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Lenalidomide before and after ASCT for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial

Running head: Lenalidomide induction and maintenance in multiple myeloma

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KEY POINTS

- Induction therapy with CRD improved PFS and OS compared with CTD in transplant-eligible patients with newly diagnosed multiple myeloma.
- The best results were achieved when patients received CRD induction therapy and lenalidomide maintenance post-ASCT.

ABSTRACT

The optimal way to use immunomodulatory drugs as components of induction and maintenance therapy for multiple myeloma is unresolved. We addressed this question in a large phase III randomized trial, Myeloma XI. Patients with newly diagnosed multiple myeloma (n = 2042) were randomized to induction therapy with cyclophosphamide, thalidomide, and dexamethasone (CTD) or cyclophosphamide, lenalidomide, and dexamethasone (CRD). Additional intensification therapy with cyclophosphamide, bortezomib, and dexamethasone (CVD) was administered before ASCT to patients with a suboptimal response to induction therapy using a response-adapted approach. After receiving high-dose melphalan with autologous stem cell transplantation (ASCT), eligible patients were further randomized to receive either lenalidomide alone or observation alone. Co-primary endpoints were progression-free survival (PFS) and overall survival (OS). The CRD regimen was associated with significantly longer PFS (median: 36 vs. 33 months; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.75-0.96; *P* = 0.0116) and OS (3-year OS: 82.9% vs. 77.0%; HR, 0.77; 95% CI, 0.63-0.93; *P* = 0.0072) compared with CTD. The PFS and OS results favored CRD over CTD across all subgroups, including patients with International Staging System stage III disease (HR for PFS, 0.73; 95% CI, 0.58-0.93; HR for OS, 0.78; 95% CI, 0.56-1.09), high-risk cytogenetics (HR for PFS, 0.60; 95% CI, 0.43-0.84; HR for OS, 0.70; 95% CI, 0.42-1.15) and ultra high-risk cytogenetics (HR for PFS, 0.67; 95% CI, 0.41-1.11; HR for OS, 0.65; 95% CI, 0.34-1.25). Among patients randomized to lenalidomide maintenance (n = 451) or observation (n = 377), maintenance therapy improved PFS (median: 50 vs. 28 months; HR, 0.47; 95% CI, 0.37-0.60; *P* < 0.0001). Optimal results for PFS and OS were achieved in the patients who received CRD induction and lenalidomide maintenance. The trial was registered with the EU Clinical Trials Register (EudraCT 2009-010956-93) and ISRCTN49407852.

Introduction

The introduction of novel agents, such as immunomodulatory drugs (IMiDs) and proteasome inhibitors, has contributed to the recent dramatic improvements in outcomes observed for patients with multiple myeloma.(1-3) Following induction, high-dose melphalan-based chemotherapy with autologous stem cell transplantation (ASCT) remains the standard of care for eligible patients.(4-9) The optimal approach to induction therapy prior to ASCT and consolidation or maintenance after ASCT in this new era has not yet been defined. However, several principles have been established, including the value of using at least triplet combinations of agents that can induce deeper, longer remissions by targeting different clonal populations.(10, 11)

The efficacy of IMiDs in multiple myeloma has been linked to their mode of action. These drugs target the cereblon ubiquitin ligase complex, which leads to both tumoricidal effects early on and immunomodulatory effects beneficial for long-term tumor control.(12-15) The IMiDs thalidomide and lenalidomide are recognized as effective treatment options in both the induction (7, 9, 10, 16-18) and maintenance settings.(6, 19-21) Lenalidomide has fewer side effects than thalidomide, enabling long-term treatment and disease control.[19-21] We have addressed how to optimize the use of these agents between induction and maintenance for patients receiving ASCT in a large, randomized trial (UK National Cancer Research Institute [NCRI] Myeloma XI).

Methods

The Myeloma XI study had a multifactorial design enabling the investigation of a number of pertinent clinical questions with adequate statistical control and power. Importantly, the influence of one phase of treatment or question on another could be separated and controlled for. This was achieved by stratifying the consolidation and maintenance randomizations for earlier treatment allocations. This report concentrates on induction and its interaction with maintenance therapy in the transplant eligible population of patients within the trial. The other questions posed by the study are addressed in separate manuscripts.

Study design and eligibility criteria

The Myeloma XI trial was a phase III, open-label, parallel-group, multi-arm, adaptive design trial with 3 randomization stages conducted at 110 National Health Service hospitals in England, Wales, and Scotland (see **Supplementary Data** for list of study sites with principal investigators and number of patients recruited). Eligible patients were aged ≥18 years and newly diagnosed with multiple myeloma. Exclusion criteria included previous or concurrent malignancies (including myelodysplastic syndromes), grade ≥2 peripheral neuropathy, acute renal failure (unresponsive to up to 72 hours of rehydration, characterized by creatinine >500 μmol/L or urine output <400 mL/day or requiring dialysis), and active or prior hepatitis C infection.

The trial design included an intensive treatment pathway for transplant-eligible patients and a less-intensive treatment pathway for transplant-ineligible patients. Strict age limits were deliberately avoided so that fit, older patients could receive intensive therapy and ASCT. The decision of treatment pathway was made on an individual patient basis taking into account performance status, clinician judgment, and patient preference.

Transplant-eligible patients were randomized on a 1:1 basis to cyclophosphamide, lenalidomide, and dexamethasone (CRD) or cyclophosphamide, thalidomide, and

dexamethasone (CTD) (induction randomization), stratified according to certain factors (**Supplementary Methods**). Patients received a minimum of 4 cycles in the absence of progressive disease (PD), and treatment continued until maximum response was achieved.

Additional intensification therapy before ASCT was administered to patients with a suboptimal response to induction therapy using a response-adapted approach: patients with stable disease (SD) after induction therapy or those with PD at any time during induction therapy received a maximum of 8 cycles of cyclophosphamide, bortezomib, and dexamethasone (CVD); patients with a minimal response (MR) or partial response (PR) were randomized (1:1) to CVD or no CVD. Patients with very good partial response (VGPR) or complete response (CR) received no additional therapy before ASCT. The results of the intensification randomisation have been published elsewhere.(22)

Three months after ASCT, eligible patients were randomized to observation or to maintenance therapy with lenalidomide alone, or in combination with vorinostat until unacceptable toxicity or PD. Patients were excluded from maintenance randomization if they did not respond to CRD induction, had no response to any prior study treatment, had PD, or relapsed after achieving CR. Randomized patients were stratified according to treatment center and previous randomization group(s). The results of the maintenance randomization have been published elsewhere.(23)

Further details on the dose and schedule of all study treatments are provided in **Supplementary Table 1**, and a flow diagram of the CRD and CTD patient groups is shown in **Supplementary Figure 1.**

The study was approved by the national ethics review board (National Research Ethics Service, London, UK), institutional review boards of the participating centres, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London, UK). All patients provided written informed consent. The trial was registered with the EU Clinical Trials Register (EudraCT number, 2009-010956-93) and ISRCTN49407852.

Study endpoints and statistical analysis

The co-primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints included PFS Two (PFS2), response, and safety. Further details regarding the statistical analysis are provided in the **Methods section in the Supplementary Data**.

Results

Patients

Between May 26, 2010 and April 20, 2016, 2042 transplant-eligible patients underwent induction randomization (**Supplementary Figure 1**). Baseline characteristics were well balanced between the 2 treatment groups (**Table 1**). Overall, the median patient age was 61 years (range, 28-75 years), 60% of patients were male, and 24% had International Staging System (ISS) stage III disease. Of the 836 (40.9%) patients for whom genetic risk could be calculated, 266 (31.8%) had high-risk and 111 (13.3%) had ultra-high-risk cytogenetics. The median follow-up duration from study entry was 36.3 months (interquartile range [IQR], 23.0-48.5 months).

Induction randomization results

PFS and OS

Disease progression or death occurred in 456 patients in the CRD group and in 509 patients in the CTD group. The CRD regimen was associated with significantly longer PFS than the CTD regimen (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.75-0.96; *P* = 0.0116; **Figure 1A**). The median PFS was 36 months (95% CI, 33-39) with CRD and 33 months (95% CI, 31-35) with CTD. Median overall survival has not yet reached with current follow up. Death occurred in 185 patients in the CRD group and in 230 patients in the CTD group. There was also a statistically significant difference in OS favoring CRD (HR, 0.77; 95% CI, 0.63-0.93; *P* = 0.0072; **Figure 1B**). The 3-year OS rate was 82.9% (95% CI, 80.2-85.7) with CRD and 77.0% (95% CI, 73.9-80.0) with CTD.

Subgroup analyses indicated that PFS and OS favored CRD over CTD across all subgroups (**Figure 2**). In the subset of patients with ISS stage III disease, CRD was superior to CTD for PFS (HR, 0.73; 95% CI, 0.58-0.93) and there was a trend toward improved OS (HR, 0.78; 95% CI, 0.56-1.09). In each case, there was no evidence of heterogeneity of

treatment effect (PFS: *P* = 0.2645; OS: *P* = 0.7606) (**Figure 2**). Similar results were seen in the subgroup of patients with high-risk cytogenetics (HR for PFS, 0.60; 95% CI, 0.43-0.84; HR for OS, 0.70; 95% CI, 0.42-1.15) and ultra-high risk cytogenetics (HR for PFS, 0.67; 95% CI, 0.41-1.11; *P* = 0.6164; HR for OS, 0.65; 95% CI, 0.34-1.25; *P* = 0.8131), with no significant heterogeneity of treatment effect observed (**Figure 2**).

PFS2, a secondary endpoint, was also analyzed. CRD was associated with significantly longer PFS2 than the CTD (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.65-0.90; *P* = 0.001; **Supplemental Figure 2**). The median PFS2 was 59 months (95% Cl, 55-63) with CRD and 54 months (95% CI, 49-60) with CTD.

Response

After induction triplet therapy, the proportion of patients with VGPR or better was significantly higher with CRD compared with CTD (60.4% vs. 52.9%; *P* = 0.0006) (**Table 2**). The odds ratio (OR) of 1.37 (95% CI, 1.15-1.65) indicates a 37% increase in the odds of achieving a deep remission in the CRD group compared with the CTD group. After ASCT, the proportion of patients achieving VGPR or better remained higher in the CRD group than in the CTD group, but the difference was not statistically significant (81.5% vs. 76.9%; OR, 1.25; 95% CI, 0.94-1.66*; P* = 0.1277) (**Table 2**).

Due to the lower induction response rate with CTD compared with CRD, more patients underwent CVD intensification as per protocol (CRD, 11.8% vs. CTD, 13.3%). The interaction between induction therapy and CVD was therefore examined further. Counterfactual estimates of the survivor function if CVD rescue treatment was not received by any patients maintained differences in median PFS (CRD: 36 months [95% CI, 33-39] vs. CTD: 33 months [95% CI, 30-34]); **Supplemental Figure 3A**) and 3-year OS rate (CRD: 82.9% [95% CI, 80.0-85.5] vs. CTD: 76.3% [95% CI, 73.0-79.2]; **Supplemental Figure 3B**). Similar counterfactual estimates obtained in the scenario where patients randomized to no CVD after PR/MR were treated with CVD provided similar estimates for median PFS (CRD:

36 months [95% CI, 33-39] vs. CTD: 33 months [95% CI, 31-36]); **Supplemental Figure 3C**) and 3-year OS rate (CRD: 83.1% [95% CI, 80.2-85.6] vs. CTD: 77.3% [95% CI, 74.1-80.2]; **Supplemental Figure 3D**). After adjustment for the effect of CVD treatment in a counterfactual analysis, the hazard ratios for PFS and OS were 0.82 (95% CI, 0.69-0.96) and 0.69 (95% CI, 0.53-0.91), respectively. This suggests a greater treatment effect of CRD induction treatment on PFS and particularly OS than apparent with the unadjusted ITT analysis (**Supplemental Figure 3A** and **3B**, respectively). Full results of the CVD intensification randomization have been presented elsewhere.(22)

Safety

The median number of cycles of induction therapy delivered was 5 (range, 1-18) for CRD and 5 (range, 1-12) for CTD. The median percentage of minimum protocol-defined delivered dose of lenalidomide and thalidomide during induction therapy was 116.7% (IQR, 96.4-150.0) and 100.0% (IQR, 71.4-128.6), respectively. Lenalidomide dose modifications occurred in 391 (38.3%) patients who received CRD induction therapy, and thalidomide dose modifications occurred in 751 (73.6%) patients who received CTD induction therapy. The rate of discontinuation of induction therapy due to AEs was similar with CRD and CTD (51 patients [5.0%] and 68 patients [6.7%], respectively). Overall, 64.4% of patients proceeded to ASCT following induction +/- intensification. There was no difference in the proportion of patients undergoing ASCT between those receiving CTD (63.3%) or CRD (65.5%) induction suggesting this was not due to induction related toxicity. The most common reason for not proceeding was “Patient not fit/clinicians decision” in 36.1% of cases.

Differences in the safety profile of CRD and CTD were consistent with the known side effects of lenalidomide and thalidomide (**Table 3**). In general, CRD was associated with a higher rate of grade ≥3 neutropenia (22.3% vs. 11.7%) and diarrhea (2.6% vs. 1.0%), whereas CTD was associated with a higher rate of grade ≥3 peripheral sensory neuropathy (1.5% vs. 0.6%) and constipation (1.9% vs. 0.8%). The incidence of deep vein thrombosis

was 5.7% in the CRD group and 4.8% in the CTD group; pulmonary embolism was reported in 3.2% and 4.9% of patients, respectively.

The 3-year cumulative incidence of invasive second primary malignancies (SPM) was low and comparable between CRD and CTD (2.9% [95% CI, 1.7-4.1] vs. 1.5% [95% CI, 0.6-2.4]; HR, 1.60 [95% CI, 0.87-2.93]; *P* = 0.1311). The SPM incidence rate per 100 patient-years was 1.2 (95% CI, 0.8-1.7) in the CRD group and 0.9 (95% CI, 0.6-1.3) in the CTD group.

The incidence of serious AEs during induction was similar with CRD and CTD (59.0% vs. 57.7%). Infection accounted for nearly half of all serious AEs reported during induction (45.2% for CRD vs. 46.4% for CTD). Fatal AEs occurred in 6 patients in the CRD group and in 3 patients in the CTD group. Of the 9 patients with grade 5 AEs, 1 had 3 concurrent events (renal failure, liver failure, and sepsis), 1 had 2 concurrent events (small bowel obstruction and sepsis), and the remaining 7 patients had 1 event each (pneumonia [n = 2]; sepsis [n = 2]; collapse/syncope [n = 2]; lower respiratory tract infection [n = 1]; hepatitis encephalopathy [n = 1]).

Interaction of lenalidomide induction and maintenance

Following ASCT, patients were randomized between maintenance lenalidomide and observation, giving us the opportunity to explore the interaction between induction and maintenance agents in this setting. Of the 2042 transplant-eligible patients that entered the first randomization, 1024 entered the maintenance phase and were randomized to lenalidomide alone (n = 451), to lenalidomide plus vorinostat (n = 196, not included in this further analysis), or to observation (n = 377). Baseline characteristics of patients undergoing maintenance randomization were well balanced between the 2 treatment groups (**Supplementary Table 2**). Approximately half of patients in both the lenalidomide and observation groups had received CRD as induction therapy (230 of 451 [51.0%] in the lenalidomide group; 190 of 377 [50.4%] in the observation group). Lenalidomide

maintenance was associated with significantly longer PFS and OS compared with observation in transplant-eligible patients (median: 50 vs. 28 months; HR, 0.47; 95% CI, 0.37-0.60; $P < 0.0001$ at a median follow-up duration of 27.2 [IQR, 12.8-42.0] months).

In a post hoc exploratory analysis, the longest PFS was observed in patients who received CRD induction and lenalidomide maintenance. Median PFS in this group was not reached, while it was 49 months in those who received CTD and lenalidomide maintenance, 32 months in those who received CTD and observation, and 24 months in those who received CRD and observation (**Figure 3A**). Similarly, the longest OS was observed in patients who received CRD induction and lenalidomide maintenance. The median OS was not reached in any group, but 3-year OS rates were 92.3% for those who received CRD induction with lenalidomide maintenance, 89.0% in those who received CTD and lenalidomide maintenance, 86.0% in those who received CTD and observation, and 90.3% in those who received CRD and observation (**Figure 3B**).

Discussion

This is the largest study to evaluate the CRD regimen as induction therapy before ASCT in patients with multiple myeloma. We show that it is associated with excellent efficacy and safety data and the results are consistent with prior studies evaluating either CTD,(17, 18, 24) CRD as induction therapy,(25) or CRD as treatment in the relapsed/refractory disease setting.(26)

A direct comparison of thalidomide and lenalidomide as the immunomodulatory agent component of induction therapy has not been previously undertaken in the context of a randomized trial for transplant eligible newly diagnosed myeloma patients. Our results demonstrate the superiority of lenalidomide over thalidomide both in terms of efficacy and tolerability in the context of combination with an alkylating agent (cyclophosphamide), supporting the findings of previous non-randomised analyses.(27, 28) Previous randomized studies in patients not eligible for stem cell transplant have compared thalidomide to lenalidomide in combination with the alkylating agent melphalan.(29, 30) In these studies no difference between lenalidomide and thalidomide in terms of response, progression-free or overall survival was identified. The differences between these prior studies and the finding from Myeloma XI might be explained by the different patient population or the different alkylating agent, cyclophosphamide, which may be better tolerated than melphalan.

Response rates obtained with CRD in the current study were good: 60% of patients achieved at least a VGPR after induction and 82% did so post ASCT. This compares favorably with other novel-agent-based triplet induction therapies, including bortezomib, doxorubicin, and dexamethasone (VAD), (31, 32) CVD,(32) bortezomib, thalidomide, and dexamethasone (VTD),(5, 10, 33, 34) and even the IMiD/proteasome inhibitor regimen bortezomib, lenalidomide, and dexamethasone (VRD) (9, 35) (**Supplementary Table 3**). However there are many caveats to trying to compare results across trials. Particularly in comparing response rates it should be noted that patients in Myeloma XI received induction until maximum response rather than for a fixed duration and this may have led to deeper

responses prior to transplant than in other studies. Although immunomodulatory drug and proteasome inhibitor combinations (e.g. VTD/VRD) have more recently become widely used in the EU and USA this was not the position when the study was initially implemented. At that time either an immunomodulatory based regimen or a proteasome inhibitor based regimen (e.g. MPV or VD) was used. The standard of care in the UK, as in a number of other countries, was CTD. The addition of a proteasome inhibitor to induction regimens offers the potential to target immunomodulatory agent resistant subclones of disease with a second novel agent. This concept was explored in the intensification randomisation aspect of the study which has been previously reported (22) and demonstrated that intensification treatment with CVD significantly improved progression-free survival in patients with newly diagnosed multiple myeloma and a suboptimal response to immunomodulatory induction therapy compared with no intensification treatment.

The combination of a fourth agent with a different mechanism of action to induction, such as Daratumumab plus VTD (Dara-VTD) in the recently published Cassiopeia trial, is able to induce even deeper responses, with 83% of patients achieving at least VGPR.(36) PFS with Dara-VTD was prolonged compared to VTD alone, suggesting the addition of further agents to active triplets can improve outcomes yet further. In contrast, however, CRD offers an all oral regimen requiring only one hospital visit per month and including only one more expensive agent, lenalidomide. As such it is comparatively easier to deliver and likely to be cheaper in terms of both drug and administration costs. The lower incidence of peripheral neuropathy seen with CRD than that seen with combinations including bortezomib and/or thalidomide may also be beneficial for some patients.

The Myeloma XI data support the continued use of ASCT, since in a previous study of CRD without ASCT,(7) the median PFS was 28.6 months, which is lower than that achieved with CRD and ASCT in the Myeloma XI trial (36 months). Similarly, in the IFM 2009 study comparing VRD with or without ASCT, the combination of VRD and ASCT led to significantly better PFS than VRD alone (median: 50 vs. 36 months; $P < 0.001$).(9) Median

OS in that study was similar in both groups, likely due to the fact that 79% of patients assigned to VRD alone received salvage ASCT at relapse and the short current follow up. These findings and data from several other studies suggest a complementary role for novel agents and ASCT.

We have shown that treatment with lenalidomide maintenance therapy after ASCT is associated with improved PFS and OS, a finding consistent with other reports.(6, 19, 20, 37) We show that in Myeloma XI, the efficacy of lenalidomide maintenance was not diminished by prior exposure to lenalidomide; in fact, the best outcomes were achieved when lenalidomide was given as both induction and maintenance. This is similar to results seen in previous lenalidomide maintenance studies, which showed significant heterogeneity of effect of lenalidomide maintenance with outcomes favoring those who had received lenalidomide induction.(20, 38) This suggests that patients with disease sensitive to immunomodulation with lenalidomide will continue to benefit from its continued use, perhaps as the maintenance therapy targets quiescent cells as they come out of cycle.

We noted that patients receiving CRD+obs appeared to have slightly inferior PFS than patients receiving CTD+obs. This was not due to any apparent difference in early discontinuation of therapy or dose modifications and so is difficult to explain. The PFS difference is small, not statistically significant and may have occurred by chance. In the analysis of OS the reverse pattern was seen with patients receiving CRD+obs having an apparent improved overall survival compared to CTD+obs.

The results of Myeloma XI are likely to be reflective of the true impact of the CRD combination in clinical practice because of the limited exclusion criteria for the study population. Notably, there were no age restrictions for the intensive pathway, allowing older but fit patients to receive ASCT. The median age in this group was 61 years, and patients up to age 75 years were included. In contrast, most previous studies of ASCT have excluded patients aged over 65 or 70 years. Evidence suggests that fit patients aged >65 years can

benefit from ASCT, especially when combined with regimens containing novel agents.(3, 39, 40) Our approach may also explain the relatively lower proportion of patients proceeding to ASCT in this study than in other studies of induction therapy which are usually limited only to patients under the age of 65. The most common reason for patients not proceeding to stem cell transplant was given as “patient not fit/clinicians decision” suggesting that clinicians may have initially entered patients in the transplant eligible pathway of the study as a ‘trial of fitness’ so as not to limit their options prior to withdrawing the patient nearer the time of transplant.

In addition, the proportion of patients with ISS stage III disease (24%) in the present study was slightly higher than that in some recent studies of induction therapy.(9, 10, 31, 35) Cytogenetic abnormalities, such as t(4;14), t(14;16), and del(17p), are important prognostic markers, and should therefore be investigated in all patients with multiple myeloma according to the International Myeloma Working Group (IMWG) molecular classification.(41) Although cytogenetic data were only available for 41% of patients in our study, this percentage is comparable to that in other trials of patients with newly diagnosed multiple myeloma.(42)

While 3-drug induction regimens are generally more effective than 2-drug regimens, they may also be more toxic.(10, 11) In the Myeloma XI trial, the safety results for CRD and CTD were consistent with the known safety profiles of these agents. Notably, rates of peripheral neuropathy were lower with CRD than with CTD. An important safety concern with lenalidomide treatment in patients with newly diagnosed multiple myeloma is the risk of SPM.(43) In this population of transplant-eligible patients, the overall 3-year cumulative incidence of invasive SPM was low (2.2%; 95% CI, 1.5-3.0) and the type of induction therapy used did not appear to affect the SPM incidence rate. Safety results for lenalidomide maintenance compared to observation including SPM incidence have been previously published.(23, 44) Despite the risks associated with continued active therapy, registry data

suggest that health-related quality of life of patients receiving lenalidomide maintenance is similar to that of patients receiving no maintenance.(45)

In summary, induction therapy with CRD improved PFS and OS compared with CTD in transplant-eligible patients with newly diagnosed multiple myeloma. The best results were achieved when patients received both lenalidomide-based induction therapy and lenalidomide maintenance.

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Authorship and Disclosures

G.H.J., F.E.D., N.H.R., and G.J.M. were chief investigators; G.H.J., F.E.D., N.H.R., W.M.G., and G.J.M. designed the trial and developed the protocol; D.A.C., A.S., and W.M.G. developed and carried out the statistical analysis plan; G.H.J., F.E.D., C.P., J.R.J., B.K., M.G., C.D.W., K.K., J.L., D.A., S.S., M.W.J., G.C., N.H.R., M.F.K., R.G.O., and G.J.M. participated in recruitment of patients; M.F.K., M.T.D., R.G.O., and G.J.M. coordinated the central laboratory investigations; C.C. and A.W. coordinated the data collection and regulatory and governance requirements; G.H.J., F.E.D., C.P., D.A.C., A.S., M.F.K., M.T.D., R.G.O., W.M.G., and G.J.M. analysed and interpreted the data; G.H.J., F.E.D., C.P., D.A.C., A.S., and G.J.M. developed the first drafts of the manuscript. All authors contributed to the review and amendments of the manuscript for important intellectual content and approve this final version for submission.

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Data sharing statement

De-identified participant data will be made available when all trial primary and secondary endpoints have been met. Any requests for trial data and supporting material (data dictionary, protocol, and statistical analysis plan) will be reviewed by the trial management group in the first instance. Only requests which have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

Table 1. Patient characteristics according to induction regimen

Characteristic	CRD (n = 1021)	CTD (n = 1021)
Median age (range), years	61 (28-75)	61 (29-74)
Age group, n (%)		
≤65 years	772 (75.6)	754 (73.8)
>65 years	249 (24.4)	267 (26.2)
Sex, n (%)		
Male	610 (59.7)	611 (59.8)
Female	411 (40.3)	410 (40.2)
Ethnicity, n (%)		
White	938 (91.9)	937 (91.8)
Black (Black Caribbean, Black African, other)	21 (2.1)	14 (1.4)
Asian (Indian, Pakistani, Bangladeshi, other)	28 (2.7)	27 (2.6)
Other	10 (0.9)	14 (1.4)
Unknown	24 (2.4)	29 (2.8)
WHO performance status, n (%)		
0	421 (41.2)	439 (43.0)
1	363 (35.6)	367 (35.9)
2	119 (11.7)	135 (13.2)
≥3	53 (5.2)	34 (3.3)
Unknown	65 (6.4)	46 (4.5)
Immunoglobin subtype, n (%)		
IgG	633 (62.0)	600 (58.8)
IgA	220 (21.5)	269 (26.3)
IgM	4 (0.4)	4 (0.4)
IgD	12 (1.2)	9 (0.9)
Light chain only	139 (13.6)	127 (12.4)
Non-secretor	6 (0.6)	7 (0.7)
Unknown	7 (0.7)	5 (0.5)
ISS stage, n (%)		
I	301 (29.5)	306 (30.0)
II	392 (38.4)	388 (38.0)
III	246 (24.1)	253 (24.8)
Unknown	82 (8.0)	74 (7.2)
Median serum creatinine (range), μmol/L	85.0 (28.0-825.0)	83.0 (30.0-897.0)
Unknown, n (%)	9 (8.8)	7 (6.9)
Median lactate dehydrogenase (range), IU/L	262.0 (3.0-2519.0)	273.0 (0.0-3550.0)
Unknown, n (%)	228 (22.3)	215 (21.1)
CVD randomization after MR/PR, n (%)		
Allocated to CVD	85 (8.3)	98 (9.6)
Allocated to no CVD	82 (8.0)	102 (10.0)
Received CVD after SD/PD, n (%)	35 (3.4)	38 (3.7)
Maintenance treatment, n (%)		
Lenalidomide	230 (22.5)	221 (21.6)
Lenalidomide plus vorinostat	103 (10.1)	93 (9.1)
Observation	190 (18.6)	187 (18.3)
Cytogenetic data available, n (%)	414 (40.5)	422 (41.3)
Cytogenetic lesions, n (% of those with data available)		
t(4;14)	56 (13.5)	70 (16.6)
t(14;16)	8 (1.9)	12 (2.8)
t(14;20)	3 (0.7)	2 (0.5)
del(17p)	31 (7.5)	42 (10.0)
gain(1q)	137 (33.1)	136 (32.2)
Cytogenetic risk category, n (% of those with data available)		
Standard	223 (53.9)	236 (55.9)
High*	149 (36.0)	117 (27.7)
Ultra-high†	42 (10.1)	69 (16.4)

Abbreviations: CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; Ig, immunoglobulin; ISS, International Staging System; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; WHO, World Health Organization. *High risk defined as the presence of any one of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q). †Ultra-high risk defined as the presence of more than 1 lesion.

Table 2. Response rates after induction and ASCT

	Response following induction therapy		Response following ASCT	
Response, n (%)	**CRD (n = 1021)**	**CTD (n = 1021)**	**CRD (n = 628)**	**CTD (n = 603)**
CR or VGPR	617 (60.4)	540 (52.9)	512 (81.5)	464 (76.9)
CR	87 (8.5)	61 (6.0)	149 (23.7)	122 (20.2)
CR w/o BM	297 (29.1)	223 (21.8)	218 (34.7)	214 (35.5)
VGPR	233 (22.8)	256 (25.1)	145 (23.1)	128 (21.2)
PR or MR	297 (29.1)	348 (34.1)	95 (15.1)	102 (16.9)
PR	261 (25.6)	301 (29.5)	94 (15.0)	98 (16.3)
MR	36 (3.5)	47 (4.6)	1 (0.2)	4 (0.7)
SD or PD	32 (3.1)	43 (4.2)	11 (1.8)	10 (1.7)
SD	8 (0.8)	8 (0.8)	0 (0.0)	0 (0.0)
PD	24 (2.4)	35 (3.4)	11 (1.8)	10 (1.7)
Death within 100 days after ASCT	13 (1.3)	17 (1.7)	1 (0.2)	6 (1.0)
Unknown	57 (5.6)	61 (6.0)	9 (0.9)	21 (2.1)

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; CR w/o BM, complete response by immunological criteria without confirmation by bone marrow; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Table 3. Adverse events according to induction regimen (safety population*)

Grade ≥3 AEs, n (%)	CRD (n = 1010)	CTD (n = 1004)
Neutropenia	225 (22.3)	117 (11.7)
Anemia	97 (9.6)	67 (6.7)
Thrombocytopenia	46 (4.5)	17 (1.7)
Diarrhea	26 (2.6)	10 (1.0)
Constipation	8 (0.8)	19 (1.9)
Peripheral sensory neuropathy	6 (0.6)	15 (1.5)
Peripheral motor neuropathy	5 (0.5)	14 (1.4)
AEs of interest (any grade), n (%)	**CRD (n = 1010)**	**CTD (n = 1004)**
Peripheral sensory neuropathy	251 (24.9)	452 (45.0)
Peripheral motor neuropathy	87 (8.6)	163 (16.2)
Deep vein thrombosis	58 (5.7)	48 (4.8)
Pulmonary embolism	32 (3.2)	49 (4.9)
Other thrombosis/embolism	8 (0.8)	11 (1.1)

Abbreviations: AE, adverse event; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone.

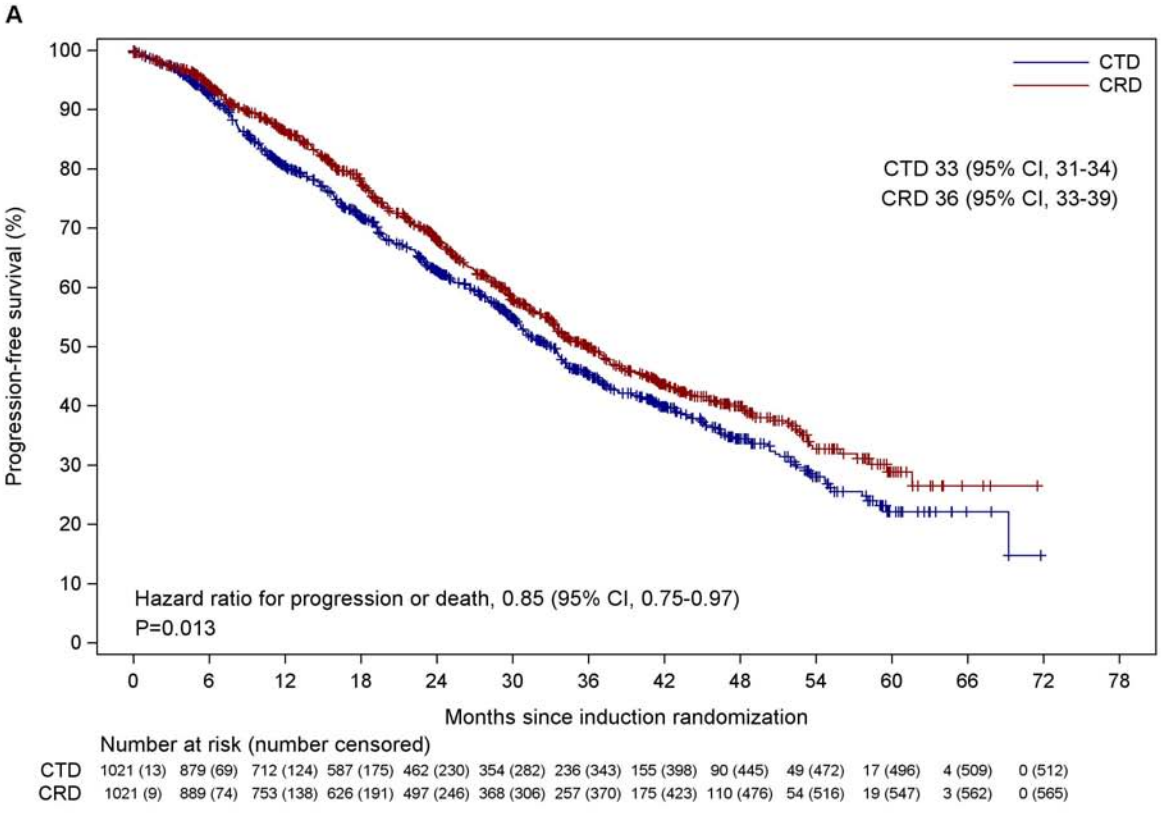
*The safety population included all randomly assigned patients who received 1 or more doses of the induction or maintenance regimen.

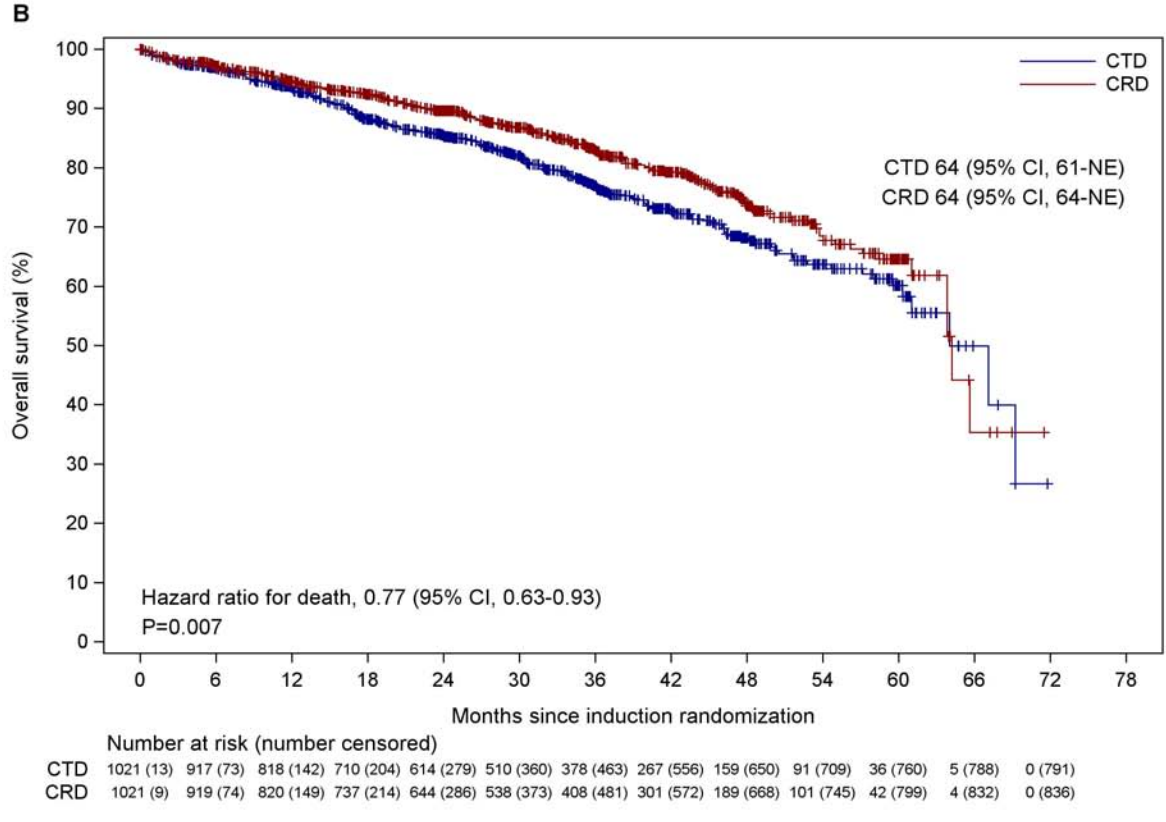
Figure Legends:

Figure 1. Outcomes according to induction regimen. (A) Progression-free survival and (B) overall survival, with dashed line showing the median. Abbreviations: CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone.

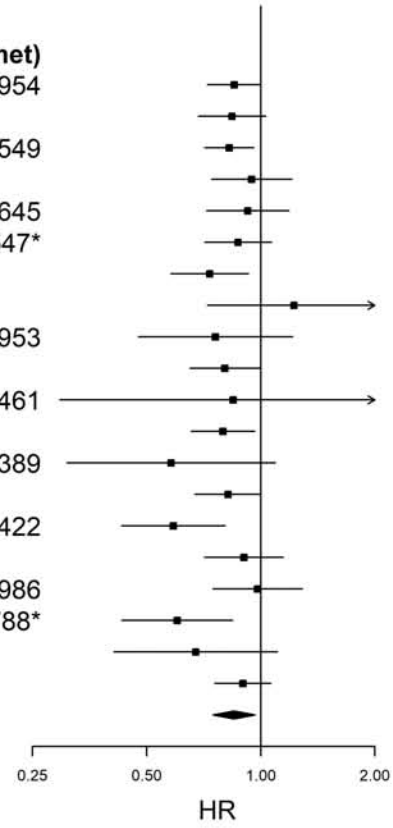
Figure 2. Outcomes according to induction regimen in selected subgroups. (A) Progression-free survival and (B) overall survival; HR < 1.00 favors CRD. *Likelihood ratio test for heterogeneity of effect amongst patients with subgroup data available. Abbreviations: CI, confidence interval; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; het, heterogeneity; HiR, high risk; HR, hazard ratio; ISS, International Staging System; SR, standard risk; UHiR, ultra-high risk.

Figure 3. Outcomes according to induction and maintenance treatment. (A) Progression-free survival and (B) overall survival. Abbreviations: CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; Obs, observation; R, lenalidomide.

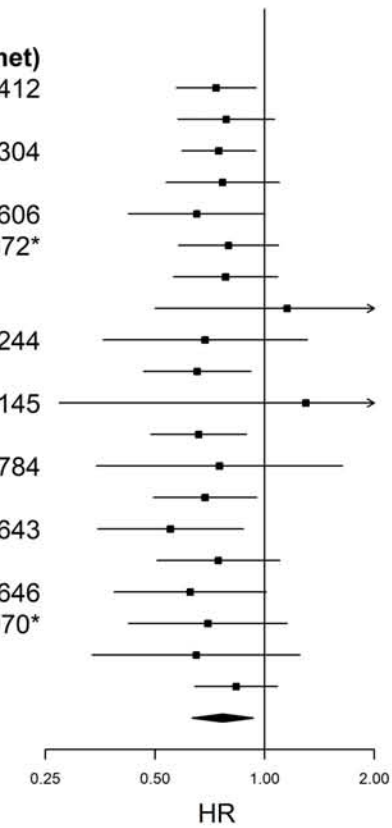

A
CTD
CRD
CTD 33 (95% CI, 31-34)
CRD 36 (95% CI, 33-39)
Progression-free survival (%)
Hazard ratio for progression or death, 0.85 (95% CI, 0.75-0.97)
P=0.013
Months since induction randomization
Number at risk (number censored)
CTD 1021 (13) 879 (69) 712 (124) 587 (175) 462 (230) 354 (282) 236 (343) 155 (398) 90 (445) 49 (472) 17 (496) 4 (509) 0 (512)
CRD 1021 (9) 889 (74) 753 (138) 626 (191) 497 (246) 368 (306) 257 (370) 175 (423) 110 (476) 54 (516) 19 (547) 3 (562) 0 (565)

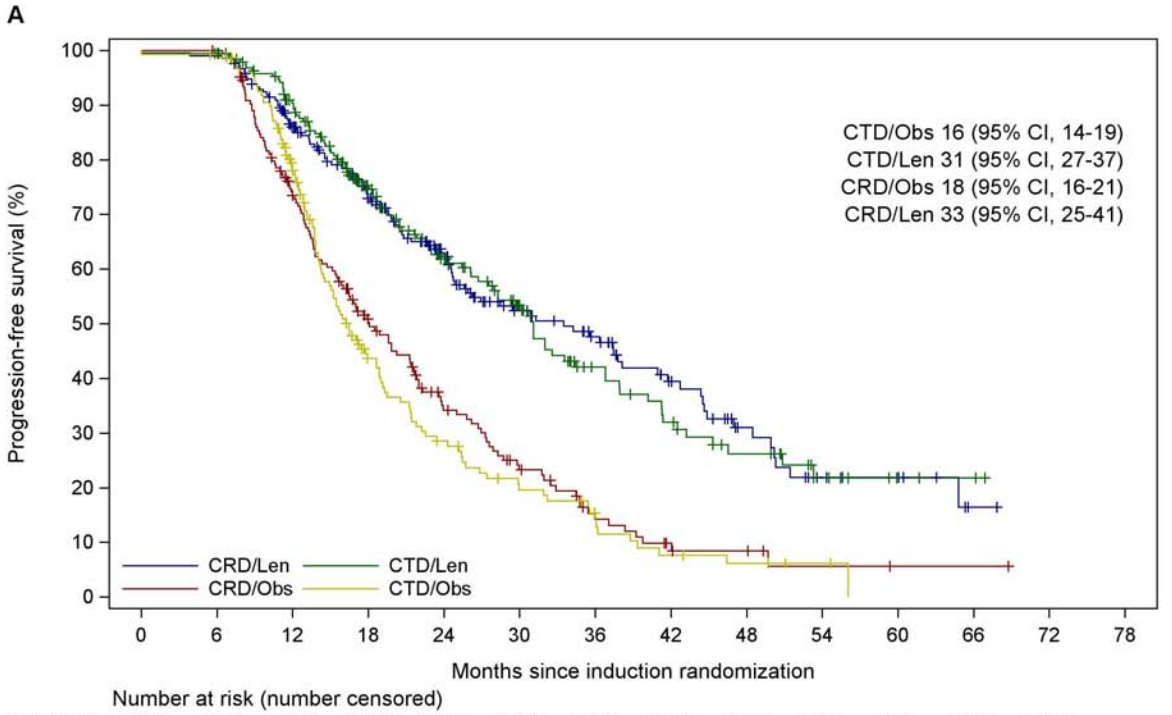

B
CTD
CRD
CTD 64 (95% CI, 61-NE)
CRD 64 (95% CI, 64-NE)
Overall survival (%)
Hazard ratio for death, 0.77 (95% CI, 0.63-0.93)
P=0.007
Months since induction randomization
Number at risk (number censored)
CTD 1021 (13) 917 (73) 818 (142) 710 (204) 614 (279) 510 (360) 378 (463) 267 (556) 159 (650) 91 (709) 36 (760) 5 (788) 0 (791)
CRD 1021 (9) 919 (74) 820 (149) 737 (214) 644 (286) 538 (373) 408 (481) 301 (572) 189 (668) 101 (745) 42 (799) 4 (832) 0 (836)

Subgroup	Level	CTD n/N	CRD n/N	HR [95%CI]	P. (het)
Sex	Male	320/611	272/610	0.85 (0.72, 1.00)	0.9954
	Female	189/410	184/411	0.84 (0.69, 1.03)	
Age	<=65 years	362/754	332/772	0.83 (0.71, 0.96)	0.2549
	>65 years	147/267	124/249	0.95 (0.74, 1.21)	
ISS	Stage I	128/306	119/301	0.92 (0.72, 1.19)	0.2645
	Stage II	196/388	178/392	0.87 (0.71, 1.07)	0.3547*
	Stage III	159/253	125/246	0.73 (0.58, 0.93)	
	Not available	26/74	34/82	1.22 (0.72, 2.07)	
t(4,14)	Present	51/70	34/56	0.76 (0.47, 1.21)	0.8953
	Absent	185/352	165/358	0.80 (0.65, 0.99)	
t(14,16)	Present	11/12	6/8	0.85 (0.30, 2.43)	0.6461
	Absent	225/410	193/406	0.79 (0.65, 0.96)	
del(17p)	Present	31/42	17/31	0.58 (0.31, 1.09)	0.2389
	Absent	205/380	182/383	0.82 (0.67, 1.00)	
gain(1q)	Present	92/136	70/137	0.59 (0.43, 0.81)	0.0422
	Absent	144/286	129/277	0.90 (0.71, 1.15)	
Cytogenetic Risk	SR	111/236	102/223	0.98 (0.75, 1.29)	0.0986
	HiR	70/117	69/149	0.60 (0.43, 0.84)	0.0788*
	UHiR	55/69	28/42	0.67 (0.41, 1.11)	
	Not Available	273/599	257/607	0.90 (0.76, 1.06)	
Overall		**509/1021**	**456/1021**	**0.85 (0.75, 0.96)**	



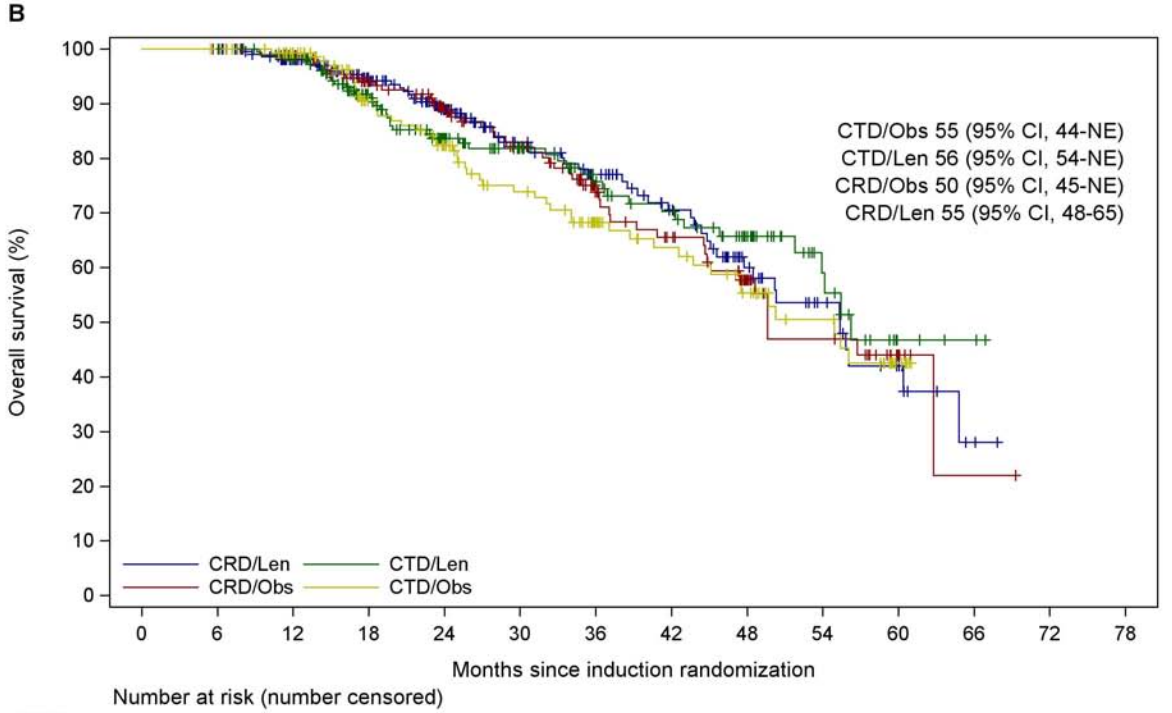
Subgroup	Level	CTD n/N	CRD n/N	HR [95%CI]	P. (het)
Sex	Male	143/611	105/610	0.74 (0.57, 0.95)	0.6412
	Female	87/410	80/411	0.78 (0.58, 1.06)	
Age	<=65 years	155/754	131/772	0.75 (0.59, 0.95)	0.6304
	>65 years	75/267	54/249	0.77 (0.54, 1.10)	
ISS	Stage I	51/306	35/301	0.65 (0.42, 1.00)	0.7606
	Stage II	86/388	71/392	0.80 (0.58, 1.09)	0.7872*
	Stage III	83/253	65/246	0.78 (0.56, 1.09)	
	Not available	10/74	14/82	1.15 (0.50, 2.66)	
t(4,14)	Present	28/70	19/56	0.69 (0.36, 1.31)	0.5244
	Absent	80/352	59/358	0.65 (0.46, 0.92)	
t(14,16)	Present	5/12	5/8	1.30 (0.27, 6.18)	0.3145
	Absent	103/410	73/406	0.66 (0.49, 0.89)	
del(17p)	Present	21/42	14/31	0.75 (0.35, 1.64)	0.7784
	Absent	87/380	64/383	0.69 (0.50, 0.95)	
gain(1q)	Present	49/136	32/137	0.55 (0.35, 0.87)	0.4643
	Absent	59/286	46/277	0.75 (0.51, 1.10)	
Cytogenetic Risk	SR	43/236	28/223	0.62 (0.39, 1.01)	0.7646
	HiR	32/117	32/149	0.70 (0.42, 1.15)	0.8970*
	UHiR	33/69	18/42	0.65 (0.34, 1.25)	
	Not Available	122/599	107/607	0.84 (0.64, 1.08)	
Overall		**230/1021**	**185/1021**	**0.77 (0.63, 0.93)**	





Number at risk (number censored)

CRD/Len	212 (0)	210 (0)	167 (16)	126 (33)	89 (54)	59 (70)	46 (78)	30 (87)	17 (94)	9 (97)	7 (99)	1 (104)	0 (105)
CRD/Obs	167 (0)	166 (1)	112 (12)	70 (20)	42 (26)	26 (29)	13 (33)	7 (35)	5 (36)	2 (38)	1 (39)	1 (39)	0 (40)
CTD/Len	194 (0)	192 (1)	163 (13)	113 (37)	79 (52)	55 (66)	34 (76)	25 (77)	16 (82)	8 (88)	3 (93)	2 (94)	0 (96)
CTD/Obs	150 (0)	148 (1)	107 (11)	49 (24)	31 (25)	19 (28)	12 (31)	6 (31)	4 (32)	2 (34)	0 (35)		



Number at risk (number censored)

CRD/Len	212 (0)	212 (0)	189 (19)	158 (44)	121 (72)	88 (98)	68 (112)	51 (124)	32 (136)	20 (145)	12 (149)	2 (157)	0 (159)
CRD/Obs	167 (0)	166 (1)	152 (13)	126 (32)	104 (48)	86 (58)	58 (78)	45 (85)	28 (97)	17 (104)	5 (115)	1 (118)	0 (119)
CTD/Len	194 (0)	194 (0)	174 (17)	132 (48)	96 (73)	75 (92)	58 (104)	49 (109)	33 (122)	16 (137)	4 (146)	2 (148)	0 (150)
CTD/Obs	150 (0)	149 (1)	136 (13)	101 (37)	84 (45)	67 (54)	49 (67)	40 (73)	31 (77)	20 (86)	5 (98)	0 (103)	

SUPPLEMENTARY DATA

Supplemental Methods

Supportive care recommendations

For all patients, bisphosphonates were recommended until PD and thromboprophylaxis was recommended for at least the first 3 months of treatment as per International Myeloma Working Group (IMWG) recommendations. Growth factor support and prophylaxis for pneumonia varicella, fungal infection, and tumor lysis syndrome were allowed as per local practice. All patients provided written informed consent.

Stratification Factors

Transplant-eligible patients were randomized on a 1:1 basis stratified according to the following minimization factors: treatment center, β_2-microglobulin level (<3.5 mg/L, 3.5-5.5 mg/L, ≥5.5 mg/L, or unknown), hemoglobin level (<11.5 vs. ≥11.5 g/dL for men; <9.5 vs. ≥9.5 g/dL for women), corrected serum calcium level (<2.6 vs. ≥2.6 mmol/L), serum creatinine level (<140 vs. ≥140 µmol/L), and platelet count (<150 × 10^9/L vs. ≥150 × 10^9/L).

Cytogenetic analysis

Cytogenetic profiling was performed using Multiplex Ligation-dependent Probe Amplification (MLPA) and quantitative real-time PCR (qRT-PCR) on samples of CD138-selected plasma cells from bone marrow biopsies of patients. These techniques have been previously validated to provide equivalent results to interphase fluorescence in situ hybridization (iFISH).[1,2] Cytogenetic risk was defined as standard risk (no adverse lesions), high risk (presence of gain(1q), t(4;14), t(14;16), t(14;20), or del(17p)), or ultra-high risk (more than 1 adverse lesion).[3]

Randomization

All randomizations were performed at the Clinical Trials Research Unit (Leeds, UK) using a centralized automated 24-hour telephone system according to a validated

minimization algorithm. Due to the nature of the intervention, patients and their physicians were aware of the treatment allocation.

Study endpoint definitions

For induction therapy comparisons, PFS was defined as the time from induction randomization to the date of confirmed disease progression or death from any cause. OS was defined as the time from induction randomization to the date of death from any cause. PFS2 was defined as the time from induction randomization to the date of second disease progression (or start of third anti-myeloma treatment), or death from any cause. For maintenance therapy comparisons, PFS and OS were defined similarly as the time from maintenance randomization. Disease progression and response were defined based on the Modified International Uniform Response Criteria [4,5] and reviewed centrally by an expert panel that was blinded to treatment allocation. Adverse event (AE) severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The intent-to-treat population included all randomly assigned patients and was used to assess efficacy. The safety population included all randomly assigned patients who received 1 or more doses of study medication. The data-cutoff date for inclusion in this analysis was July 25, 2016.

Statistical analysis

Statistical analyses were undertaken in SAS (version 9.4; SAS Institute, Cary, NC, USA), Stata IC (StataCorp, College Station, TX, USA), and R: A Language and Environment for Statistical Computing (R Core Team, Vienna, Austria). Analysis followed the Myeloma XI statistical analysis plan (SAP) unless reported as post hoc exploratory analysis. Cox regression was used to analyze progression-free survival (PFS) and overall survival (OS) and estimate hazard ratios (HR) and 95% confidence intervals. All analyses were adjusted for the minimization factors (excluding center). The Kaplan-Meier method was used to estimate survivor functions. Flexible parametric survival models were used to estimate median survival in OS.[6] Subgroup analysis was pre-specified for the presence or absence of adverse

cytogenetic lesions. Response rates (specifically, remission defined as a very good partial response [VGPR] or better, vs. no VGPR) were compared with logistic regression analysis adjusted for the minimization factors (excluding center).

The use of additional therapy (cyclophosphamide, bortezomib, and dexamethasone [CVD]) for patients with a suboptimal response (ie, minimal response [MR] or partial response [PR]) or no response (ie, stable disease [SD] or progressive disease [PD]) after induction therapy was a potential source of bias in the comparison of outcomes associated with cyclophosphamide, lenalidomide, and dexamethasone (CRD) and cyclophosphamide, thalidomide, and dexamethasone (CTD) (ie, a lower response rate in one treatment group could lead to more patients being 'rescued' with CVD). Post hoc exploratory analysis considered rank-preserving structural failure time models relating the observed PFS and OS, to the counterfactual estimates observable without subsequent treatment with CVD after suboptimal or no response.[7-9]

The percentage of minimum protocol-defined dose delivered for induction therapy was calculated as the sum of the study drug doses delivered to a patient out of the total dose expected to be delivered for the protocol-defined minimum of 4 cycles in the absence of PD. The percentage of maximum protocol-defined dose delivered for lenalidomide maintenance therapy was calculated as the sum of the study drug doses delivered to a patient out of the total dose expected to be delivered up to PD.

Cumulative incidence function curves were estimated by non-parametric maximum likelihood estimation.[10] Fine and Gray competing risks regression[11] was used to compare the hazard of second primary malignancies (SPM) by treatment, adjusting for the minimization factors with unrelated deaths specified as a competing risk. Person-years on trial were calculated as the sum over all patients receiving at least 1 dose of study treatment of the time in years from randomization to death or last date known to be alive. Incidence rates were calculated with the number of events as the numerator and the number of person-years on

trial as the denominator. Confidence intervals for incidence rate were calculated using approximations to the Poisson distribution.

The trial was designed to demonstrate an increase in median OS of 18 months in the CRD group (median, 84 months) compared with the CTD group (median, 66 months; HR, 0.79) when 545 OS events had been observed. This calculation assumed the time-to-event was exponentially distributed and that recruitment would last 4 years with 4 years of further follow-up, a 2-sided 5% significance level, and 80% power. A minimum recruitment target of 1183 patients randomized (1:1) between CRD and CTD was specified, allowing for 5% drop-out. Under similar assumptions, this recruitment also allowed the demonstration of a PFS increase of 6 months in the CRD group (median, 35 months) compared with the CTD group (median, 29 months; HR, 0.83) when 893 PFS events had been observed. The standard therapy estimates were taken from the MRC Myeloma IX trial.[12]

A formal interim analysis for OS was pre-specified in the study protocol when at least 50% of required OS events had been observed (273 deaths). To ensure that an overall significance level of 0.05 was maintained, the O'Brien and Fleming alpha-spending function[13] was used with pre-specified bounds of 0.005 for interim analysis and 0.047 for final analysis. The bound for the interim analysis was advisory with decision to release results at the recommendation of the Independent Myeloma XI Data Monitoring and Ethics Committee (DMEC) and Independent Myeloma XI Trial Steering Committee (TSC). On September 1, 2016, the Myeloma XI DMEC reviewed the interim analysis for OS that showed that the pre-specified boundary had been achieved based on 407 OS events (74.7% of required OS events). Based on the DMEC review, the Myeloma XI TSC recommended that the results be unmasked. The results presented in this manuscript were updated based on final cleaned data and the addition of 8 late-reported deaths.

All the authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol (study protocol and statistical analysis plan are available upon request).

SUPPLEMENTAL REFERENCES

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Supplementary Table 1. Study regimens

CRD (cyclophosphamide, lenalidomide, dexamethasone)	C: 500 mg po on days 1, 8 R: 25 mg daily po on days 1-21 D: 40 mg daily po on days 1-4, 12-15	Cycles repeat every 28 days for at least 4 cycles and until maximum response achieved. Patients with PD will proceed directly to CVD (without having to complete 4 cycles of induction) and patients with SD after 4 cycles will go straight to CVD.
CTD (cyclophosphamide, thalidomide, dexamethasone)	C: 500 mg po on days 1, 8, 15 T: 100 mg daily po for 3 weeks, increasing to 200 mg daily po D: 40 mg daily po on days 1-4, 12-15	Cycles repeat every 21 days for at least 4 cycles and until maximum response achieved. Patients with PD will proceed directly to CVD (without having to complete 4 cycles of induction) and patients with SD after 4 cycles will go straight to CVD.
CVD (cyclophosphamide, bortezomib, dexamethasone)	C: 500 mg daily po on days 1, 8, 15 V: 1.3 mg/m^2 sc or iv on days 1, 4, 8, 11 D: 20 mg daily po on days 1-2, 4-5, 8-9, 11-12	Cycles repeat every 21 days until maximum response or intolerance (maximum 8 cycles). If CR is achieved, treatment was continued for a maximum of 2 additional cycles. Varicella prophylaxis was recommended as per local practice.
Lenalidomide maintenance*	R: 10 mg daily po on days 1-21	Cycles repeat every 28 days and continue, in the absence of toxicity, until disease progression.
Lenalidomide plus vorinostat maintenance*	R: 10 mg daily po on days 1–21 Vorinostat: 300 mg daily po on days 1–7 and 15–21	Cycles repeat every 28 days and continue, in the absence of toxicity, until disease progression

Abbreviations: C, cyclophosphamide; CR, complete response; D, dexamethasone; iv, intravenously; PD, progressive disease; po, orally; R, lenalidomide; sc, subcutaneously; SD, stable disease; T, thalidomide; V, bortezomib.

* Patients were accrued to the maintenance randomization between January 13, 2011 and August 11, 2017. Patients were initially randomized in a 1:1 ratio, using minimization with a bias element of 80%, to either R 25 mg/day (po on days 1–21 of each 28-day cycle) or observation, stratified by induction and intensification treatment. Following a protocol amendment on September 14, 2011 and after accrual of 442 patients under protocol versions 2·0–4·0, patients were randomized in a 1:1:1 ratio to R 10 mg/day (po on days 1–21 of each 28-day cycle), R plus vorinostat, or observation. Following a further protocol amendment on June 28, 2013 and after accrual of 615 further patients under protocol version 5·0, patients were randomized in a 2:1 ratio to R 10 mg/day or observation; R plus vorinostat was discontinued under protocol version 6·0. These changes were made to add research questions to this adaptive design study. Abbreviations: a, attenuated-dose; C, cyclophosphamide; CR, complete response; D, dexamethasone; iv, intravenously; PD, disease progression; po, orally; R, lenalidomide; sc, subcutaneously; T, thalidomide; V, bortezomib.

Supplementary Table 2. Baseline characteristics of transplant-eligible patients who entered maintenance randomization

Characteristic	Lenalidomide (n = 451)	Observation (n = 377)
Induction regimen, n (%)		
CRD	230 (51.0)	190 (50.4)
CTD	221 (49.0)	187 (49.6)
CVD randomization after MR/PR, n (%)		
Allocated to CVD	47 (10.4)	37 (9.8)
Allocated to no CVD	47 (10.4)	40 (10.6)
Received CVD after SD/PD, n (%)	357 (79.2)	300 (79.6)
Response status before maintenance, n (%)		
CR	101 (22.4)	85 (22.5)
VGPR	264 (58.5)	230 (61.0)
PR	74 (16.4)	53 (14.1)
MR	2 (0.4)	1 (0.3)
SD	0 (0.0)	0 (0.0)
PD	4 (0.9)	3 (0.8)
Unable to assess	4 (0.9)	3 (0.8)
Unknown	2 (0.4)	2 (0.5)
Median age (range), years	61.0 (29.0-75.0)	61.0 (30.0-74.0)
Sex, n (%)		
Male	294 (65.2)	235 (62.3)
Female	157 (34.8)	142 (37.7)
Ethnicity, n (%)		
White	418 (92.7)	350 (92.8)
Black (Black Caribbean, Black African, other)	6 (1.3)	9 (2.4)
Asian (Indian, Pakistani, Bangladeshi, other)	6 (1.3)	8 (2.1)
Other	6 (1.3)	4 (1.1)
Unknown	15 (3.4)	6 (1.6)
ISS stage, n (%)		
I	149 (33.0)	137 (36.3)
II	168 (37.3)	148 (39.3)
III	97 (21.5)	71 (18.8)
Unknown	37 (8.2)	21 (5.6)
Cytogenetic data available, n (%)	178	155
Cytogenetic lesions, n (% of those with data available)		
t(4;14)	29 (16.3)	17 (11.1)
t(14;16)	5 (2.8)	5 (3.2)
t(14;20)	2 (1.1)	0 (0.0)
del(17p)	17 (9.6)	9 (5.8)
gain(1q)	69 (38.8)	44 (28.4)
Cytogenetic risk category, n (% of those with data available)		
Standard	86 (48.3)	97 (62.6)
High*	66 (37.1)	41 (26.5)
Ultra-high†	26 (14.6)	17 (11.0)

Abbreviations: CR, complete response; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; ISS, International Staging System; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

*High risk defined as the presence of any one of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q).

†Ultra-high risk defined as the presence of more than 1 lesion.

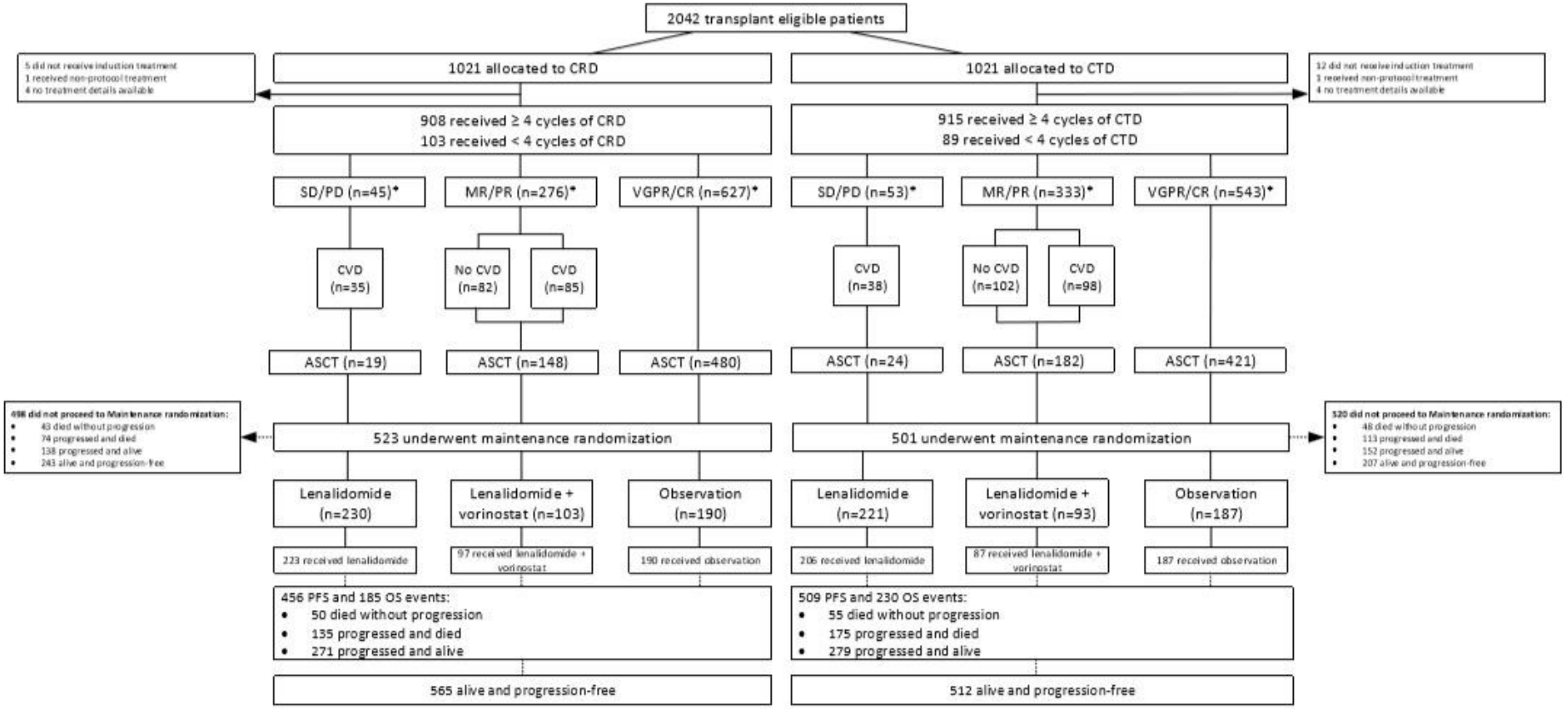
Supplementary Table 3. Published randomized studies evaluating 3/4-drug combinations of newer agents as induction therapy prior to ASCT

Induction regimen	Phase	N	Age restriction (median), years	ISS stage III, %	Response after induction, %		Response after ASCT, %		Median PFS, months	Median OS, months	Reference
					≥PR	≥VGPR	≥PR	≥VGPR			
VAD	III	413	≤65 (57)	20	78	42	88	62	35	5-year: 61%	Sonneveld et al[32]
VAD	III	251	≤70 (59.4)	29	72	34	NR	NR	NR	NR	Mai et al[33]
CVD	III	251	≤70 (58.7)	30	78	37	NR	NR	NR	NR	Mai et al[33]
CTD	III	555	None (59)	29	83	43	92	74	27	Not reached	Morgan et al[17]
VTD	III	236	≤65 (58)	16	93	62	93	79	3-year: 68%	3-year: 86%	Cavo et al[10]
VTD	III	130	≤65 (56)	NR	85	60	NR	NR	56.2	4-year: 74%	Rosiñol et al[34]
VTD	III	100	≤65 (58)	23	88	49	89	74	26	NR	Moreau et al[5]
VRD	III	350	≤65 (60)	17	NR	47	NR	78	36	4-year: 82%	Attal et al[9]
VRD	Rand II	42	None (60)	19	85	51	NR	NR	1-year: 83%	1-year: 100%	Kumar et al[36]
CVRD	Rand II	48	None (61.5)	21	80	33	NR	NR	1-year: 86%	1-year: 92%	Kumar et al[36]
Dara-VTd	III	543	≤65 (59)	15	93	65	93	83	18m: 93%	NR	Moreau et al[37]
VTd	III	542	≤65 (58)	15	90	56	90	78	18m: 85%	NR	Moreau et al[37]
CTD	III	1021	None (61)	25	82	53	93	77	33	64	Myeloma XI (present study)
CRD	III	1021	None (61)	24	86	60	97	82	36	64	Myeloma XI (present study)

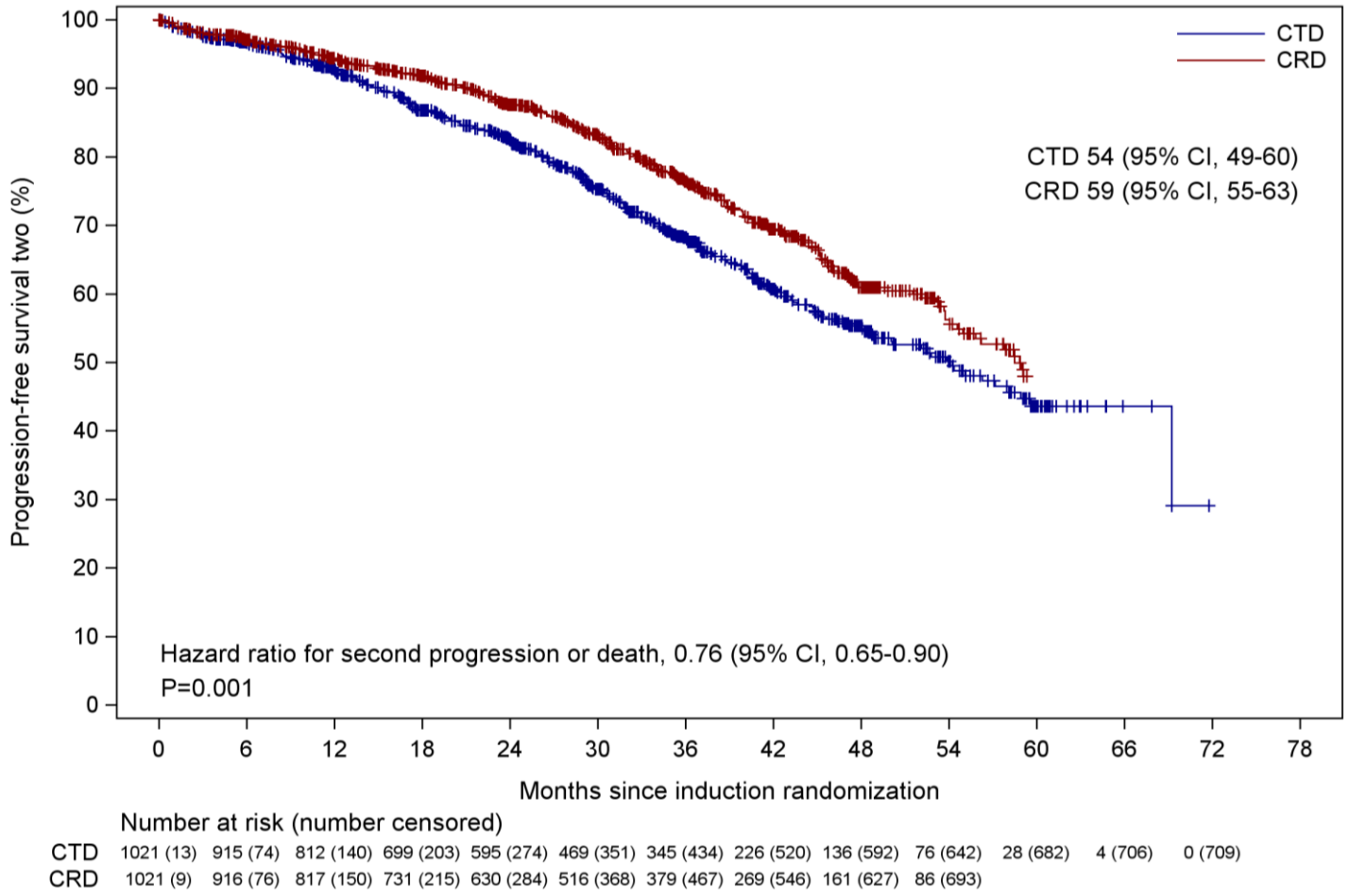
Abbreviations: ASCT, autologous stem cell transplantation; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; CVRD, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone; CVTD, cyclophosphamide, bortezomib, thalidomide, and dexamethasone; ISS, International Staging System; KCD, carfilzomib, cyclophosphamide, and dexamethasone; KRD, carfilzomib, lenalidomide, and dexamethasone; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response; Rand, randomized; VAD, bortezomib, doxorubicin, and dexamethasone; VGPR, very good partial response; VRD, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

Supplementary Figure 1. Patient disposition. Dashed-outline boxes: outcomes for patients assigned to lenalidomide plus vorinostat maintenance therapy not included in the present manuscript. *Across the intensive pathway, 34 patients with final response classified as 'Missing' or 'Unable to assess' carried on with trial treatment based on their clinician's decision. The CONSORT diagram presents the local response assessment and may not correspond with the reviewed response as presented in the main text.

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

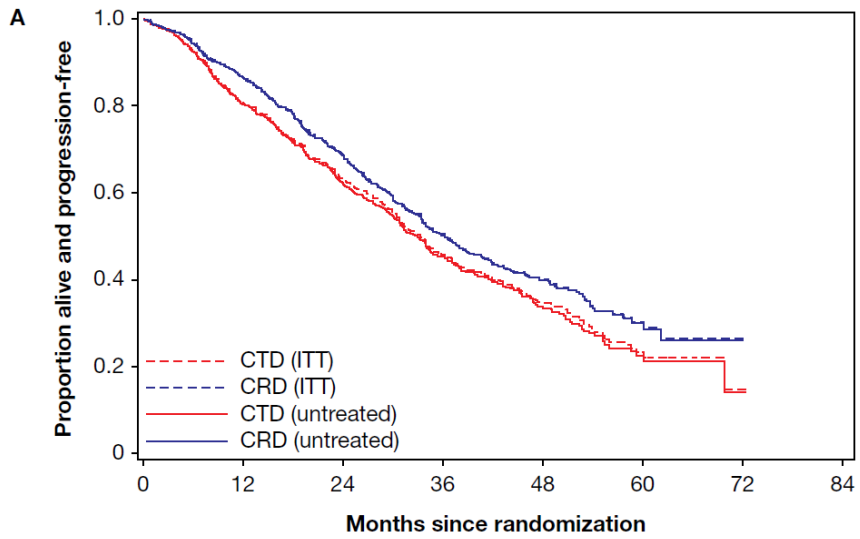


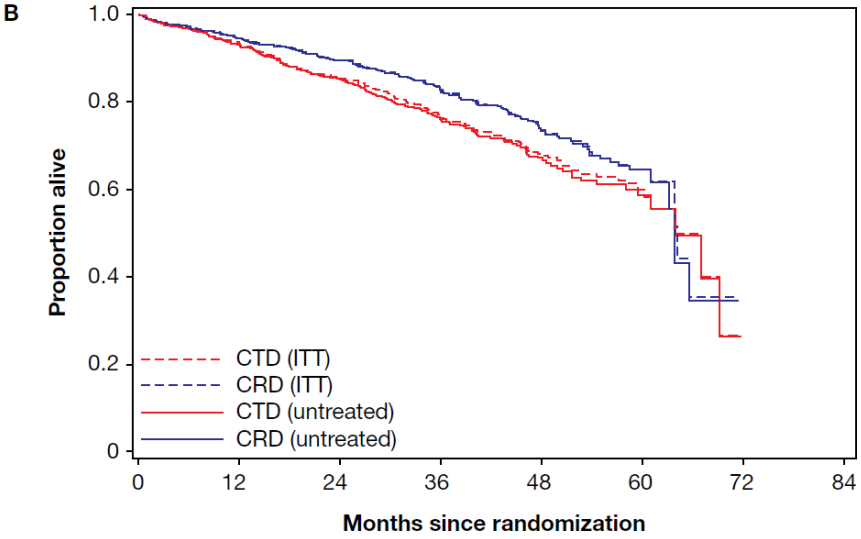
Supplementary Figure 2. PFS2 according to induction regimen. Abbreviations: CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone.

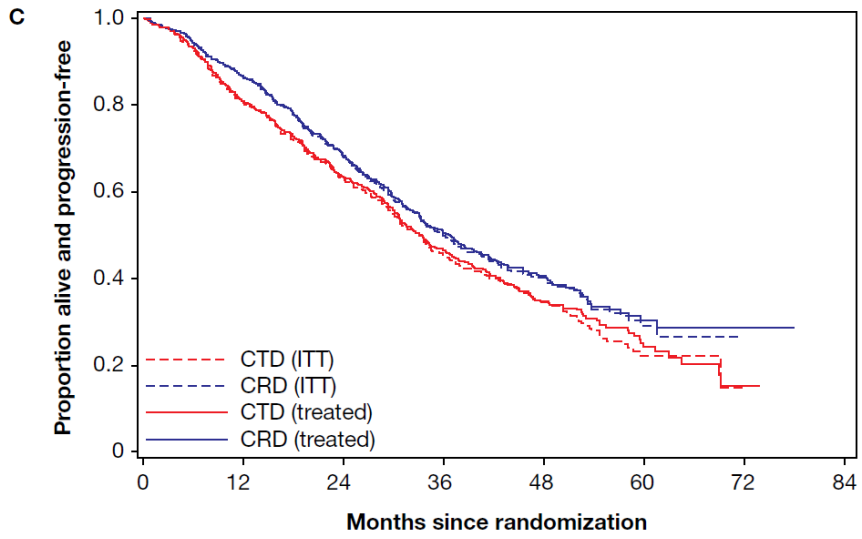


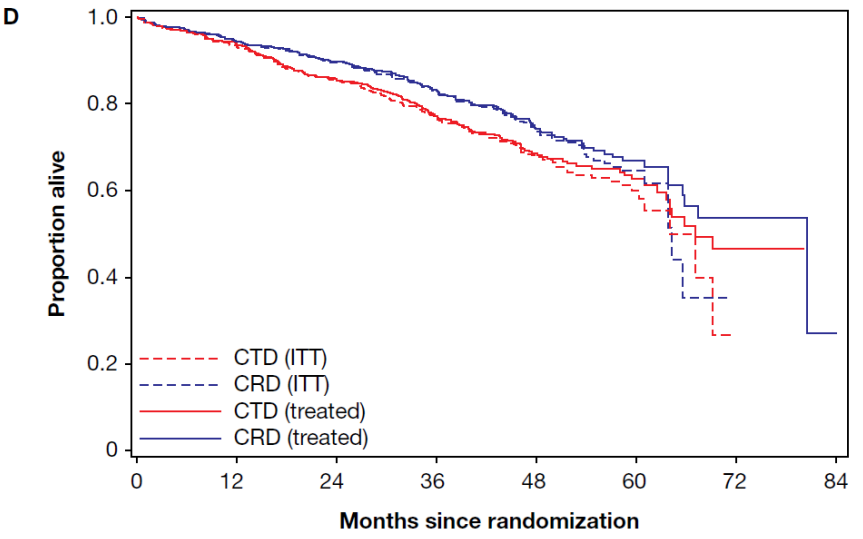
Supplementary Figure 3. RPSFTM counterfactual adjusted survivor function for CRD vs. CTD. (A) PFS without treatment rescue with CVD, (B) OS without treatment rescue with CVD, (C) PFS with treatment rescue with CVD, and (D) OS with treatment rescue with CVD.

Abbreviations: CI, confidence interval; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; RPSFTM, rank-preserving structural failure time model.


A
Proportion alive and progression-free
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
72
84
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (untreated)
CRD (untreated)


B
Proportion alive
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
72
84
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (untreated)
CRD (untreated)


C
Proportion alive and progression-free
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
72
84
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (treated)
CRD (treated)


D
Proportion alive
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
72
84
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (treated)
CRD (treated)

Study sites, principal investigators, and number of patients recruited

Site	Principal Investigator(s)	Recruited patients
Leicester Royal Infirmary	Dr. Mamta Garg, Dr. Claire Chapman	65
Nottingham City Hospital	Dr. Cathy Williams, Prof. Nigel Russell	60
Royal Derby Hospital	Dr. David Allotey	55
Royal Stoke University Hospital, Stafford County Hospital (University Hospital North Staffordshire)	Dr. Kamaraj Karunanithi, Dr. Paul Revell	55
Worcestershire Royal Hospital, Alexandra Hospital Redditch, Kidderminster General Hospital	Dr. Salim Shafeek	54
Manchester Royal Infirmary, Trafford General Hospital	Dr. Alberto Rocci, Dr. Eleni Tholouli, Dr. John Alderson, Dr. Simon Gibbs	52
Lincoln County Hospital, Grantham and District General Hospital, Pilgrim Hospital Boston	Dr. Caroline Harvey, Dr. Charlotte Kallmeyer, Dr. Kandeepan Saravanmuttu	50
Birmingham Heartlands Hospital, Good Hope Hospital	Dr. Bhuvan Kishore, Prof. Donald Milligan	48
Royal Hallamshire Hospital, Sheffield	Prof. John Snowden	48
Royal Cornwall Hospital, Truro	Dr. Julie Blundell	40
New Cross Hospital, Wolverhampton	Dr. Supratik Basu	36
University Hospital of Wales Cardiff, Llandough Hospital	Dr. Ceri Bygrave, Dr. Christopher Fegan, Dr. Belinda Austin	35
Doncaster Royal Infirmary	Dr. Joe Joseph, Dr. Youssef Sorour	34
Southmead Hospital, Bristol (Frenchay)	Dr. Alastair Whiteway	33
Western General Hospital, Edinburgh	Dr. Huw Roddie	33
Royal Oldham Hospital	Dr. Hayley Greenfield	31
Southampton General Hospital	Dr. Matthew Jenner, Dr. Alastair Smith	31
The Christie, Manchester	Dr. Samar Kulkarni, Dr. Jim Cavet	31
Cheltenham General Hospital, Gloucestershire Royal Hospital	Dr. Sally Chown	30
Royal Marsden Hospital, London	Dr. Martin Kaiser, Prof. Gareth Morgan	30
Stoke Mandeville Hospital, Wycombe Hospital	Dr. Robin Aitchison	30
Blackpool Victoria Hospital	Dr. Mark Grey, Dr. Marian Paul Macheta	29
Royal Preston Hospital	Dr. Mark Grey, Dr. Frederick Kanyike, Dr. Maqsood Punekar	29
St James's University Hospital, Leeds	Prof. Gordon Cook	29
Freeman Hospital, Newcastle	Prof. Graham Jackson	28
Singleton Hospital, Swansea	Dr. Hamdi Sati	28
Worthing Hospital, St Richards Hospital Chichester	Dr. Jamie Wilson, Dr. Sarah Janes, Dr. Phillip Bevan, Dr. Santosh Narat	28
Derriford Hospital, Plymouth	Dr. Hannah Hunter	27
James Cook University Hospital, Middlesbrough	Dr. Raymond Dang	27
Royal Bournemouth Hospital	Dr. Rachel Hall	27
Medway Maritime Hospital	Dr. Sarah Arnott, Dr. Vijay Dhanapal, Dr. Vivienne Andrews	26
York Hospital, Scarborough General Hospital	Dr. Laura Munro, Dr. Haz Sayala	26
Kent and Canterbury Hospital	Dr. Jindriska Lindsay	25
Stepping Hill Hospital, Stockport	Dr. Montaser Haj	25
Diana Princess of Wales Hospital, Grimsby	Dr. Susan Levison-Keating, Dr. Sanjeev Jalihal, Dr. Hannah Ciepluch	24
Norfolk and Norwich University Hospital	Dr. Martin Auger, Dr. Kristian Bowles	24
Russells Hall Hospital, Dudley	Dr. Craig Taylor	24
Bristol Haematology and Oncology Centre	Dr. Jenny Bird, Dr. Roger Evely	23
Calderdale Royal Hospital, Huddersfield Royal Infirmary	Dr. Kate Rothwell, Dr. Sylvia Feyler	23
Ipswich Hospital	Dr. Isobel Chalmers	23
Royal Berkshire Hospital, Reading	Dr. Henri Grech	23
Chesterfield Royal Hospital	Dr. Peter Toth, Dr. Emma Welch	22
Queen's Hospital, Romford	Dr. Sandra Hassan, Dr. Biju Krishnan, Dr. Jane Stevens	22

Site	Principal Investigator(s)	Recruited patients
Royal Devon and Exeter Hospital	Dr. Tony Todd, Dr. Claudius Rudin	22
Aberdeen Royal Infirmary	Dr. Jane Tighe	21
Castle Hill Hospital, Hull	Dr. David Allsup, Dr. Haz Sayala	21
Beatson Oncology Centre, Glasgow	Dr. Richard Soutar	20
University Hospital Coventry	Dr. Beth Harrison, Dr. Syed Bokhari	20
Ninewells Hospital Dundee, Perth Royal Infirmary	Dr. Duncan Gowans	19
Sandwell General Hospital, West Bromwich	Dr. Farooq Wandroo	18
Queen Elizabeth Hospital, Birmingham	Dr. Mark Cook	17
Royal Gwent Hospital, Newport	Dr. Helen Jackson	17
Dorset County Hospital	Dr. Dietman Hofer, Dr. Akeel Moosa	16
Kettering General Hospital	Dr. Mark Kwan	16
King's Mill Hospital, Sutton-in-Ashfield	Dr. Tim Moorby, Dr. Rowena Faulkner	16
Salisbury District Hospital	Dr. Jonathan Cullis	16
Victoria Hospital Kirkcaldy	Dr. Lorna McClintock	16
Royal Blackburn Hospital	Dr. Malgorzata Rokicka, Dr. Jagdish Adiyodi	15
Royal Lancaster Infirmary	Dr. David Howarth	15
Colchester General Hospital	Dr. Michael Hamblin, Dr. Sudhakaran Makkuni	14
Eastbourne Hospital, Conquest Hospital	Dr. Sunil Gupta, Dr. Simon Weston-Smith, Dr. Satyajit Sahu	14
Salford Royal Hospital	Dr. Simon Jowitt	14
Torbay Hospital, Torquay	Dr. Heather Eve, Dr. Deborah Turner	14
Countess of Chester Hospital	Dr. Gillian Brearton, Dr. Salah Tueger	13
Monklands Hospital, Hairmyres Hospital, Wishaw General Hospital	Dr. Iain Singer	13
Pinderfields General Hospital Wakefield, Dewsbury & District Hospital, Pontefract Hospital	Dr. John Ashcroft	13
Poole Hospital	Dr. Ram Jayaprakash, Dr. Fergus Jacki	13
Sunderland Royal Hospital	Dr. Victoria Hervey, Dr. Scott Marshall, Dr. Simon Lyons	13
Wythenshawe Hospital, Manchester	Dr. Simon Watt	13
Borders General Hospital, Melrose	Dr. Jenny Buxton, Dr. Srivnivasa Dasari, Dr. John Tucker, Dr. Ashok Okhandiar	12
Hereford County Hospital	Dr. Lisa Robinson	12
Maidstone Hospital, Tunbridge Wells Hospital	Dr. Don Gillett, Dr. Lalita Banerjee	12
Royal Liverpool Hospital	Dr. Stephen Hawkins, Prof. Patrick Chu	12
Rotherham General Hospital	Dr. Richard Went, Dr. Helen Barker	11
Royal Bolton Hospital	Dr. Chetan Patalappa, Dr. Suzanne Roberts, Dr. Mark Grey, Dr. Claire Barnes	11
Bradford Royal Infirmary	Dr. Sam Ackroyd	10
George Eliot Hospital, Nuneaton	Dr. Mekkali Narayanan	10
Nevill Hall Hospital, Abergavenny	Dr. Nilima Parry-Jones	10
North Devon District Hospital, Barnstaple	Dr. Paul Kerr, Dr. Malcolm Hamilton	10
St Helens Hospital, Whiston Hospital	Dr. Toby Nicholson	10
University Hospital Aintree	Dr. Lynny Yung, Dr. Barbara Hammer	10
Scunthorpe General Hospital	Dr. Sanjeev Jalihal	9
Warwick Hospital	Dr. Carolina Arbuthnot	9
Glan Clwyd Hospital, Rhyl	Dr. Earnest Hartin, Dr. Christina Hoyle	7
James Paget Hospital, Great Yarmouth	Dr. Cesar Gomez, Dr. Shalal Sadullah	7
Arrowe Park, Wirral	Dr. Ranjit Dasgupta, Dr. Nauman Butt	5
Darent Valley Hospital	Dr. Tariq Shafi, Dr. Anil Kamat	4
Ysbyty Gwynedd, Bangor	Dr. Sally Evans, Dr. Melinda Hamilton, Dr. David Edwards	4
Addenbrookes Hospital, Cambridge	Dr. Jenny Craig, Dr. Charles Crawley	3
Royal Alexandra Hospital, Paisley	Dr. Alison McCaig, Dr. Alison Sefcick	2