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

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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).

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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.

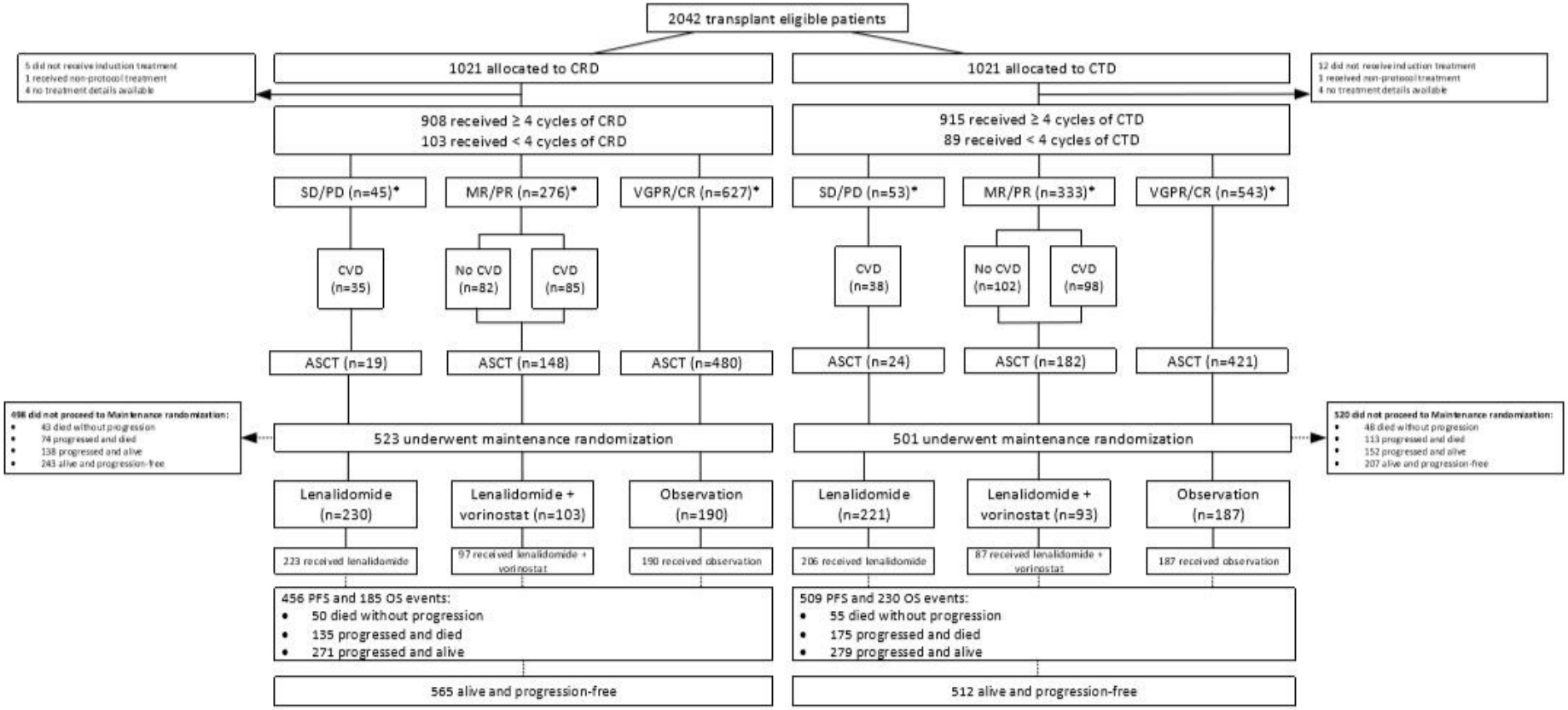
Supplementary Table 3. Published randomized studies evaluating 3/4-drug combinations of newer agents as induction therapy prior to ASCT

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)

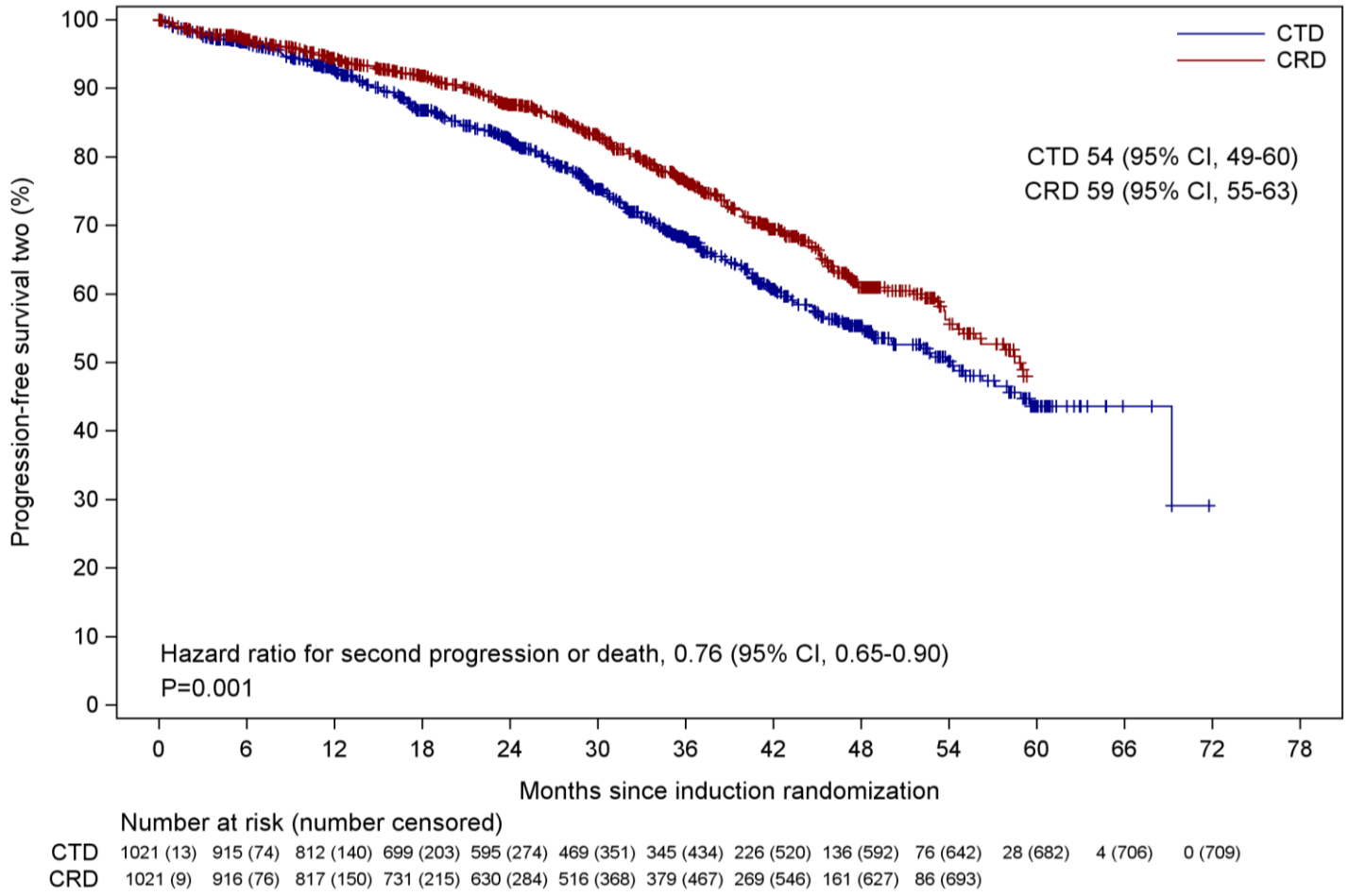
Abbreviations: ASCT, autologous stem cell transplantation; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; CVD, cyclophosphamide, bortezomib, and dexamethasone; CVRD, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone; CVTD, cyclophosphamide, 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.

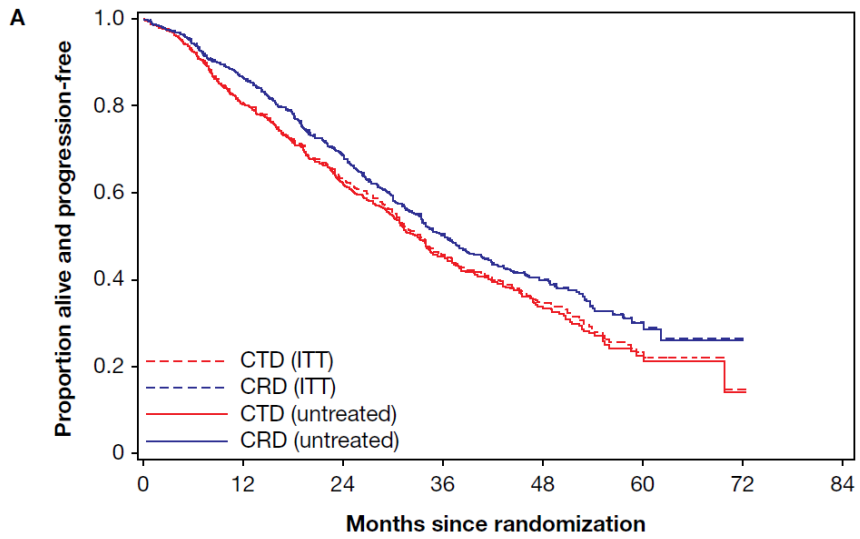


Supplementary Figure 2. PFS2 according to induction regimen. Abbreviations: CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone.



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
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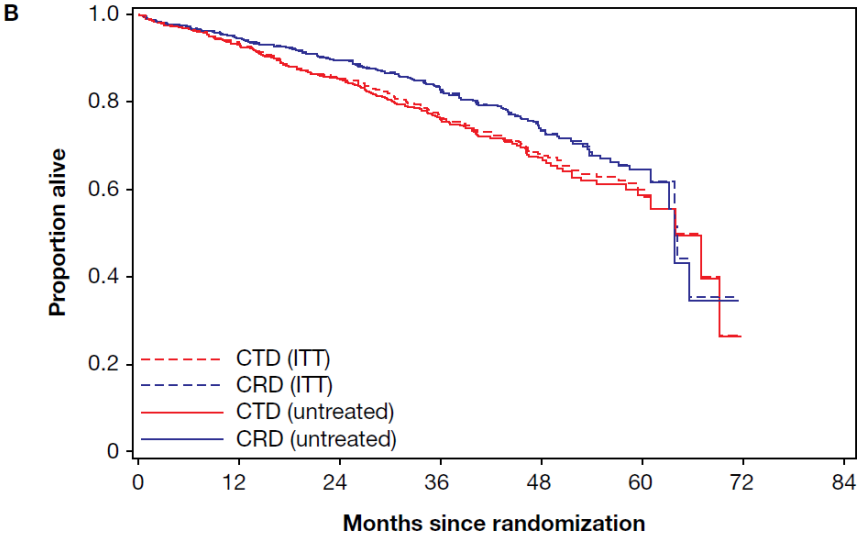
72
84
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (untreated)
CRD (untreated)


B
Proportion alive
1.0
0.8
0.6
0.4
0.2
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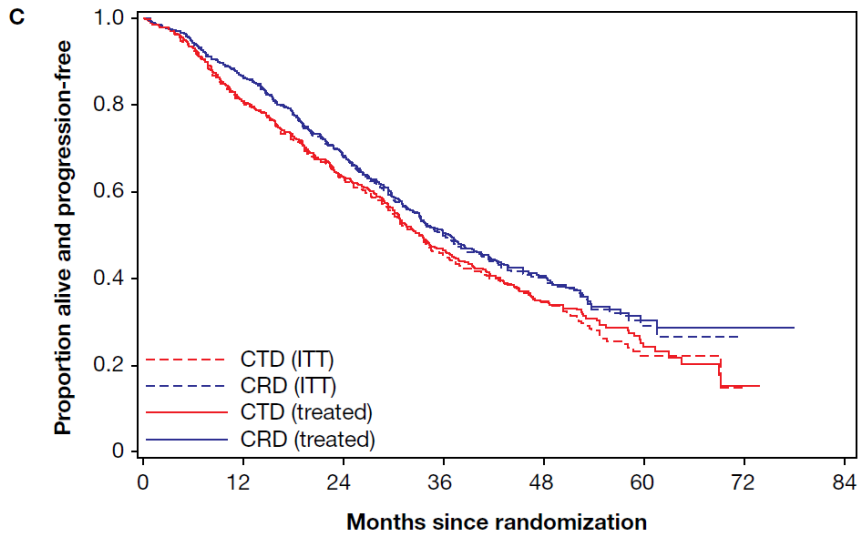
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (untreated)
CRD (untreated)


C
Proportion alive and progression-free
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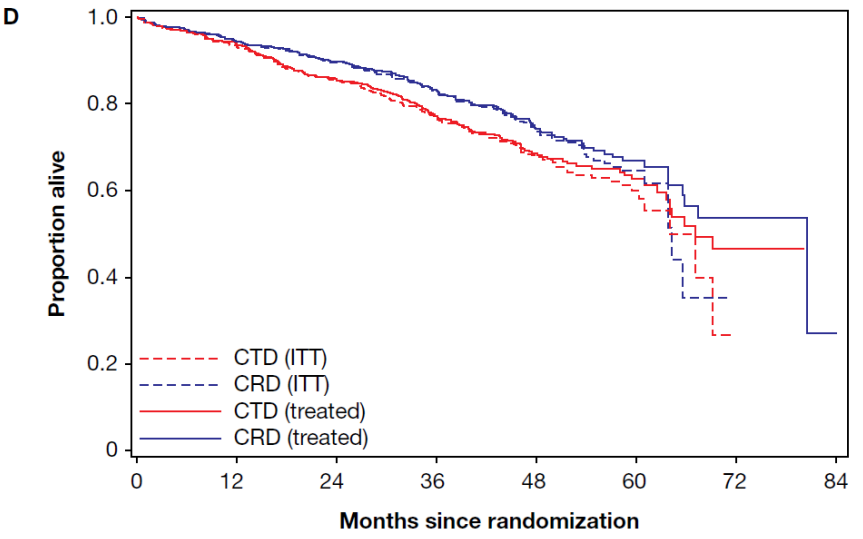
Months since randomization
CTD (ITT)
CRD (ITT)
CTD (treated)
CRD (treated)


D
Proportion alive
1.0
0.8
0.6
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0.2
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12
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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