bjh research paper

Optimising the value of immunomodulatory drugs during induction and maintenance in transplant ineligible patients with newly diagnosed multiple myeloma: results from Myeloma XI, a multicentre, open-label, randomised, Phase III trial

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Summary

Second-generation immunomodulatory agents, such as lenalidomide, have a more favourable side-effect profile than the first-generation thalidomide, but their optimum combination and duration for patients with newly diagnosed transplant-ineligible myeloma (ND-TNE-MM) has not been defined. The most appropriate delivery and dosing regimens of these therapies for patients at advanced age and frailty status is also unclear. The Myeloma XI study compared cyclophosphamide, thalidomide and dexamethasone (CTDa) to cyclophosphamide, lenalidomide and dexamethasone (CRDa) as induction therapy, followed by a maintenance randomisation between ongoing therapy with lenalidomide or observation for patients with ND-TNE-MM. CRDa deepened response but did not improve progression-free (PFS) or overall survival (OS) compared to CTDa. However, analysis by age group highlighted significant differences in tolerability in older, frailer patients that may have limited treatment delivery and impacted outcome. Deeper responses and PFS and OS benefits with CRDa over CTDs were seen in patients aged ≤70 years, with an increase in toxicity and discontinuation observed in older patients. Our results highlight the importance of considering age and frailty in the approach to therapy for patients with ND-TNE-MM, highlighting the need for prospective validation of frailty adapted therapy approaches, which may improve outcomes by tailoring treatment to the individual.

Keywords: myeloma, transplant-ineligible, lenalidomide, thalidomide, immunomodulatory agent.

 British Journal of Haematology, 2021, **192,** 853–868
First published online 12 July 2020
doi: 10.1111/bjh.16945

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Introduction

In patients unsuitable for high doses of chemotherapy optimising the type, nature and duration of induction therapy is becoming increasingly important. Immunomodulatory agents (IMiDs) act via modulation of the cullin-4 E3 ubiquitin ligase complex $CRL4^{CRBN}$ leading to the degradation of neo-substrates and alteration of critical myeloma cell survival pathways.[1] We have shown previously that the combination of cyclophosphamide, thalidomide and dexamethasone (CTD), given as induction, outperformed melphalan and prednisone (MP) (Medical Research Council Myeloma IX trial). While CTD increased both the number and depth of responses, and was associated with a significantly improved progression-free survival (PFS), an emergent overall survival (OS) benefit was only noted after 24 months.[2,3] In the same study, maintenance thalidomide was associated with a small PFS advantage compared to observation, but its impact was potentially reduced by a median of only 6 months of maintenance being delivered, with more than half of patients stopping therapy early due to treatment-emergent adverse events (AEs).[4] The impact of age on tolerability and outcomes within the Myeloma IX population was not explored.

Second-generation IMiDs have a better side-effect profile than thalidomide and understanding where best to use of them in patients not destined for transplantation has become an important question. Previous studies have suggested that age and frailty may impact the effectiveness of lenalidomide combined with steroids and melphalan. In the Multiple Myeloma 015 (MM-015) trial (n = 459; ClinicalTrials.gov number, NCT00405756), a survival benefit was seen with melphalan, prednisolone and lenalidomide followed by lenalidomide maintenance (MPR-R) *versus* melphalan and prednisolone without maintenance (MP) in those aged 65–75 years, but not in patients aged >75 years.[5] In the Dutch-Belgian Hematology-Oncology Cooperative Group (HOVON)87/Nordic Myeloma Study Group (NMSG)18 trial [n = 637; European Union Drug Regulating Authorities Clinical Trials (EudraCT) number:2007-004007-34], no difference in PFS or OS was detected between the combinations MPR-R and melphalan, prednisolone and thalidomide with thalidomide maintenance (MPT-T), with similar response rates.[6] Toxicity associated with melphalan use in both induction combinations was significant, leading to high rates of early discontinuation of induction; 49% with MPT and 41% with MPR. Rates of discontinuation were higher in patients aged >75 years than in younger patients, but analysis of outcome by age group was not reported. In a study conducted in Italy and the Czech Republic (n = 654, NCT01093196), the induction combination cyclophosphamide, lenalidomide and prednisolone (CPR) was compared to MPR and lenalidomide and dexamethasone (Rd).[7] There was no significant difference in outcomes between the arms, but much higher rates of neutropenia were seen with MPR than CPR or Rd. An analysis by frailty suggested younger fitter patients may have tolerated this better and benefitted from the more intensive MPR combination, but subgroups for this analysis were small.

These findings and the adverse impact of the triplet combination with the alkylator melphalan in combination with lenalidomide on haemopoiesis and the excess of second haematological malignancies,[8] led to the more detailed evaluation of the doublet lenalidomide and dexamethasone in the FIRST (MM-020; ClinicalTrials.gov number, NCT00689936) study (n = 1623). This study showed a significant benefit for the Rd doublet compared to the MPT triplet[9]; for the first time challenging the accepted concept that triplet combinations outperform doublets. Within the FIRST trial, findings were consistent across age groups.[10] These studies raised the idea that as age and frailty increase, the capacity to see a benefit of a therapy based on the competing factors of tolerability and exposure may become important.

We have previously published data demonstrating that molecular risk factors are less important as predictors of outcome in older patient than younger patients.[11] We, therefore, developed a clinical prediction model for outcome and therapy delivery that is readily applicable to routinely collected trial data in patients ineligible for transplant called the UK Myeloma Research Alliance Risk Profile (MRP).[12] In the present study, we report the results of the UK National Cancer Research Institute (NCRI) Myeloma XI trial comparing the use of either thalidomide or lenalidomide combined with the alkylator cyclophosphamide and dexamethasone, followed by a randomisation to either lenalidomide or no further therapy in 1852 newly diagnosed patients deemed by the patient/clinician to be unsuitable for autologous stem cell transplant (transplant ineligible). Using this very large cohort of patients we examined outcomes by age and MRP score to explore the impact of age and other factors on outcome.

Patients and methods

Patients

Eligible patients were aged ≥18 years and newly diagnosed with multiple myeloma but deemed unsuitable for autologous stem cell transplant due to comorbidities and patient/clinician preference. Exclusion criteria included previous treatment for myeloma (excluding local radiotherapy, bisphosphonates, and corticosteroids), previous or concurrent malignancies (including myelodysplastic syndromes), Grade ≥2 peripheral neuropathy, acute renal failure (unresponsive to up to 72 h of rehydration, characterised by creatinine >500 μmol/l or urine output <400 ml/day or requiring dialysis), and active or prior hepatitis C infection.

The trial was performed in accordance with the Declaration of Helsinki 1996, and 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 EudraCT (number: 2009-010956-93) and the International Standard Randomised Controlled Trial Number registry (ISRCTN49407852). 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).

Study design and treatment

The UK NCRI Myeloma XI trial was a Phase III, open-label, parallel-group, multi-arm, adaptive design trial with three randomisation stages conducted at 110 National Health Service hospitals in England, Wales and Scotland.

The trial design included an intensive treatment pathway for transplant-eligible patients and a less-intensive treatment pathway for transplant-ineligible patients. Transplant-ineligible patients were randomised on a 1:1 basis to attenuated cyclophosphamide, lenalidomide and dexamethasone (CRDa: C: 500 mg orally on days 1, 8, R: 25 mg daily orally on days 1–21, D: 20 mg daily orally on days 1–4, 15–18) or attenuated cyclophosphamide, thalidomide and dexamethasone (CTDa: C: 500 mg orally on days 1, 8, 15, 22, T: 50 mg daily orally for 4 weeks, increasing in 50 mg increments every 4 weeks to 200 mg daily, D: 20 mg daily orally on days 1–4, 15–18). This induction randomisation was stratified according to the following minimisation factors: treatment centre, β_2-microglobulin level (<3·5 mg/l, 3·5–5·5 mg/l, ≥5·5 mg/l, or unknown), haemoglobin level (<115 g/l vs. ≥115 g/l for males; <95 g/l vs. ≥95 g/l for females), corrected serum calcium level (<2·6 vs. ≥2·6 mmol/l), serum creatinine level (<140 μmol/l vs. ≥ 140 μmol/l), platelet count (<150 × 10^9/l vs. ≥150 × 10^9/l) and centre (each centre is listed in Table S1). Patients received a minimum of six cycles in the absence of progressive disease (PD), and treatment continued until maximum response was achieved.

Additional induction intensification therapy 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 eight cycles of cyclophosphamide, bortezomib, and dexamethasone (CVD); patients with a minimal response (MR) or partial response (PR) were randomised (1:1) to CVD or no CVD. Randomised patients were stratified according to initial induction randomisation, response to initial induction treatment and treatment centre. Patients with a very good PR (VGPR) or complete response (CR) received no additional therapy. The results of the CVD randomisation have been reported elsewhere.[13]

At maximum response following induction, or induction intensification if given, eligible patients were randomised to maintenance therapy with lenalidomide alone (10 mg/day on days 1–21 of each 28-day cycle) or combined with vorinostat (300 mg/day on day 1–7 and 15–21 of each 28-day cycle) until unacceptable toxicity or PD, or to observation. Patients were excluded from maintenance randomisation if they did not respond to CRDa induction, had no response to any prior study treatment, had PD or relapsed after achieving CR. Randomised patients were stratified according to treatment centre and previous randomisation group(s). The results of the maintenance randomisation comparing lenalidomide and observation have been reported elsewhere[14] and the results of comparing combination lenalidomide-vorinostat and lenalidomide will be reported shortly.

All randomisations were performed at the Clinical Trials Research Unit (Leeds, UK) using a centralised automated 24-h telephone system according to a validated minimisation algorithm. Due to the nature of the intervention, patients and their physicians were aware of the treatment allocation.

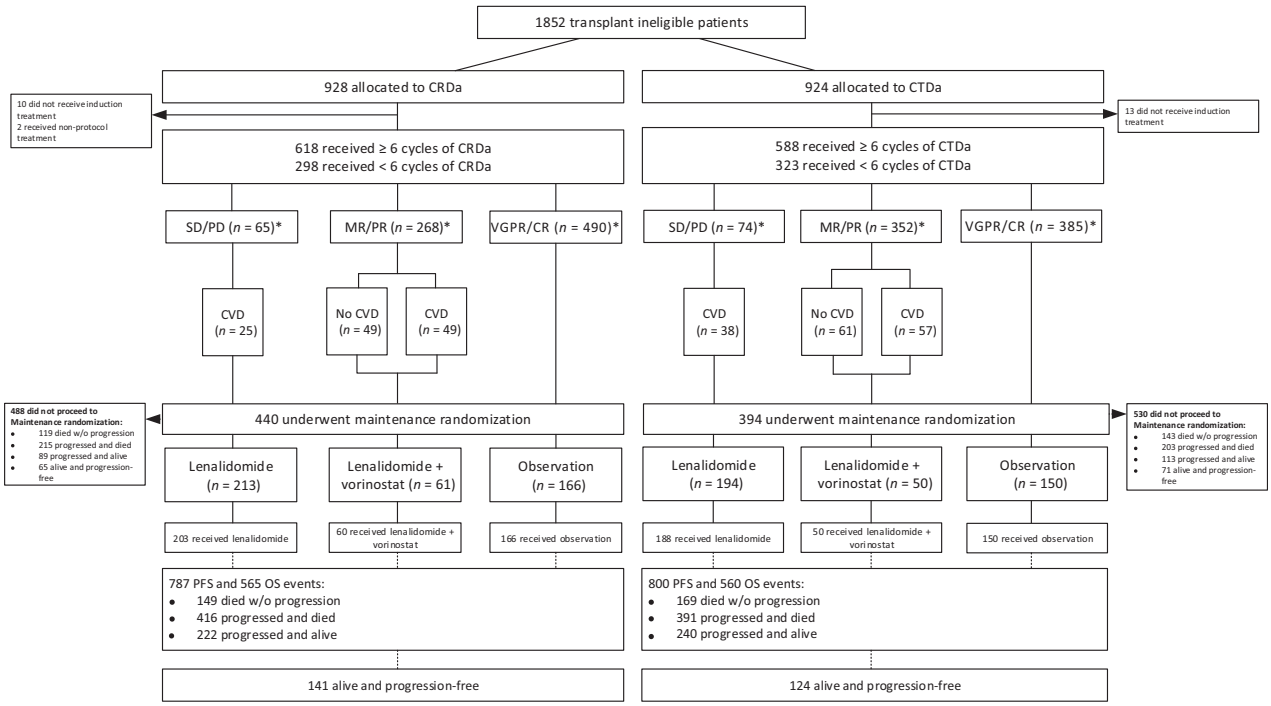


Fig 1. Consolidated Standards of Reporting Trials (CONSORT) diagram for the Myeloma XI trial non-intensive pathway. CRDa, attenuated cyclophosphamide, lenalidomide and dexamethasone; CTDa, attenuated cyclophosphamide, thalidomide and dexamethasone; CVD, cyclophosphamide, bortezomib and dexamethasone; SD, stable disease; PD, progressive disease; MR, minimal response; PR, partial response; VGPR, very good partial response; CR, complete response; PFS, progression-free survival; OS, overall survival. *Responses as assessed by local centres guided treatment pathway decisions.

Efficacy and safety measurements were performed at predefined time points; all patients in the study followed the same visit and assessment schedule. The analyses presented here focus on outcomes according to induction regimen (CRDa vs. CTDa) among transplant-ineligible patients. Further details on the dose and schedule of all study treatments are provided in Table S2.

Study endpoints

The co-primary endpoints were PFS and OS. Secondary endpoints included PFS Two (PFS2), response, and safety. For time-to-event endpoints, the relative difference in hazard was quantified with a hazard ratio (HR), where a HR <1 indicates a benefit for CRDa over CTDa or lenalidomide over observation. For a binary endpoint, such as response, the relative difference in the odds of remission were quantified using an odds ratio (OR), where an OR >1 indicated a benefit for CRDa over CTDa. The data cut-off date for inclusion in this analysis was 31 May 2019. The Statistical Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC, USA); Stata/IC, version 14.2 (StataCorp., College Station, TX, USA), and R, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. Endpoint definitions and further details of the statistical analysis are included in the Methods S1.

Results

Patients

Between May 2010 and April 2016, 1852 transplant-ineligible patients underwent induction randomisation (Fig 1), 924 to CTDa and 928 to CRDa. Baseline characteristics were balanced between the two treatment groups (Table 1). Overall, the median (range) patient age was 74 (54–92) years, 463 (25%) patients had a World Health Organization Performance Status (WHO PS) of ≥2, and 659 (35·6%) had International Staging System (ISS) Stage III disease. In all, 790 (42·7%) patients were aged >75 years, with 245 (13·2%) aged >80 years. A third of patients fell into the low, medium and high MRP risk groups respectively.

Impact of induction treatment

The lenalidomide-containing triplet induced deeper responses with VGPR or better achieved in 52% of patients in the CRDa group compared to 43% in the CTDa group ($P = 0{\cdot}0003$) (Table 2). The OR of 1·45 [95% confidence interval (CI) 1·20, 1·75] indicated a 45% increase in the odds of achieving remission in the CRDa group compared with the CTDa group. The difference in response persisted across all age groups, but was most

Table 1. Patient characteristics according to induction regimen (intention-to-treat population).

Characteristic	CRDa (n = 928)	CTDa (n = 924)
Age, years		
Median (range)	75·0 (60–92)	74·0 (54–89)
Age, years, *n* (%)		
≤70	222 (23·9)	195 (21·1)
71–75	306 (33·0)	339 (36·7)
76–80	280 (30·2)	265 (28·7)
>80	120 (12·9)	125 (13·5)
MRP, *n* (%)		
Low	311 (33·5)	306 (33·1)
Medium	310 (33·4)	308 (33·3)
High	307 (33·1)	310 (33·5)
Sex, *n* (%)		
Male	511 (55·1)	536 (58·0)
Female	417 (44·9)	388 (42·0)
Ethnicity, *n* (%)		
White	868 (93·5)	882 (95·5)
Black (e.g., Black Caribbean, Black African)	12 (1·3)	20 (2·2)
Asian (e.g., Indian, Pakistani, Bangladeshi)	19 (2·1)	10 (1·1)
Other	4 (0·4)	4 (0·4)
Unknown	25 (2·7)	9 (0·9)
WHO Performance Status, *n* (%)		
0	251 (27·0)	229 (24·8)
1	409 (44·1)	402 (43·5)
2	148 (15·9)	194 (21·0)
≥3	61 (6·6)	49 (5·3)
Not available	6 (0·6)	5 (0·5)
Immunoglobulin subtype, *n* (%)		
IgG	580 (62·5)	587 (63·5)
IgA	234 (25·2)	231 (25·0)
IgM	3 (0·3)	2 (0·2)
IgD	8 (0·9)	3 (0·3)
Light chain only	93 (10·0)	95 (10·3)
Non-secretor	5 (0·5)	6 (0·6)
Not available	5 (0·5)	0 (0·0)
ISS stage, *n* (%)		
I	153 (16·5)	166 (18·0)
II	370 (39·9)	362 (39·2)
III	327 (35·2)	332 (35·9)
Not available	78 (8·4)	64 (6·9)
CVD after MR/PR, *n* (%)		
Randomised to No CVD after PR/MR	49 (5·3)	61 (6·6)
Randomised to CVD after PR/MR	49 (5·3)	57 (6·2)
Received CVD After SD/PD, *n* (%)	25 (2·7)	38 (4·1)
Maintenance treatment, *n* (%)		
Observation	166 (17·9)	150 (16·2)
Lenalidomide maintenance	213 (23·0)	194 (21·0)
Lenalidomide-vorinostat maintenance	61 (6·6)	50 (5·4)
Cytogenetic data available, *n* (%)	374 (40·3)	376 (40·7)
Cytogenetic risk category, *n* (%)		
Standard	202 (55·5)	197 (53·7)
High[a]	128 (35·2)	137 (37·3)
Ultra-high[b]	34 (9·3)	33 (9·0)

C, cyclophosphamide; D, dexamethasone; Ig, immunoglobulin; ISS, International Staging System; R, lenalidomide; T, thalidomide; WHO, World Health Organization.

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

[b]Ultra-high risk defined as the presence of more than one lesion.

Table 2. Response after induction immunomodulatory triplet (intention-to-treat population)

Response, *n* (%)	Response following induction therapy								
	CRDa (*n* = 928)				CTDa (*n* = 924)				
Age group, years	ALL	≤70 *n* = 222	71–75 *n* = 306	76–80 *n* = 280	>80 *n* = 120	ALL	≤70 *n* = 195	71–75 *n* = 339	76–80 *n* = 265	>80 *n* = 125
CR or VGPR	485 (52·3)	139 (62·6)	175 (57·1)	125 (44·6)	46 (38·3)	398 (43·1)	76 (39·0)	169 (49·9)	108 (40·8)	45 (36·0)
CR	67 (7·2)	24 (10·8)	22 (7·2)	13 (4·6)	8 (6·7)	35 (3·8)	6 (3·1)	15 (4·4)	11 (4·2)	3 (2·4)
VGPR	418 (45·0)	115 (51·8)	153 (50·0)	112 (40·0)	38 (31·7)	363 (39·3)	70 (35·9)	154 (45·4)	97 (36·6)	42 (33·6)
PR or MR	268 (28·9)	48 (21·6)	81 (26·5)	91 (32·5)	48 (40·0)	343 (37·1)	78 (40·0)	126 (37·2)	99 (37·4)	40 (32·0)
PR	230 (24·8)	39 (17·6)	73 (23·9)	76 (27·1)	42 (35·0)	289 (31·3)	63 (32·3)	106 (31·3)	87 (32·8)	33 (26·4)
MR	38 (4·1)	9 (4·1)	8 (2·6)	15 (5·4)	6 (5·0)	54 (5·8)	15 (7·7)	20 (5·9)	12 (4·5)	7 (5·6)
SD or PD	68 (7·3)	19 (8·6)	15 (4·9)	25 (8·9)	9 (7·5)	74 (8·0)	18 (9·2)	23 (6·8)	20 (7·5)	13 (10·4)
SD	25 (2·7)	5 (2·3)	8 (2·6)	6 (2·1)	6 (5·0)	33 (3·6)	8 (4·1)	8 (2·4)	8 (3·0)	9 (7·2)
PD	43 (4·6)	14 (6·3)	7 (2·3)	19 (6·8)	3 (2·5)	41 (4·4)	10 (5·1)	15 (4·4)	12 (4·5)	4 (3·2)
Death within 60 days of randomisation	51 (5·5)	5 (2·3)	17 (5·6)	21 (7·5)	8 (6·7)	47 (5·1)	12 (6·2)	13 (3·8)	17 (6·4)	5 (4·0)
Unable to assess	45 (4·8)	11 (5·0)	18 (5·9)	18 (6·4)	9 (7·5)	52 (5·6)	11 (5·6)	8 (2·4)	21 (7·9)	22 (17·6)

C, cyclophosphamide; CR, complete response; D, dexamethasone; MR, minimal response; PD, progressive disease; PR, partial response; R, lenalidomide; SD, stable disease; T, thalidomide; VGPR, very good partial response.

pronounced in those aged ≤70 years and narrowed with increasing age (Table 2).

At the time of this analysis the median [interquartile range (IQR)] follow-up from randomisation was 50 [48–78] months, 773 progressions or deaths had occurred in the CRDa group and 791 in the CTDa group, with no significant difference in median PFS, 16 and 16 months respectively (HR 0·91, 95% CI 0·83, 1·01; $P = 0·072$) (Fig 2A). In all, 537 deaths occurred in the CRDa group compared to 538 in the CTDa group, with no significant difference in median OS, 50 and 48 months respectively (HR 0·95, 95% CI 0·84, 1·07; $P = 0·403$) (Fig 2B). Counterfactual analysis did not suggest any difference in the treatment effect of CRD *versus* CTD when adjusting for the CVD intensification randomisation of the trial (Data S1: Results).

Subgroup analysis showed heterogeneity in outcomes by age (Fig 2C,D), this was not significant when examined across all age groups [PFS P(het.) = 0·1276, OS P (het.) = 0·2697], but was significant for PFS when comparing those aged ≤70 years to all older patients [PFS P (het.) = 0·0252, OS P(het.) = 0·0557] or when considering a simple trend test [PFS P(trend) = 0·0415, OS P (trend) = 0·2184]. For patients aged ≤70 years, CRDa was associated with a significantly improved median PFS (CTDa 15 months vs. CRDa 20; HR 0·73, 95% CI 0·59, 0·91; $P = 0·004$; Fig 3A) and OS (CTDa 55 months vs. CRDa 61 months; HR 0·76, 95% CI 0·58, 0·99; $P = 0·045$; Fig 3B). However, with advancing age the PFS and OS differences diminished (PFS: 71–75 years, HR 0·93, 95% CI 0·78, 1·10; 76–80 years, HR 1·01, 95% CI 0·84, 1·21; >80 years, HR 1·05, 95% CI 0·79, 1·40; OS: 71–75 years, HR 0·98, 95% CI 0·80, 1·21; 76–80 years, HR 1·05, 95% CI 0·84, 1·30; >80 years, HR 0·94, 95% CI 0·69, 1·30; Kaplan–Meier curves shown in Figure S1).

Combined analysis of induction and maintenance therapy

Of the 1852 transplant-ineligible patients, 833 (45%) entered the maintenance phase and were randomised to lenalidomide ($n = 406$), combination lenalidomide-vorinostat ($n = 111$) or observation ($n = 316$). In an exploratory analysis, limited to those receiving only lenalidomide alone *versus* observation, we sought to investigate the effect of sequencing lenalidomide between induction and maintenance. The baseline characteristics for the patients included in this analysis (Table S3) demonstrates that broadly the groups were similar. CRDa induction followed by lenalidomide maintenance was the treatment combination associated with the longest PFS: [median PFS: CRDa-R, 38 months (95% CI 31, 44); CTDa-R, 30 months (95% CI 26, 35); CRDa-obs., 19 months (95% CI 16, 22); CTDa-obs., 16 months (95% CI 14, 19) (Fig 4A]. The excellent outcome for this regimen was predominantly driven by the previously reported benefit of lenalidomide maintenance, which was associated with a

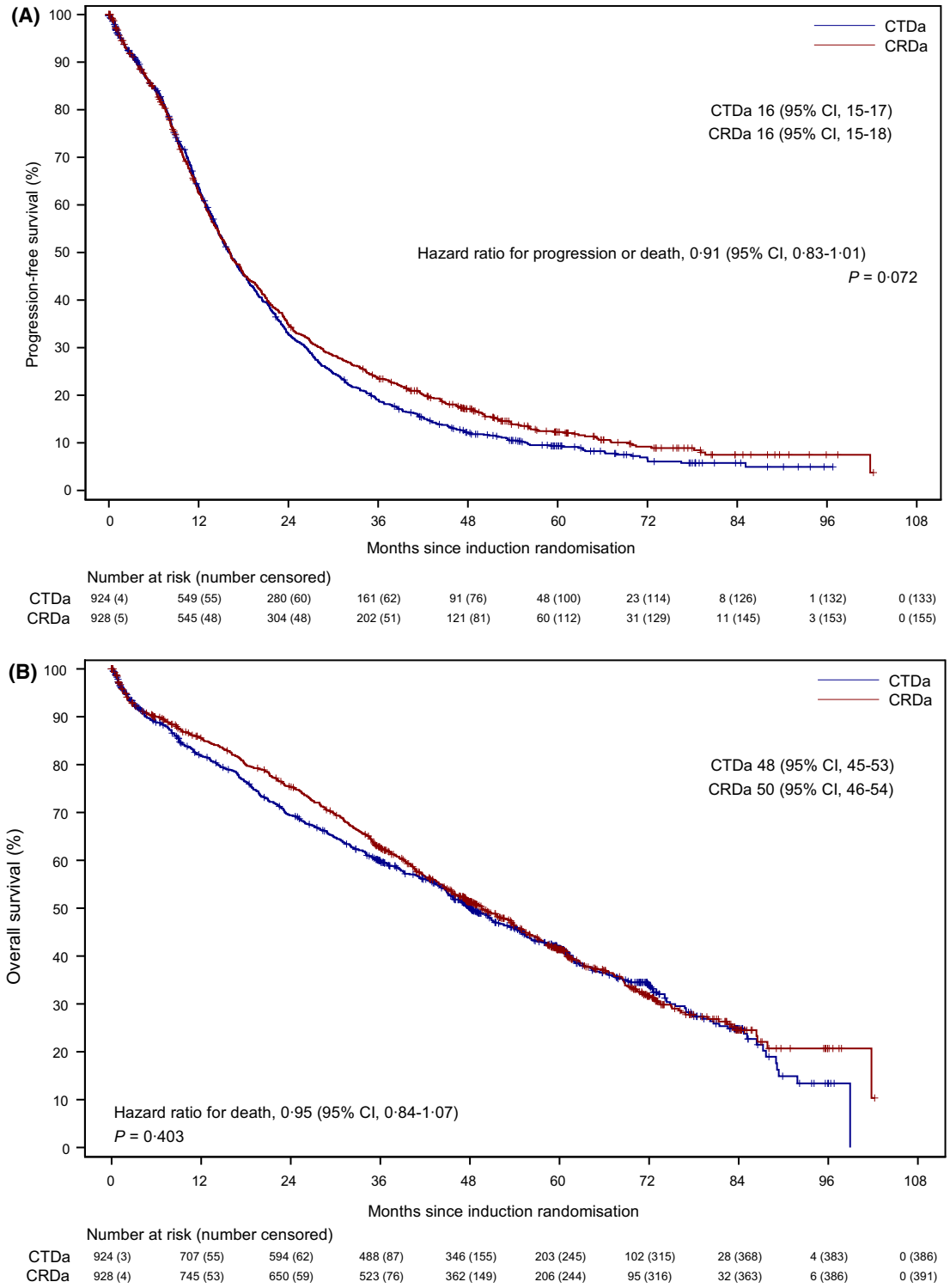
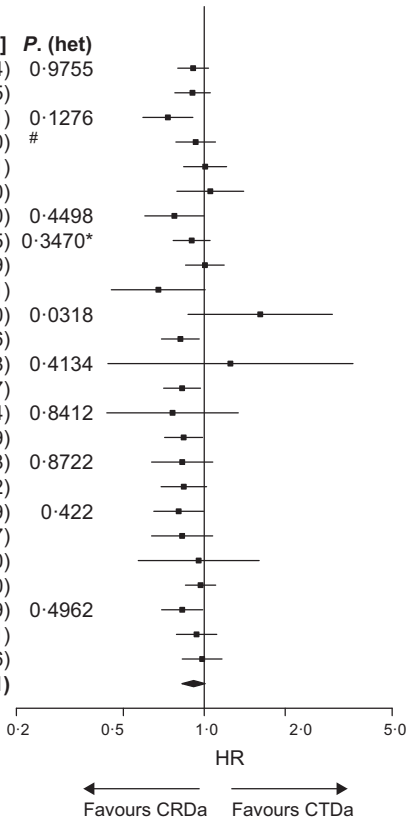


Fig 2. Progression-free survival (PFS) and overall survival (OS) primary endpoint analysis. (A) PFS by randomised treatment. (B) OS by randomised treatment. (C) Forest plot of the subgroup analysis for PFS. (D) Forest plot of the subgroup analysis for OS. The black squares and horizontal lines represent the hazard ratio (HR) and the associated 95% confidence interval (95% CI) of the hazard of progression or death (PFS) and hazard of death (OS) in the CRDa group compared to the CTDa group, *P*(het) represents the *P* value from the likelihood ratio test assessing heterogeneity of treatment effect between subgroups. ISS, international staging system; SR, standard risk; HiR, high-risk; UHiR; ultra-high-risk; UK-MRA, UK Myeloma Research Alliance; NE, not estimable. *Likelihood ratio test for heterogeneity of effect among patients with subgroup data available. #Comparison between the groups aged ≤70 and >70 years: *P*(het) = 0·0252. ~Comparison between the groups aged ≤70 and >70 years: *P*(het) = 0·0557. [Colour figure can be viewed at wileyonlinelibrary.com]

(C)

Subgroup	Level	CTDa n/N	CRDa n/N	HR [95%CI]	*P*. (het)
Gender	Male	464/536	428/511	0·91 (0·80, 1·04)	0·9755
	Female	327/388	345/417	0·90 (0·78, 1·05)	
Age	<=70 years	168/195	180/222	0·73 (0·59, 0·91)	0·1276
	71−75 years	291/339	252/306	0·93 (0·78, 1·10)	#
	76−80 years	227/265	242/280	1·01 (0·84, 1·21)	
	>80 years	105/125	99/120	1·05 (0·79, 1·40)	
ISS	Stage I	137/166	119/153	0·77 (0·60, 1·00)	0·4498
	Stage II	313/362	310/370	0·90 (0·77, 1·05)	0·3470*
	Stage III	283/332	282/327	1·01 (0·85, 1·19)	
	Not available	58/64	62/78	0·67 (0·45, 1·01)	
t(4,14)	Present	25/28	23/26	1·61 (0·87, 3·00)	0·0318
	Absent	306/346	294/350	0·81 (0·69, 0·96)	
t(14,16)	Present	13/15	8/9	1·25 (0·44, 3·58)	0·4134
	Absent	318/359	309/367	0·83 (0·71, 0·97)	
del(17p)	Present	29/31	30/34	0·76 (0·43, 1·34)	0·8412
	Absent	302/343	287/342	0·84 (0·71, 0·99)	
gain(1q)	Present	122/133	111/128	0·83 (0·64, 1·08)	0·8722
	Absent	209/241	206/248	0·84 (0·69, 1·02)	
Cytogenetic Risk	SR	171/200	174/209	0·80 (0·65, 0·99)	0·422
	HiR	129/140	110/133	0·83 (0·64, 1·07)	
	UHiR	31/34	33/34	0·95 (0·57, 1·60)	
	Not Available	460/550	456/552	0·97 (0·85, 1·10)	
UK−MRA Risk Profile	Low	262/306	246/311	0·83 (0·69, 0·99)	0·4962
	Medium	263/308	255/310	0·94 (0·79, 1·11)	
	High	266/310	272/307	0·98 (0·83, 1·16)	
Overall		**791/924**	**773/928**	**0·91 (0·83, 1·01)**	



(D)

Subgroup	Level	CTDa n/N	CRDa n/N	HR [95%CI]	*P*. (het)
Gender	Male	328/536	305/511	0·97 (0·83, 1·13)	0·822
	Female	210/388	232/417	0·93 (0·77, 1·12)	
Age	<=70 years	108/195	107/222	0·76 (0·58, 0·99)	0·2692
	71−75 years	189/339	174/306	0·98 (0·80, 1·21)	~
	76−80 years	153/265	174/280	1·05 (0·84, 1·30)	
	>80 years	88/125	82/120	0·94 (0·69, 1·30)	
ISS	Stage I	74/166	64/153	0·77 (0·55, 1·09)	0·7964
	Stage II	197/362	203/370	0·97 (0·80, 1·18)	0·6087*
	Stage III	229/332	227/327	0·97 (0·81, 1·17)	
	Not available	38/64	43/78	0·83 (0·53, 1·31)	
t(4,14)	Present	18/28	17/26	1·61 (0·76, 3·44)	0·2071
	Absent	210/346	197/350	0·87 (0·71, 1·05)	
t(14,16)	Present	10/15	8/9	1·66 (0·55, 5·04)	0·2076
	Absent	218/359	206/367	0·87 (0·72, 1·05)	
del(17p)	Present	22/31	23/34	0·71 (0·37, 1·36)	0·957
	Absent	206/343	191/342	0·89 (0·73, 1·08)	
gain(1q)	Present	96/133	84/128	0·85 (0·63, 1·14)	0·8256
	Absent	132/241	130/248	0·90 (0·71, 1·16)	
Cytogenetic Risk	SR	107/200	107/209	0·84 (0·64, 1·10)	0·6954
	HiR	94/140	79/133	0·88 (0·65, 1·20)	
	UHiR	27/34	28/34	0·98 (0·54, 1·79)	
	Not Available	310/550	323/552	1·01 (0·87, 1·18)	
UK−MRA Risk Profile	Low	136/306	136/311	0·97 (0·76, 1·24)	0·6538
	Medium	179/308	185/310	1·00 (0·82, 1·23)	
	High	223/310	216/307	0·89 (0·74, 1·07)	
Overall		**538/924**	**537/928**	**0·95 (0·84, 1·07)**	

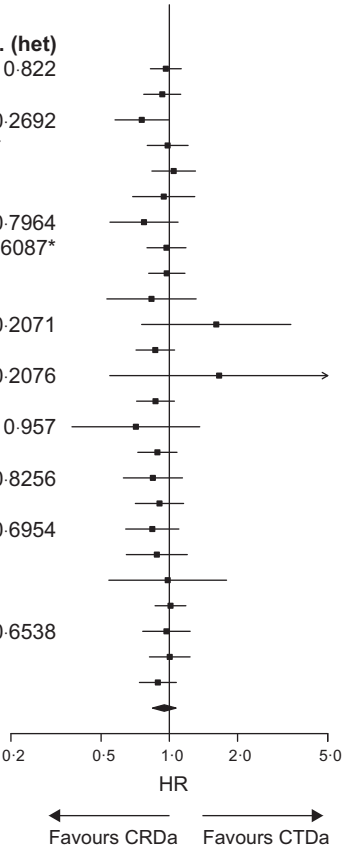


Fig 2. (Continued).

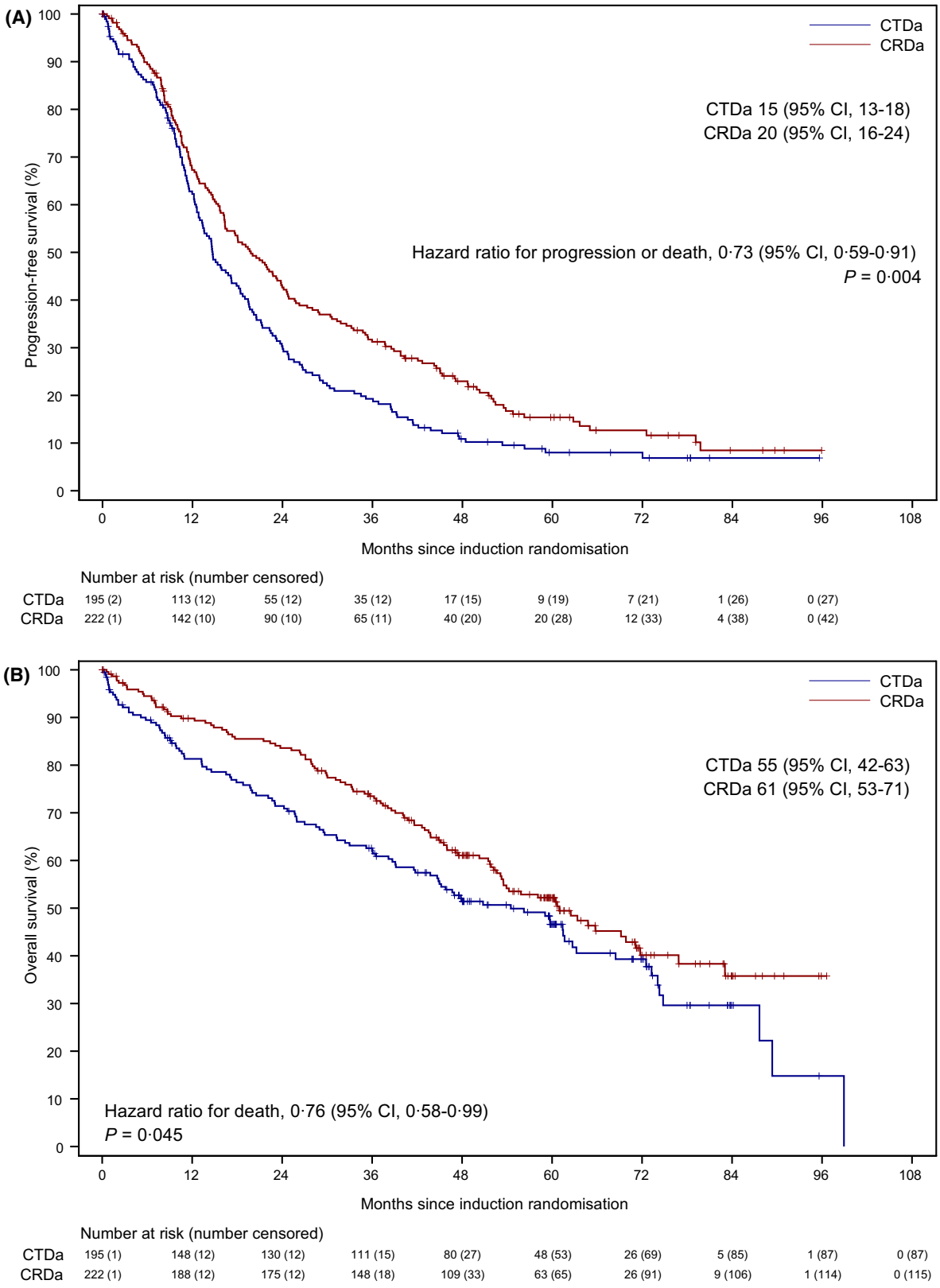
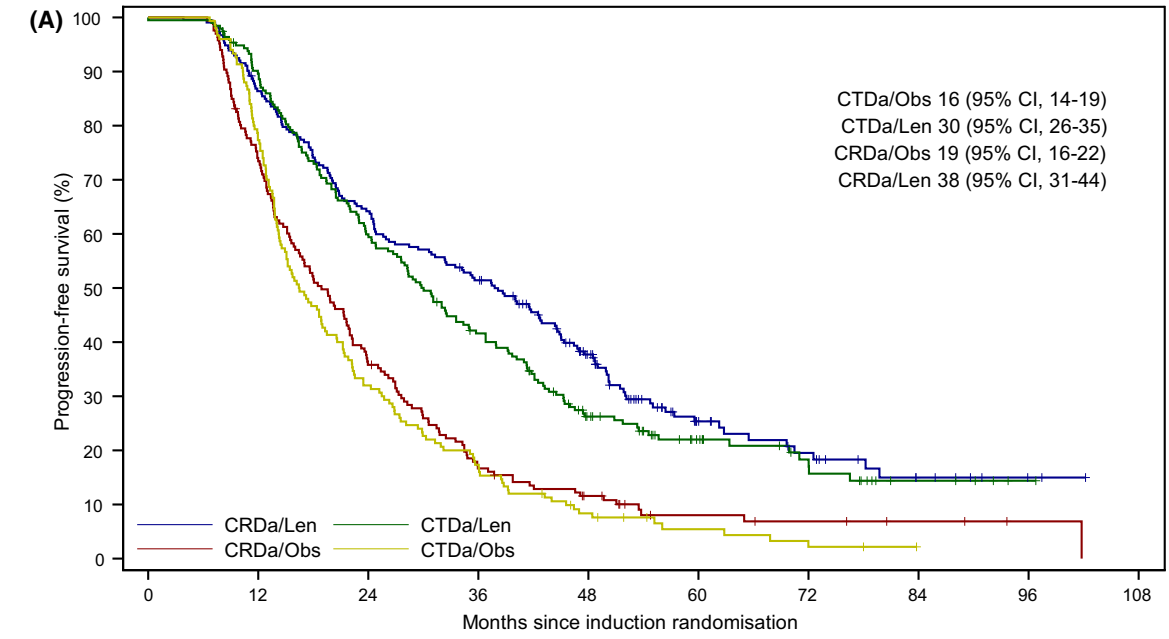
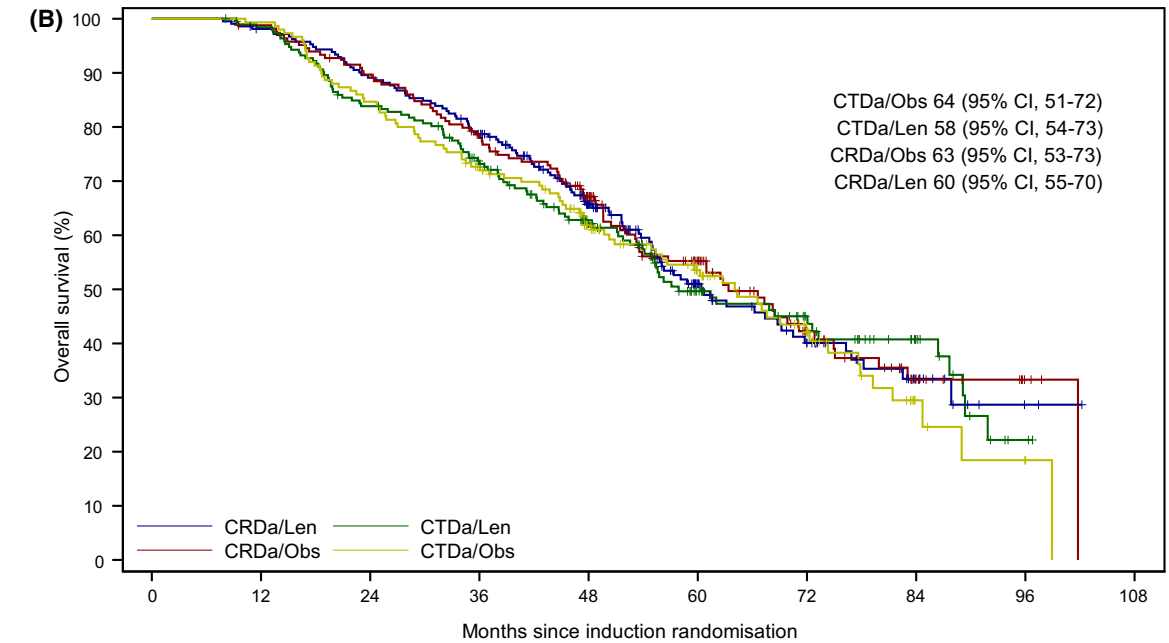


Fig 3. Progression-free survival (PFS) and overall survival (OS) primary endpoint analysis for those aged ≤70 years at randomisation. (A) PFS (B) OS. [Colour figure can be viewed at wileyonlinelibrary.com]



Number at risk (number censored)

CRDa/Len	213 (0)	183 (1)	136 (1)	108 (2)	65 (18)	25 (40)	16 (44)	7 (50)	2 (55)	0 (57)
CRDa/Obs	166 (0)	121 (1)	59 (1)	27 (2)	16 (5)	7 (10)	5 (11)	3 (13)	1 (15)	0 (15)
CTDa/Len	194 (0)	172 (2)	115 (2)	78 (4)	42 (12)	23 (25)	14 (31)	5 (37)	1 (41)	0 (42)
CTDa/Obs	150 (0)	116 (0)	48 (0)	26 (0)	11 (2)	5 (5)	2 (5)	0 (7)		



Number at risk (number censored)

CRDa/Len	213 (0)	207 (2)	188 (2)	164 (4)	112 (32)	53 (70)	33 (80)	12 (97)	2 (106)	0 (108)
CRDa/Obs	166 (0)	163 (1)	147 (2)	124 (6)	96 (17)	57 (41)	27 (60)	12 (70)	3 (79)	0 (81)
CTDa/Len	194 (0)	189 (2)	160 (3)	133 (10)	87 (38)	49 (60)	32 (73)	15 (87)	2 (95)	0 (97)
CTDa/Obs	150 (0)	149 (0)	127 (0)	106 (3)	76 (18)	48 (37)	28 (48)	6 (64)	2 (66)	0 (67)

Fig 4. Progression-free survival (PFS) and overall survival (OS) primary endpoint analysis for patients undergoing maintenance randomisation. (A) PFS (B) OS. CRDa/Len, patients receiving CRDa induction followed by lenalidomide maintenance; CRDa/Obs, patients receiving CRDa induction followed by observation; CTDa/Len, patients receiving CTDa induction followed by lenalidomide maintenance; CTDa/Obs, patients receiving CTDa induction followed by observation. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3. Adverse events (safety population)

	CRDa (n = 916)				CTDa (n = 910)				
	ALL	≤70 n = 220	71–75 n = 305	76–80 n = 273	>80 n = 118	ALL	≤70 n = 191	71–75 n = 335	76–80 n = 262	>80 n = 122
Haematological adverse events (Grade ≥3), n (%)										
Neutropenia	318 (34·7)	67 (30·5)	104 (34·1)	109 (39·9)	39 (33·1)	199 (21·9)	39 (20·4)	68 (20·3)	57 (21·8)	35 (28·7)
Anaemia	153 (16·7)	34 (15·5)	53 (17·4)	44 (16·1)	22 (18·6)	106 (11·6)	27 (14·1)	36 (10·7)	28 (10·7)	16 (13·1)
Thrombocytopenia	93 (10·2)	9 (4·1)	31 (10·2)	38 (13·9)	14 (11·9)	20 (2·2)	4 (2·1)	7 (2·1)	9 (3·4)	0 (0·0)
Adverse events of interest (any grade), n (%)										
Peripheral sensory neuropathy	205 (22·4)	55 (25·0)	67 (22·0)	59 (21·6)	24 (20·3)	354 (38·9)	79 (41·4)	129 (38·5)	102 (38·9)	42 (34·4)
Peripheral motor neuropathy	79 (8·6)	21 (9·5)	25 (8·2)	20 (7·7)	13 (11·0)	150 (16·5)	33 (17·3)	58 (17·3)	40 (15·3)	19 (15·6)
Deep vein thrombosis	34 (3·7)	16 (7·3)	4 (1·3)	11 (4·0)	3 (2·5)	33 (3·6)	8 (4·1)	1 (0·3)	8 (3·1)	4 (3·3)
Pulmonary embolism	38 (4·1)	16 (7·3)	11 (3·6)	6 (2·2)	5 (4·2)	33 (3·6)	4 (2·1)	12 (3·6)	12 (4·6)	5 (4·1)
Other thrombosis/embolism	20 (2·2)	5 (2·3)	4 (1·3)	5 (1·8)	4 (3·4)	4 (0·4)	0 (0·0)	1 (0·3)	3 (1·1)	0 (0·0)
Diarrhoea	264 (28·8)	62 (28·2)	78 (25·6)	91 (33·3)	33 (28·0)	117 (12·9)	17 (8·9)	33 (9·9)	47 (17·9)	20 (16·4)
Constipation	435 (47·5)	100 (45·5)	150 (49·2)	128 (46·9)	57 (48·3)	522 (57·4)	107 (56·0)	209 (62·4)	142 (54·2)	64 (52·5)

significantly longer PFS than observation alone both across all age groups HR 0·47 (95% CI 0·40, 0·55) and within all age categories: ≤70 years, HR 0·39 (95% CI0·28, 0·55); 71–75 years, HR 0·54 (95% CI 0·41, 0·70); 76–80 years, HR 0·49 (95% CI 0·35, 0·69); >80 years, HR 0·34 (95% CI 0·19, 0·62). As previously reported the benefit of lenalidomide maintenance on PFS was not seen for OS (Fig 4B).

Impact of age on side-effects

The median (range) number of cycles of induction therapy delivered was 6 (1–12) for CRDa and 6 (1–13) for CTDa, with 588 (63·6%) of CTDa and 618 (66·6%) of CRDa patients completing ≥6 cycles, the protocol prescribed minimum.

CRDa was better tolerated with fewer dose modifications. Lenalidomide dose modifications occurred in 566 (61·0%) patients who received CRDa induction therapy, and thalidomide dose modifications occurred in 785 (85·0%) who received CTDa induction therapy (Table S4). The median (IQR) percentage of minimum protocol dose delivered during induction therapy of lenalidomide was 73·3% (33·3–100·0%) and of thalidomide was only 50·0% (24·0–77·8%). The rate of discontinuation of induction therapy due to toxicity was slightly higher with CTDa compared to CRDa, at 12·7% and 11·0% respectively (Table S5).

The side-effect profile of the two regimens differed with patients receiving CTDa having higher rates of peripheral sensory neuropathy (all Grades: CTDa 38·9% vs. CRDa 22·4%) and peripheral motor neuropathy (CTDa 16·5% vs. CRDa 8·6%), whereas those receiving CRDa had higher rates of neutropenia (Grade ≥3: CTDa 21·9% vs. CRDa 34·7%) (Table 3). Deep vein thrombosis occurred in 3·6% of patients in the CTDa group and 4·1% in the CRDa group. There was no difference in the 3-year cumulative incidence of invasive second primary malignancies between CTDa and CRDa induction (4·7% vs. 3·8%; HR 1·01, 95% CI 0·72, 1·44; P = 0·9344). Serious AEs during induction were similar in each group and largely accounted for by infections. Fatal AEs during induction were most commonly due to infection, with lung infection the most common cause in both arms. Safety data relating to the lenalidomide maintenance phase has been published previously.[14]

There was a notable increase in AEs (Table 3) and dose modifications (Table S3) with age across both arms. For example, dose modification of lenalidomide was required in 79% of patients aged >80 years compared to only 50% of patients aged ≤70 years. There were higher rates of cessation of induction due to toxicity and fewer cycles delivered with increasing age (Table S4). In patients aged ≤70 years toxicity was cited as a reason for stopping induction therapy in 8·2% and 9·9% of patients receiving CTDa and CRDa respectively; this increased to 16% and 15% for those aged >80 years. In addition, a lower proportion of patients in the older age

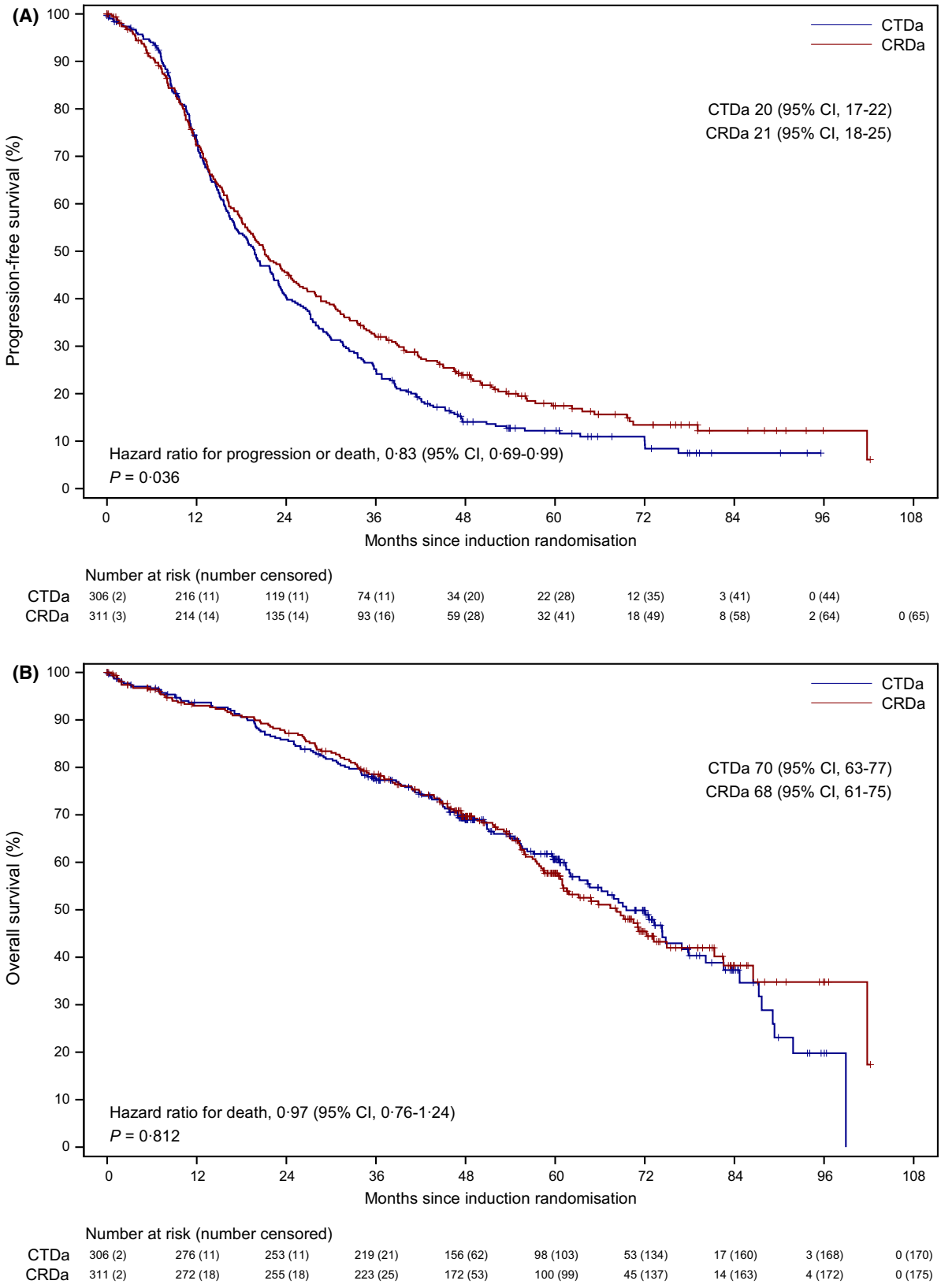


Fig 5. Progression-free survival (PFS) and overall survival (OS) primary endpoint analysis by UK Myeloma Research Alliance Risk Profile. (A) PFS: Low risk. (B) OS: Low risk. [Colour figure can be viewed at wileyonlinelibrary.com]

groups received maintenance either through clinician/patient choice, progression or toxicity during induction (Table S5). Whilst 59% and 41% of patients aged ≤70 years receiving CTDa and CRDa respectively were not able to undergo maintenance randomisation, this increased to 76% and 67% for those aged >80 years.

Outcomes according to MRP risk group

Outcomes for patients receiving CTDa and CRDa were compared within each of the risk groups identified by the MRP score (Fig 5 and Figure S2). Within the low-risk group there was a significant benefit for CRDa over CTDa for PFS (HR 0·47, 95% CI 0·40, 0·55; $P = 0·036$) that was not seen in any of the other groups. Importantly for the clinical use of such scores, the total number of patients identified within the low-risk group was 617 compared to 417 patients aged <70 years, showing that the groups do not have a high degree of overlap. Indeed, of these 617 patients, 217 were aged ≤70 years, 237 were aged 71–75 years, 133 were aged 76–80 years and 30 were aged >80 years, highlighting that even older patients can fall within the low-risk category and may be fit for full-dose therapy.

Discussion

This is, to our knowledge, the largest trial of transplant-ineligible patients in myeloma, comprising a total of 1852 patients with almost half aged >75 years, giving the opportunity to address the impact of age and other factors on treatment outcomes. For induction therapy, there was no difference in outcome between CTDa and CRDa. However, CRDa was better tolerated than CTDa and associated with a lower incidence of peripheral neuropathy and constipation, symptoms that may significantly impact quality of life.

When the impact of age was taken into account, although there was no evidence of significant heterogeneity when looking across all age groups; within the group of patients aged ≤70 years, there was a significant PFS and OS benefit when they were treated with lenalidomide-based induction compared to thalidomide. We therefore went on to look for heterogeneity between those aged <70 years and all other patients and this was significant for PFS. This raises the hypothesis that this group of younger patients may have benefitted from CRDa *versus* CTDa, a result that we also found in the transplant-eligible population.[15]

In the overall population, we identified a significantly longer PFS associated with the use of lenalidomide maintenance compared to observation, consistent across all age groups, but this was not associated with an improved OS. In an exploratory analysis, we found that CRDa induction followed by lenalidomide maintenance was the treatment combination associated with the longest PFS.

Although the analysis of CTDa *versus* CRDa did not meet its endpoint in the overall population, understanding the basis for possible improved outcome with CRDa for patients within the younger age group is important, as it may reflect an adverse impact of frailty in older patients. In the group aged ≤70 years, patients receiving CRDa were more likely to receive the protocol specified dose and less likely to stop therapy due to toxicity; twice as many patients aged >80 years stopped therapy due to toxicity compared to those aged ≤70 years. Consistent with this, patients aged ≤70 years receiving CRDa had deeper responses and there was an associated improvement in PFS and OS. Our present findings support the importance of side-effect profile and patients' ability to remain on therapy as being significant factors that impact on the interpretation of results in this age group. This observation is important because it focusses attention on what is one of the major drivers of outcome in this group, tolerability. The increased incidence of AEs and higher rates of cessation of therapy due to toxicity in patients at older ages may have reduced the potential for beneficial differences to be identified and may explain why this trial as well as several other recent trials in patients with newly diagnosed transplant-ineligible myeloma have failed to meet their primary endpoint, including the HOVON87/NMSG18 trial, the GERMAIN trial [6,16] and the TOURMALINE-MM2 (ClinicalTrials.gov Identifier: NCT01850524) and ELOQUENT-1 (ClinicalTrials.gov Identifier: NCT01335399) trials recently reported via press release.

Several other studies have looked at the value of triplet combinations with alkylating agents in newly diagnosed transplant-ineligible patients.[5–7] In the MM-015 study, the benefit of MPR-R was only seen in the group aged <75 years, consistent with a similar impact of age on the outcomes of treatment seen in our present study.[5] Similarly in the Italian/Czech study an analysis by frailty suggested a benefit for MPR in younger fitter patients.[7] In our present study, neither initial induction triplet combination included a proteasome inhibitor, as patients were randomised to this treatment only in the event of a suboptimal response to induction. Combination treatment with lenalidomide and bortezomib is now considered a standard of care in the EU and USA based on the results of the Southwest Oncology Group (SWOG) S0777 study, although this was not the case at the time of trial design. Importantly the SWOG study recruited patients 'who were not planned for immediate autologous stem cell transplant' and the median age of patients was 63 years.[17] Only patients aged <65 years had a significant improvement in PFS with VRd *versus* Rd, again demonstrating the difficulty in improving outcomes in older patients.

More recently combinations including the monoclonal antibody, daratumumab (Dara), have been trialled in transplant-ineligible patients. The ALCYONE study (ClinicalTrials.gov, NCT02195479) compared Dara combined with bortezomib, melphalan and prednisolone (VMP) to VMP alone. Although the significant improvement in PFS with

Dara-VMP was seen in all age groups, the benefit for OS was not significant in the subgroup aged >75 years.[18,19] Similarly, in the MAIA trial (ClinicalTrials.gov number, NCT02252172) comparing Dara-Rd to Rd, the PFS improvement was consistent across age groups, but OS outcomes are not yet mature.[20] These studies demonstrated that the monoclonal antibody daratumumab is a useful addition to the current therapies used in older patients and seems well tolerated. However, for some patients all-oral regimens may be preferable with the associated reduction in visits to the clinic. The results of our present study provide important data on the use of CRDa as an all-oral option and, although not a current standard of care, may be considered in a subset of patients.

It remains clear from various studies that improving outcomes particularly OS, in older, frailer patients with myeloma remains challenging and an unmet need. It is important to take advantage of the clinical observations from our present study to understand ways in which we could optimise therapy in these older age groups. It is unlikely that age alone is the primary driver of increased toxicity in older patients, but rather an increase in frailty in subsets of patients' affecting their ability to tolerate treatment. As International Myeloma Working Group (IMWG) frailty scoring was not collected for the patients in Myeloma XI, we used an easily applicable outcome risk score, the MRP.[12] Applying this to the study result, we found a significant PFS benefit for CRDa over CTDa for patients in the low-risk MRP group identified by the score. Supporting the validity of the score and the concept that it may help predict treatment tolerability, patients in this group had less toxicity and fewer dose reductions.[12] Importantly, by applying this approach we were able to identify a large number of patients distributed throughout the older age group, but with low-risk MRP, where the use of lenalidomide induction and maintenance may be associated with improved outcomes. The use of scores such as this could also improve the value proposition for expensive drugs used in this population. The IMWG has also recently proposed a frailty score for transplant-ineligible myeloma patients,[21] but data to complete this score was not collected in the present study, whereas the MRP uses routinely collected clinical data. Quality-of-life data were also not collected in the study to allow comparison of the impact of the different induction regimens, but the difference in side-effect profiles suggested this may have been improved with CRDa compared to CTDa.

Taken together our present results suggest that if patients fall into the intermediate or high MRP risk groups or frailty group equivalents that dose reduction of the induction treatment with CRD or an anti-CD38 antibody combination therapy, such as those explored more recently, should be implemented. Dose reduction based on frailty scoring may be able to improve outcomes irrespective of induction regimen and we will explore this prospectively in our follow on study, FiTNEss (Frailty-adjusted Therapy in Transplant Non-Eligible Patients With Newly Diagnosed Multiple Myeloma, Myeloma XIV), which is due to open in 2020.

Authors' disclosures for potential conflicts of interest

Graham H. Jackson: Roche – consultancy, honoraria, speakers bureau; Amgen – consultancy, honoraria, speakers bureau; Janssen – consultancy, honoraria, speakers bureau; Merck Sharp and Dohme – consultancy, honoraria, speakers bureau; Celgene Corporation – consultancy, honoraria, travel support, research funding, speakers bureau; Takeda – consultancy, honoraria, travel support, research funding, speakers bureau. Charlotte Pawlyn: Amgen – consultancy, honoraria, travel support; Takeda Oncology – consultancy, travel support; Janssen – honoraria, travel support; Celgene Corporation – consultancy, honoraria, travel support. David A. Cairns: Celgene Corporation, Amgen, Merck Sharp and Dohme – research funding. Alina Striha: Celgene Corporation, Amgen, Merck Sharp and Dohme – research funding. Corinne Collett: Celgene Corporation, Amgen, Merck Sharp and Dohme – research funding. Anna Waterhouse: Celgene Corporation, Amgen, Merck Sharp and Dohme – research funding. John R. Jones: Celgene Corporation – honoraria, research funding. Jamie N Wilson: nothing to disclose. Craig Taylor: nothing to disclose. Bhuvan Kishore: Celgene Corporation, Takeda, and Janssen – consultancy, travel support, speakers bureau. Mamta Garg: Janssen – travel support, research funding, speakers bureau; Takeda – travel support; Novartis – travel support, research funding. Cathy D. Williams: Takeda – honoraria, travel support, speakers bureau; Amgen – honoraria, speakers bureau; Novartis – honoraria; Janssen – honoraria, travel support, speakers bureau; Celgene Corporation – honoraria, travel support, speakers bureau. Kamaraj Karunanithi: Celgene Corporation – travel support, research funding; Janssen – travel support, research funding. Jindriska Lindsay: Janssen – consultancy; Novartis – travel support; Takeda – honoraria, travel support; Bristol-Myers Squibb – consultancy, travel support; Celgene Corporation – consultancy, honoraria, travel support. Matthew W. Jenner: Janssen – consultancy, honoraria, travel support, research funding; Takeda – consultancy, honoraria, travel support; Amgen – consultancy, honoraria, travel support; Celgene Corporation – consultancy, honoraria, research funding; Novartis – consultancy, honoraria. Gordon Cook: Takeda – consultancy, honoraria, research funding, speakers bureau; Glycomimetics – consultancy, honoraria; Sanofi – consultancy, honoraria, speakers bureau; Celgene Corporation – consultancy, honoraria, research funding, speakers bureau; Janssen – consultancy, honoraria, research funding, speakers bureau; Bristol-Myers Squibb – consultancy, honoraria; Amgen – consultancy, honoraria, research funding, speakers bureau. Nigel H. Russell: nothing to disclose. Mark T. Drayson: Abingdon Health – equity ownership, membership on an entity's board of directors or advisory committees. Martin

F. Kaiser: Bristol-Myers Squibb – consultancy, travel support; Chugai – consultancy; Janssen – consultancy, honoraria; Amgen – consultancy, honoraria; Takeda – consultancy, travel support; Celgene Corporation – consultancy, honoraria, research funding. Roger G. Owen: Takeda – honoraria, travel support; Janssen – consultancy, travel support; Celgene Corporation – consultancy, honoraria, research funding. Walter M. Gregory: Celgene Corporation – consultancy, research funding; Amgen, Merck Sharp and Dohme – research funding; Janssen – honoraria. Faith E. Davies: Amgen – consultancy, honoraria; AbbVie – consultancy, honoraria; Takeda – consultancy, honoraria; Janssen – consultancy, honoraria; Celgene Corporation – consultancy, honoraria, research funding; Roche – consultancy, honoraria. Gareth J. Morgan: Janssen – research funding; Bristol-Myers Squibb – consultancy, honoraria; Takeda – consultancy, honoraria; Celgene Corporation – consultancy, honoraria, research funding; Roche – consultancy, honoraria; Amgen – consultancy, honoraria; GSK – consultancy, honoraria; Karyopharm – consultancy, honoraria.

Funding

Financial support for the Myeloma XI trial was obtained from Cancer Research [C1298/A10410]. Unrestricted educational grants from Celgene Corporation and Merck Sharp and Dohme, as well as funding from Myeloma UK supported the trial coordination and the laboratory studies. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

We thank all the patients at centres throughout the United Kingdom whose willingness to participate made this study possible. We are grateful to the UK National Cancer Research Institute Haematological Oncology subgroup, UK Myeloma Research Alliance, and to all principal investigators, sub-investigators, and local centre staff for their dedication and commitment to recruiting patients to the study. We thank the members of the Myeloma XI Trial Steering Committee and Data Monitoring and Ethics Committee. The support of the Clinical Trials Research Unit at The University of Leeds was essential to the successful running of the study; we thank all their staff who have contributed, past and present. Central laboratory analysis was performed at the Institute of Immunology and Immunotherapy, The University of Birmingham; The Institute of Cancer Research, London; and The Haematological Malignancy Diagnostic Service, St James's University Hospital, Leeds. We are very grateful to the laboratory teams for their contribution to the study. We also acknowledge support from the National Institute of Health Biomedical Research Centre at the Royal Marsden Hospital and the Institute of Cancer Research.

Author contributions

Graham H. Jackson, Nigel H. Russell, Faith E. Davies, and Gareth J. Morgan were chief investigators; Graham H. Jackson, Nigel H. Russell, Walter M. Gregory, Faith E. Davies, and Gareth J. Morgan designed the trial and developed the protocol; David A. Cairns, Alina Striha, and Walter M. Gregory developed and carried out the statistical analysis plan; Graham H. Jackson, Faith E. Davies, Charlotte Pawlyn, John R. Jones, Jamie Wilson, Craig Taylor, Bhuvan Kishore, Mamta Garg, Cathy D. Williams, Kamaraj Karunanithi, Jindriska Lindsay, Matthew W. Jenner, Gordon Cook, Nigel H. Russell, Martin F. Kaiser, Roger G. Owen, and Gareth J. Morgan participated in recruitment of patients; Martin F. Kaiser, Mark T. Drayson, Roger G. Owen, and Gareth J. Morgan coordinated the central laboratory investigations; Corinne Collett and Anna Waterhouse coordinated the data collection and regulatory and governance requirements; Graham H. Jackson, Charlotte Pawlyn, David A. Cairns, Alina Striha, Martin F. Kaiser, Mark T. Drayson, Roger G. Owen, Walter M. Gregory, Faith E. Davies, and Gareth J. Morgan analysed and interpreted the data; Graham H. Jackson, Charlotte Pawlyn, David A. Cairns, Alina Striha, Faith E. Davies, and Gareth J. Morgan 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.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Optimising the value of immunomodulatory drugs during induction and maintenance in transplant ineligible patients with newly diagnosed multiple myeloma: results from Myeloma XI, a multicenter, open-label, randomised, phase 3 trial.

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