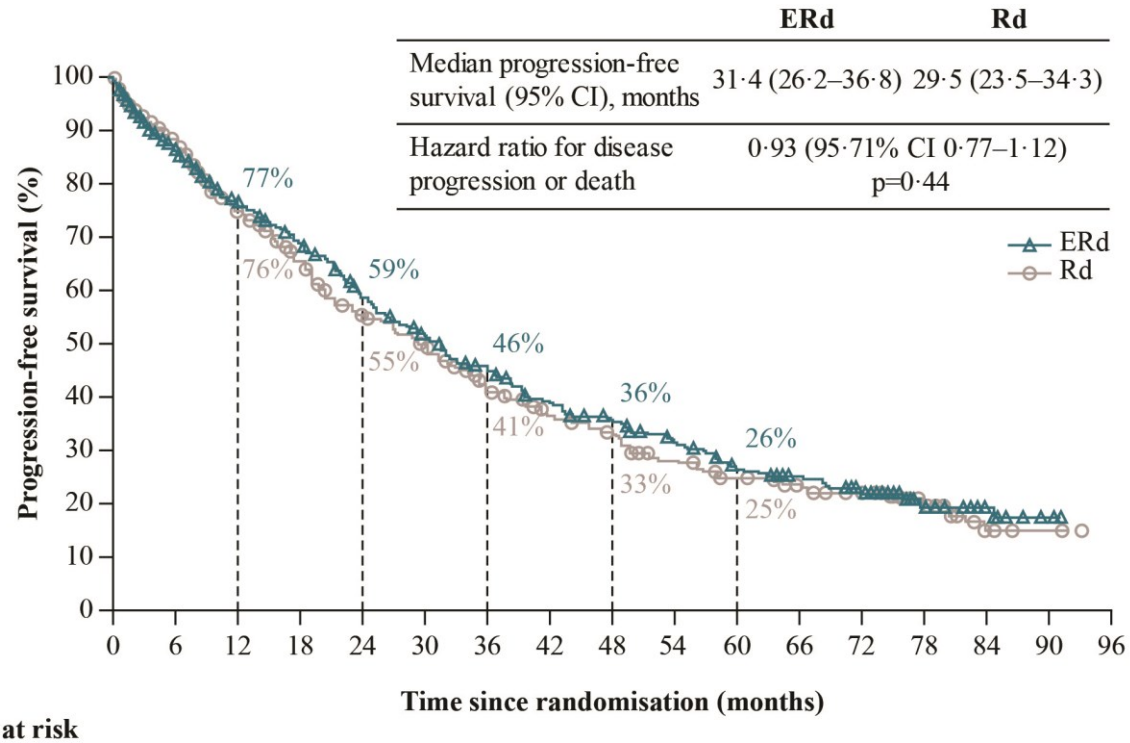


ECOG= Eastern Cooperative Oncology Group. ERd=elotuzumab, lenalidomide, and dexamethasone. Rd=lenalidomide and dexamethasone.

*The reasons for patients failing to meet eligibility requirements are as follows: did not meet criteria of having newly diagnosed, untreated, symptomatic, measurable myeloma and ineligibility for high-dose therapy plus SCT (n=72); did not meet protocol thresholds for creatinine clearance (n=22), neutrophil count, platelet count, or haemoglobin level (n=10), or alanine or aspartate aminotransferase level (n=2); significant cardiac disease, uncontrolled diabetes, HIV or hepatitis A–C infection, or any medical conditions that would impose excessive risk (n=22); prior or concurrent malignancy (n=12); not willing to comply with protocol requirements (n=3); ECOG performance status >2 (n=2); age (n=1); began treatment earlier than planned due to aggressive myeloma (n=1); unable to tolerate thromboembolic prophylaxis (n=1); unable to obtain bone marrow aspirate (n=1); inadvertently took dose of study drug (excluded by medical monitor, n=1); did not meet eligibility criteria for other reason (n=13).

Figure 2: **Progression-free survival**

(A) Kaplan–Meier plot of progression-free survival at final analysis in all randomised patients

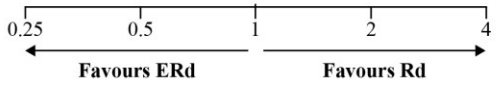


Number at risk (number censored)

ERd	374 (0)	294 (31)	252 (41)	222 (45)	186 (50)	158 (56)	133 (63)	109 (67)	97 (71)	78 (78)	61 (83)	54 (87)	41 (94)	21 (110)	11 120)	4 (126)	0 (130)
Rd	374 (0)	296 (37)	242 (51)	193 (64)	160 (69)	142 (71)	112 (77)	96 (81)	85 (83)	69 (86)	58 (89)	50 (94)	42 (98)	30 (109)	8 (126)	3 (131)	0 (34)

(B) Subgroup analysis of progression-free survival

Subgroup	ERd	Rd	Hazard ratio for disease progression or death (95% CI)
	Events/patients		
Overall	244/374	240/374	0·93 (95·71% CI 0·77–1·12)
Age, years			
<75	157/228	144/226	0·97 (0·77–1·22)
⩾75	87/146	96/148	0·91 (0·68–1·22)
⩾65	230/354	233/354	0·92 (0·76–1·10)
Sex			
Male	135/211	135/201	0·85 (0·67–1·08)
Female	109/163	105/173	1·08 (0·83–1·42)
Baseline serum beta–2 microglobulin			
<3.5 mg/L	77/137	69/117	0·89 (0·64–1·23)
⩾3.5 mg/L	166/235	170/256	1·01 (0·82–1·26)
ISS Stage at enrolment			
I or II	166/269	167/271	0·92 (0·74–1·14)
III	78/105	73/103	0·99 (0·72–1·36)
Baseline LDH			
<300 U/L	191/284	176/287	1·01 (0·82–1·24)
⩾300 U/L	45/78	57/78	0·70 (0·48–1·04)
Region			
North America	66/117	75/135	0·82 (0·59–1·15)
Europe	153/214	141/207	1·02 (0·81–1·29)
Baseline ECOG performance status			
0	85/134	94/135	0·77 (0·58–1·04)
1 or 2	159/240	146/239	1·05 (0·84–1·32)
Risk catergory			
High risk	27/31	28/35	0·96 (0·56–1·64)
Standard risk	205/328	199/314	0·93 (0·76–1·12)
del(17p), t(4;14), or t(14;16)			
Yes	35/43	35/45	0·97 (0·61–1·56)
No	191/307	191/303	0·93 (0·76–1·13)
del(17p), t(4;14), t(14;16), t(14;20), or 1q21			
Yes	108/140	106/138	1·03 (0·78–1·34)
No	109/186	105/179	0·95 (0·73–1·25)
Baseline creatinine clearance			
<60 mL/min	95/146	111/171	1·04 (0·79–1·37)
⩾60 mL/min	149/226	129/203	0·92 (0·73–1·17)



Symbols represent censored observations in panel A.

CI=confidence interval. ECOG=Eastern Cooperative Oncology Group. ERd=elotuzumab, lenalidomide and dexamethasone. ISS=International Staging System. LDH=lactate dehydrogenase. Rd=lenalidomide and dexamethasone.

Tables

Table 1: **Baseline characteristics and demographics**

	Elotuzumab, lenalidomide, and dexamethasone group (n=374)	**Lenalidomide and dexamethasone group (n=374)**
Age, years	73·0 (47·0–95·0)	73·0 (46·0–92·0)
<65	20 (5%)	20 (5%)
≥65 to <75	208 (56%)	206 (55%)
≥75	146 (39%)	148 (40%)
Sex		
Male	211 (56%)	201 (54%)
Female	163 (44%)	173 (46%)
Race*		
White	360 (96%)	351 (94%)
Black or African American	13 (3%)	16 (4%)
Asian	1 (<1%)	4 (1%)
Native Hawaiian or other Pacific Islander	0	1 (<1%)
ECOG performance status		
0	134 (36%)	135 (36%)
1	196 (52%)	172 (46%)
2	44 (12%)	67 (18%)
ISS stage		
Stage I	114 (31%)	101 (27%)
Stage II	155 (41%)	170 (46%)
Stage III	105 (28%)	103 (28%)
Lactate dehydrogenase (U/L)		
<300	284 (76%)	287 (77%)
≥300	78 (21%)	78 (21%)
Not reported	12 (3%)	9 (2%)
Lytic bone lesions		
0	122 (33%)	116 (31%)
1–3	51 (14%)	69 (18%)
≥3	196 (52%)	184 (49%)
Not reported	5 (1%)	5 (1%)

Risk category†		
High risk	31 (8%)	35 (9%)
Low risk	1 (<1%)	3 (1%)
Standard risk	328 (88%)	314 (84%)
Not evaluable	14 (4%)	22 (6%)
del(17p)‡		
Yes	12 (3%)	20 (5%)
No	343 (92%)	333 (89%)
Not reported	19 (5%)	21 (6%)
t(4;14)‡		
Yes	26 (7%)	23 (6%)
No	335 (90%)	326 (87%)
Not reported	13 (4%)	25 (7%)
1q21‡		
Yes	122 (33%)	115 (31%)
No	242 (65%)	241 (64%)
Not reported	10 (3%)	18 (5%)
Creatinine clearance (mL/min)		
<60	146 (39%)	171 (46%)
≥60	226 (60%)	203 (54%)
Not reported	2 (1%)	0
Plasmacytoma		
Yes	37 (10%)	42 (11%)
No	218 (58%)	212 (57%)
Not reported/unknown	119 (32%)	120 (32%)

Data are median (range) or n (%).

*In the lenalidomide and dexamethasone group, one patient's race was reported as "other" and one patient's race was not reported. †High risk: ISS stage II or III and t(4;14) or del(17p) abnormality. Low risk: ISS stage I or II and absence of t(4;14), del(17p), and 1q21 abnormalities and age <55 years. Standard risk: any patients not meeting the definition of high or low risk. Not evaluable: Patients having missing data preventing the classification in the other three categories. Definition of risk based on International Myeloma Working Group consensus criteria.[23]

‡Positive score for each abnormality tested was assigned based on identifying at least one abnormal cell out of the cells examined for all aberrations except del(17p) where a 7·5% cut-off was applied. Fluorescence in situ hybridisation was performed without CD138+ enrichment.

ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System.

Table 2: **Overall response rate and best overall response per IRC in all randomised patients**

	Elotuzumab, lenalidomide, and dexamethasone group (n=374)	**Lenalidomide and dexamethasone group (n=374)**
Overall response rate*,†	310 (83%)	297 (79%)
95% CI	78·7–86·6	75·0–83·4
Odds ratio (95% CI)‡	1·26 (0·87–1·82)	
Best overall response		
Stringent complete response	32 (9%)	32 (9%)
Complete response	35 (9%)	38 (10%)
Very good partial response	130 (35%)	114 (31%)
Partial response	113 (30%)	113 (30%)
Minimal response	16 (4%)	31 (8%)
Stable disease	19 (5%)	19 (5%)
Progressive disease	6 (2%)	6 (2%)
Could not be determined/not reported	23 (6%)	21 (6%)

Data are n (%) unless indicated otherwise.

*sCR + CR + VGPR + PR. CI is based on the Clopper and Pearson method. †Alpha for overall response rate is 0·05. ‡Stratified by ISS stage (I–II *vs* III), age (<75 years old *vs* ≥75 years old), and ECOG performance status (0 *vs* 1–2) at randomization. Common odds ratio calculated using the Cochran–Mantel–Haenszel method for the ratio or ERd to Rd. CI=confidence interval. CR=complete response. ECOG=Eastern Cooperative Oncology Group. ERd=elotuzumab, lenalidomide, and dexamethasone. IRC=independent review committee. ISS=International Staging System. PR=partial response. Rd=lenalidomide and dexamethasone. sCR=stringent CR. VGPR=very good partial response.

Table 3: **Summary of adverse events in all treated patients**

	Elotuzumab, lenalidomide, and dexamethasone group (n=371)				Lenalidomide and dexamethasone group (n=371)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	32 (9%)	174 (47%)	78 (21%)	86 (23%)	30 (8%)	203 (55%)	82 (22%)	55 (15%)
Non-haematological adverse events								
Diarrhoea	163 (44%)	31 (8%)	1 (<1%)	0	160 (43%)	21 (6%)	0	0
Peripheral oedema	154 (42%)	8 (2%)	0	0	165 (44%)	16 (4%)	0	0
Constipation	138 (37%)	5 (1%)	0	0	140 (38%)	5 (1%)	0	0
Fatigue	137 (37%)	42 (11%)	3 (1%)	0	145 (39%)	41 (11%)	1 (<1%)	0
Cough	116 (31%)	3 (1%)	0	0	101 (27%)	5 (1%)	0	0
Nausea	114 (31%)	3 (1%)	0	0	104 (28%)	4 (1%)	0	0
Back pain	110 (30%)	26 (7%)	2 (1%)	0	118 (32%)	18 (5%)	0	0
Pyrexia	110 (30%)	9 (2%)	0	0	80 (22%)	2 (1%)	0	0
Decreased appetite	99 (27%)	2 (1%)	0	0	83 (22%)	2 (1%)	0	0
Insomnia	88 (24%)	9 (2%)	1 (<1%)	0	88 (24%)	7 (2%)	0	0
Arthralgia	88 (24%)	7 (2%)	0	0	90 (24%)	12 (3%)	0	0
Rash	88 (24%)	3 (1%)	0	0	76 (20%)	12 (3%)	0	0
Muscle spasms	79 (21%)	5 (1%)	0	0	83 (22%)	0	0	0
Dizziness	75 (20%)	8 (2%)	1 (<1%)	0	58 (16%)	8 (2%)	0	0
Dyspnoea	75 (20%)	19 (5%)	2 (1%)	0	74 (20%)	16 (4%)	4 (1%)	1 (<1%)
Upper respiratory tract infection	74 (20%)	8 (2%)	0	0	81 (22%)	2 (1%)	0	1 (<1%)
Weight decreased	74 (20%)	3 (1%)	0	0	62 (17%)	4 (1%)	0	0
Pain in extremity	71 (19%)	3 (1%)	1 (<1%)	0	67 (18%)	11 (3%)	0	0
Asthenia	67 (18%)	22 (6%)	0	0	63 (17%)	13 (4%)	0	0
Vomiting	66 (18%)	5 (1%)	0	0	48 (13%)	0	0	0
Musculoskeletal pain	66 (18%)	4 (1%)	0	0	61 (16%)	4 (1%)	0	0
Hyperglycaemia	63 (17%)	51 (14%)	7 (2%)	0	32 (9%)	33 (9%)	4 (1%)	0
Hypotension	62 (17%)	4 (1%)	0	0	41 (11%)	4 (1%)	0	1 (<1%)
Tremor	60 (16%)	1 (<1%)	0	0	52 (14%)	3 (1%)	0	0
Nasopharyngitis	59 (16%)	1 (<1%)	0	0	62 (17%)	0	0	0
Headache	59 (16%)	2 (1%)	0	0	47 (13%)	2 (1%)	0	0
Bone pain	55 (15%)	4 (1%)	1 (<1%)	0	48 (13%)	10 (3%)	1 (<1%)	0

	Elotuzumab, lenalidomide, and dexamethasone group (n=371)				Lenalidomide and dexamethasone group (n=371)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Peripheral sensory neuropathy	52 (14%)	5 (1%)	0	0	56 (15%)	3 (1%)	0	0
Blood creatinine increased	49 (13%)	5 (1%)	1 (<1%)	0	68 (18%)	4 (1%)	1 (<1%)	0
Hypokalaemia	49 (13%)	27 (7%)	8 (2%)	0	57 (15%)	30 (8%)	3 (1%)	0
Abdominal pain	48 (13%)	3 (1%)	0	0	45 (12%)	6 (2%)	0	0
Contusion	47 (13%)	0	0	0	53 (14%)	0	0	0
Urinary tract infection	47 (13%)	17 (5%)	2 (1%)	0	50 (13%)	11 (3%)	0	0
Musculoskeletal chest pain	47 (13%)	2 (1%)	0	0	47 (13%)	1 (<1%)	0	0
Hypertension	45 (12%)	8 (2%)	0	0	35 (9%)	11 (3%)	0	0
Dysphonia	44 (12%)	1 (<1%)	0	0	27 (7%)	0	0	0
Dyspepsia	43 (12%)	0	0	0	29 (8%)	1 (<1%)	0	0
Hypocalcaemia	42 (11%)	14 (4%)	18 (5%)	0	57 (15%)	11 (3%)	10 (3%)	0
Anxiety	41 (11%)	3 (1%)	0	0	25 (7%)	3 (1%)	0	0
Respiratory tract infection	40 (11%)	2 (1%)	1 (<1%)	1 (<1%)	32 (9%)	2 (1%)	0	0
Influenza-like illness	39 (11%)	0	0	0	25 (7%)	3 (1%)	0	0
Peripheral neuropathy	39 (11%)	3 (1%)	0	0	41 (11%)	7 (2%)	0	0
Pruritus	39 (11%)	1 (<1%)	0	0	44 (12%)	0	0	0
Paraesthesia	39 (11%)	0	0	0	44 (12%)	1 (<1%)	0	0
Depression	38 (10%)	5 (1%)	0	0	27 (7%)	4 (1%)	0	0
Bronchitis	37 (10%)	16 (4%)	0	0	49 (13%)	6 (2%)	0	0
Muscular weakness	37 (10%)	9 (2%)	0	0	45 (12%)	8 (2%)	0	0
Hypomagnesaemia	36 (10%)	6 (2%)	0	0	21 (6%)	1 (<1%)	1 (<1%)	0
Confusional state	36 (10%)	3 (1%)	1 (<1%)	0	27 (7%)	5 (1%)	1 (<1%)	0
Pneumonia	27 (7%)	43 (12%)	5 (1%)	9 (2%)	23 (6%)	34 (9%)	5 (1%)	5 (1%)
Cataract	26 (7%)	42 (11%)	0	0	29 (8%)	29 (8%)	0	0
Atrial fibrillation	21 (6%)	17 (5%)	2 (1%)	1 (<1%)	24 (6%)	10 (3%)	2 (1%)	0
Syncope	4 (1%)	17 (5%)	0	0	8 (2%)	16 (4%)	0	0
Acute kidney injury	4 (1%)	17 (5%)	5 (1%)	2 (1%)	8 (2%)	11 (3%)	6 (2%)	1 (<1%)
Haematological adverse events	103 (28%)	97 (26%)	23 (6%)	0	95 (26%)	112 (30%)	25 (7%)	0
Anaemia	103 (28%)	45 (12%)	4 (1%)	0	96 (26%)	62 (17%)	5 (1%)	0
Thrombocytopenia	43 (12%)	15 (4%)	8 (2%)	0	46 (12%)	15 (4%)	9 (2%)	0
Neutropenia	30 (8%)	57 (15%)	7 (2%)	0	39 (11%)	65 (18%)	14 (4%)	0

	Elotuzumab, lenalidomide, and dexamethasone group (n=371)				Lenalidomide and dexamethasone group (n=371)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Adverse events of special interest								
Infections and infestations	151 (41%)	99 (27%)	19 (5%)	25 (7%)	174 (47%)	75 (20%)	8 (2%)	15 (4%)
Cardiac disorders	76 (20%)	33 (9%)	12 (3%)	19 (5%)	59 (16%)	25 (7%)	6 (2%)	12 (3%)
Secondary primary malignancy	42 (11%)				36 (10%)			

Data are n (%). Includes adverse events and serious adverse events reported between the first dose of study drug and 60 days after the last dose of study drug, regardless of causality. Grade 1–2 adverse events that were reported in at least 10% of patients in either treatment group and grade 3, 4, and 5 adverse events that were reported in at least 5% of patients in either treatment group are shown, with the exception of adverse events of special interest.