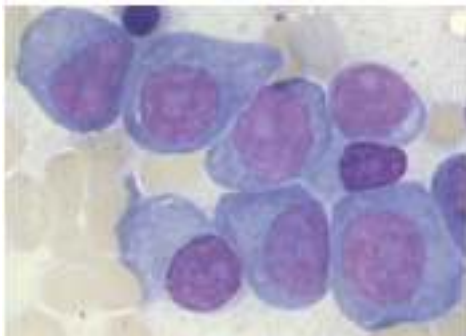


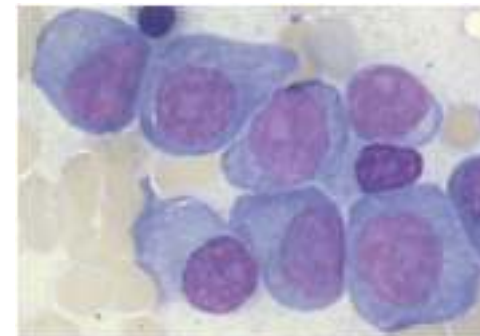
Minimal residual disease (MRD) assessment using multiparameter flow cytometry (MFC) predicts outcome in both intensively and non-intensively treated patients: Results from the MRC Myeloma IX trial.

A Rawstron, R de Tute, A Child, F Davies, W Gregory, S Bell, A Szubert, N Navarro-Coy, M Drayson, S Feyler, F Ross, G Cook, G Jackson, G Morgan & R Owen.



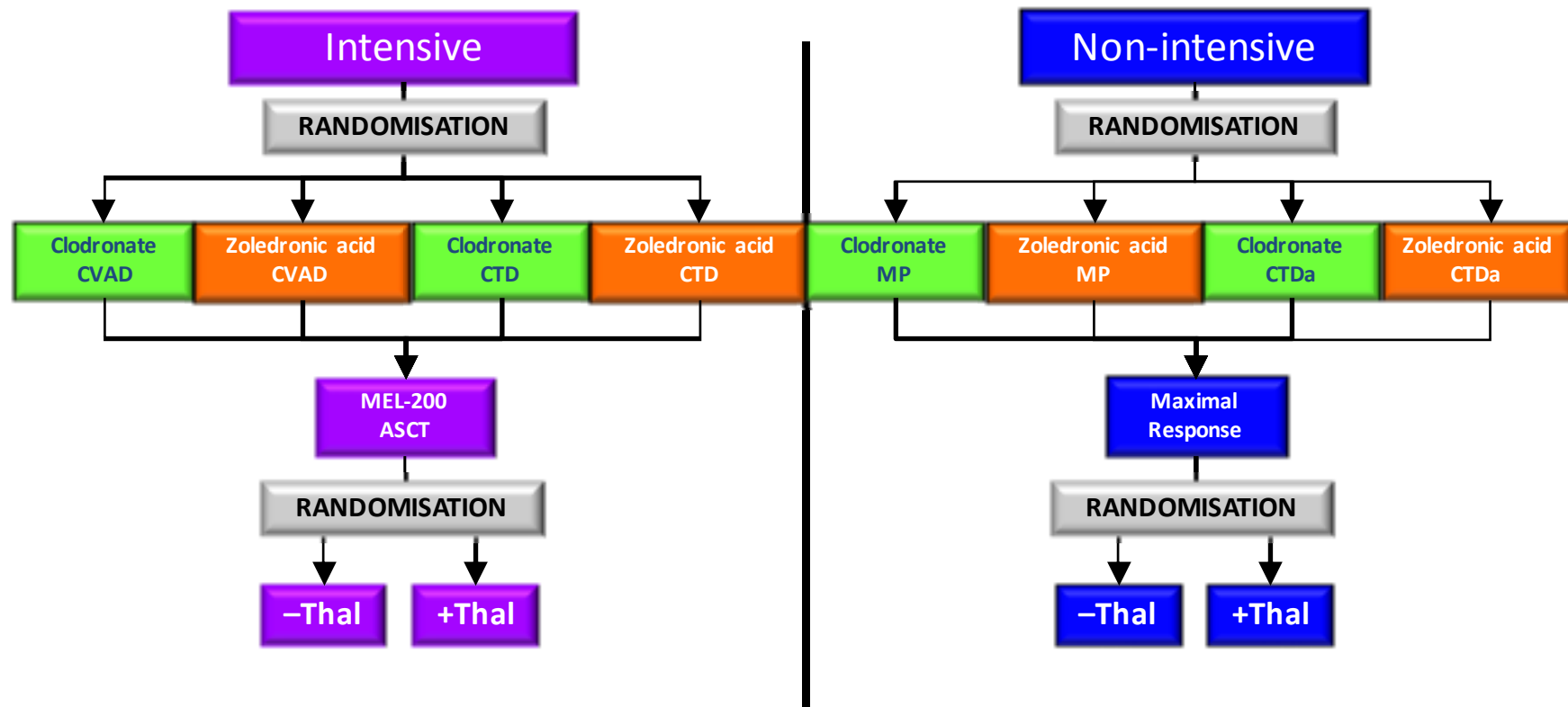
Disclosures

- The trial was funded by the Medical Research Council (UK).
- Support for the linked scientific investigational studies was received from Bayer-Schering, Celgene, Chugai, Novartis, Pharmion, and Ortho Biotech in the form of unrestricted educational grants.
- Dr RG Owen has received honoraria from Celgene and Ortho Biotech.



MRC Myeloma IX— Trial Design

N = 1,960



Flow cytometry in MM.

Report of the European Myeloma Network (EMN) on multiparametric flow cytometry in multiple myeloma and related disorders

Andy C. Rawstron, Alberto Orfao^{2*}, Meral Beksac³, Ludmila Bezdicikova⁴, Rik A. Brooimans⁵, Horia Bumbea⁶, Klara Dalva³, Gwenny Fuhler⁷, Jan Gratama⁵, Dirk Hose⁸, Lucie Kovarova⁹, Michael Lioznov¹⁰, Gema Mateo², Ricardo Morilla¹¹, Anne K. Mylin¹², Paola Omede¹³, Catherine Pellat-Deceunynck¹⁴, Martin Perez Andres, Maria Petrucci¹⁵, Marina Ruggeri¹³, Grzegorz Rymkiewicz¹⁶, Alexander Schmitz¹⁷, Martin Schreder¹⁸, Carine Seynaeve¹⁹, Martin Spacek⁴, Ruth M. de Tute, Els Van Valckenborgh¹⁹, Nicky Weston-Bell²⁰, Roger G. Owen¹, Jesús San Miguel, Pieter Sonneveld²¹, Hans E. Johnsen²² on behalf of the European Myeloma Network²³

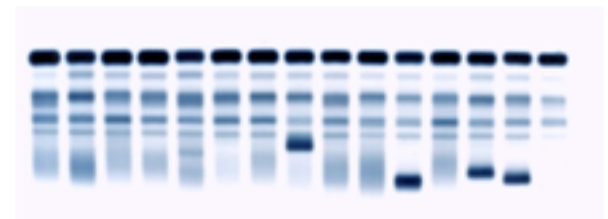


- Minimum four colour method
- Gating using CD38, CD138 and CD45
- MRD+ defined by a minimum of 100 events (10^6 total events acquired for a sensitivity of 0.01%)
- Clonality assessment suboptimal for MRD due to the presence of normal cells in post treatment samples
- Aberrant phenotype defined by CD19 and CD56
- Leeds - CD138/CD38/CD45/CD19/CD56/CD27

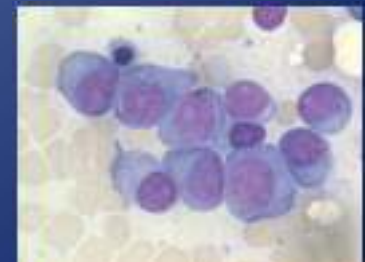
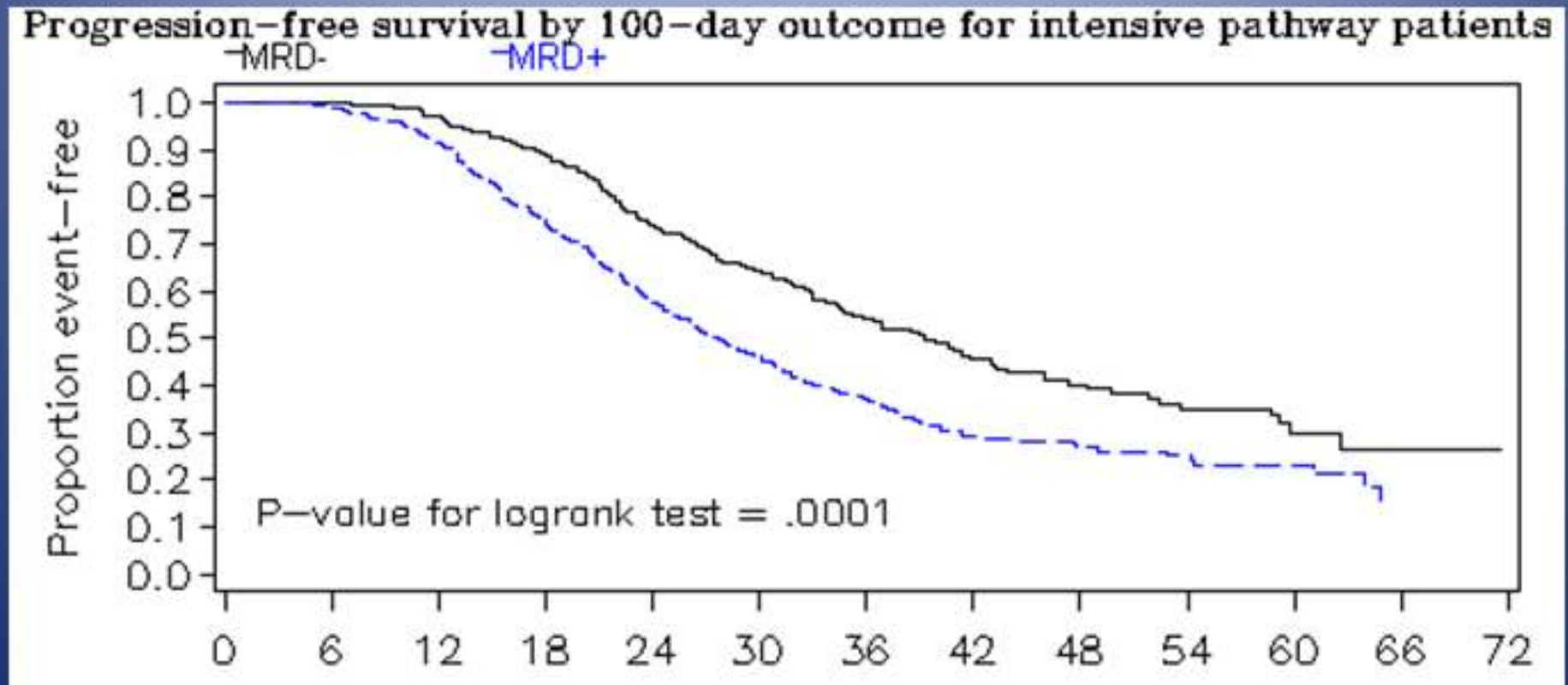
MRD negativity: Superiority of CTD/CTDa.

	CVAD	CTD	
Post induction (n=774)	8%	16%	P=0.0029
Day 100 (n=526)	38%	53%	P=0.0009

	M & P	CTDa	
End of treatment (n=510)	2%	13%	P=0.000007

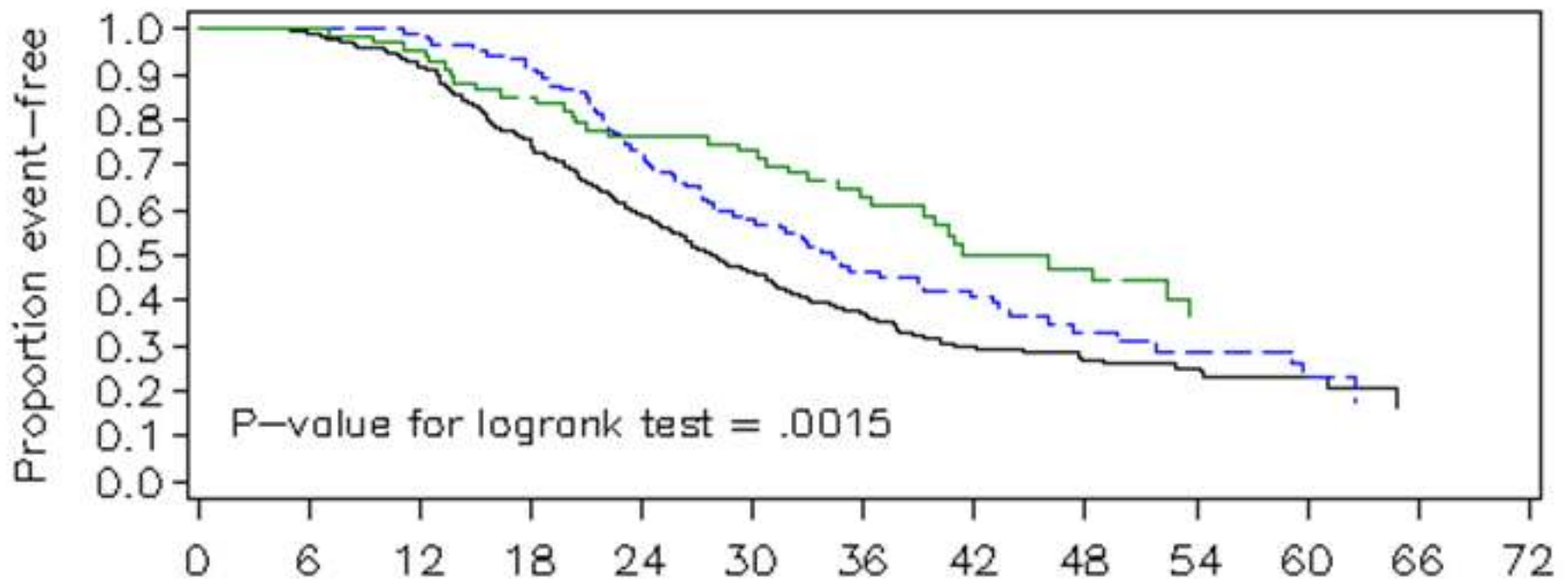


PFS: Day 100 MRD assessment.



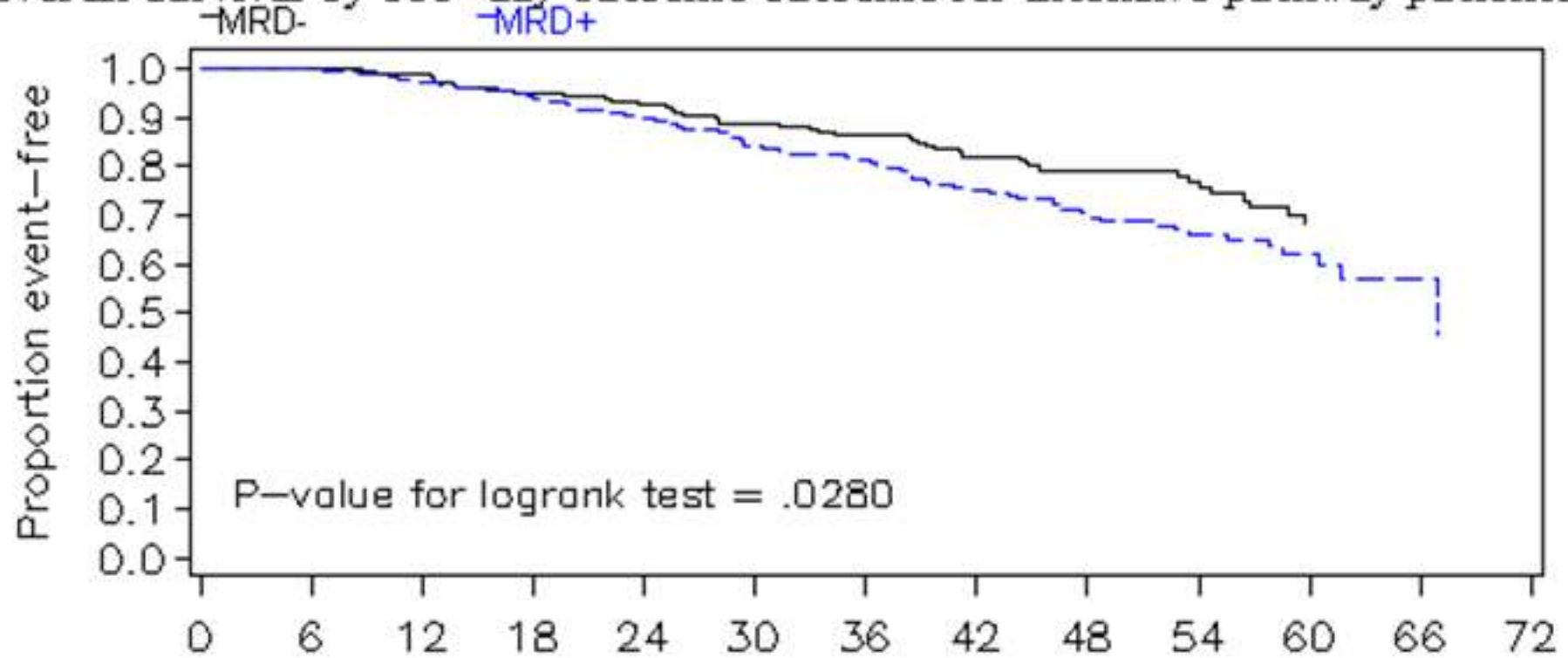
PFS according to end of induction and day 100 MRD.

Progression-free survival by outcome for intensive pathway patients
-1:IND+;HDM+ -2:IND+;HDM- -3:IND-;HDM+ -4:IND-;HDM-



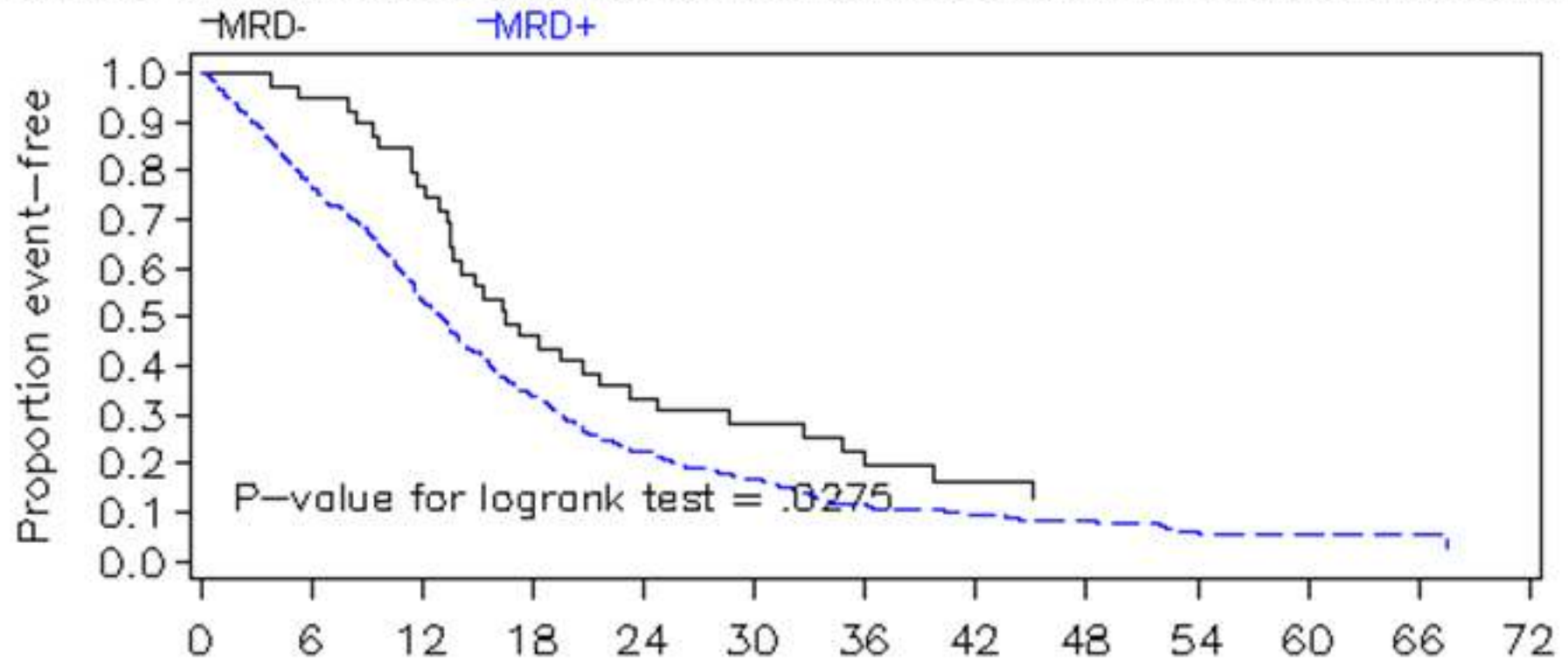
Overall survival: Day 100 MRD status.

Overall survival by 100-day outcome for intensive pathway patients



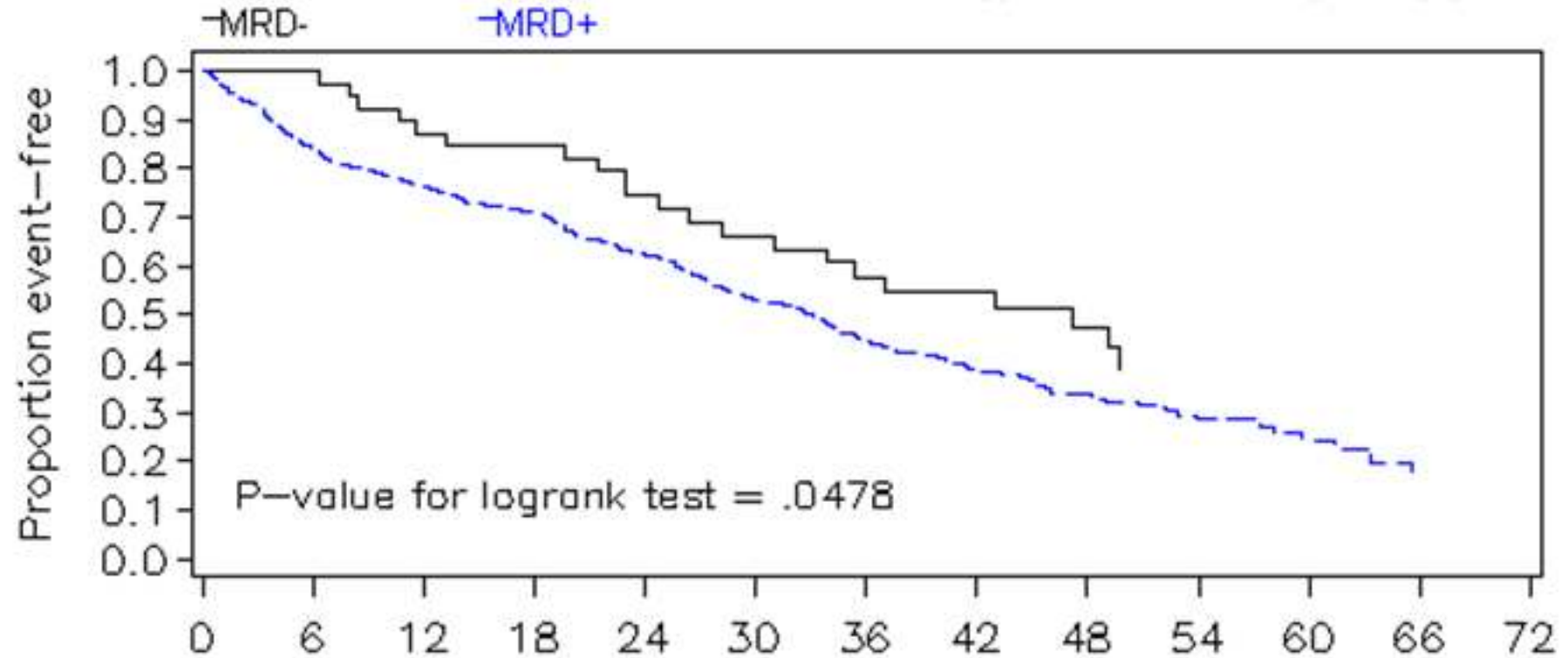
PFS: Non-intensive pathway (n=510).

Progression-free survival by outcome at the end of induction chemotherapy for non-intensive pathway patients

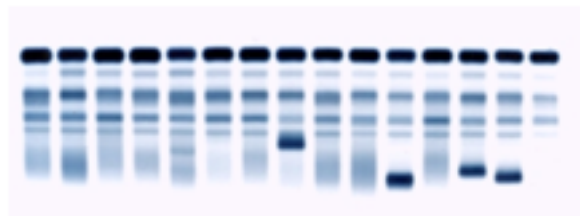
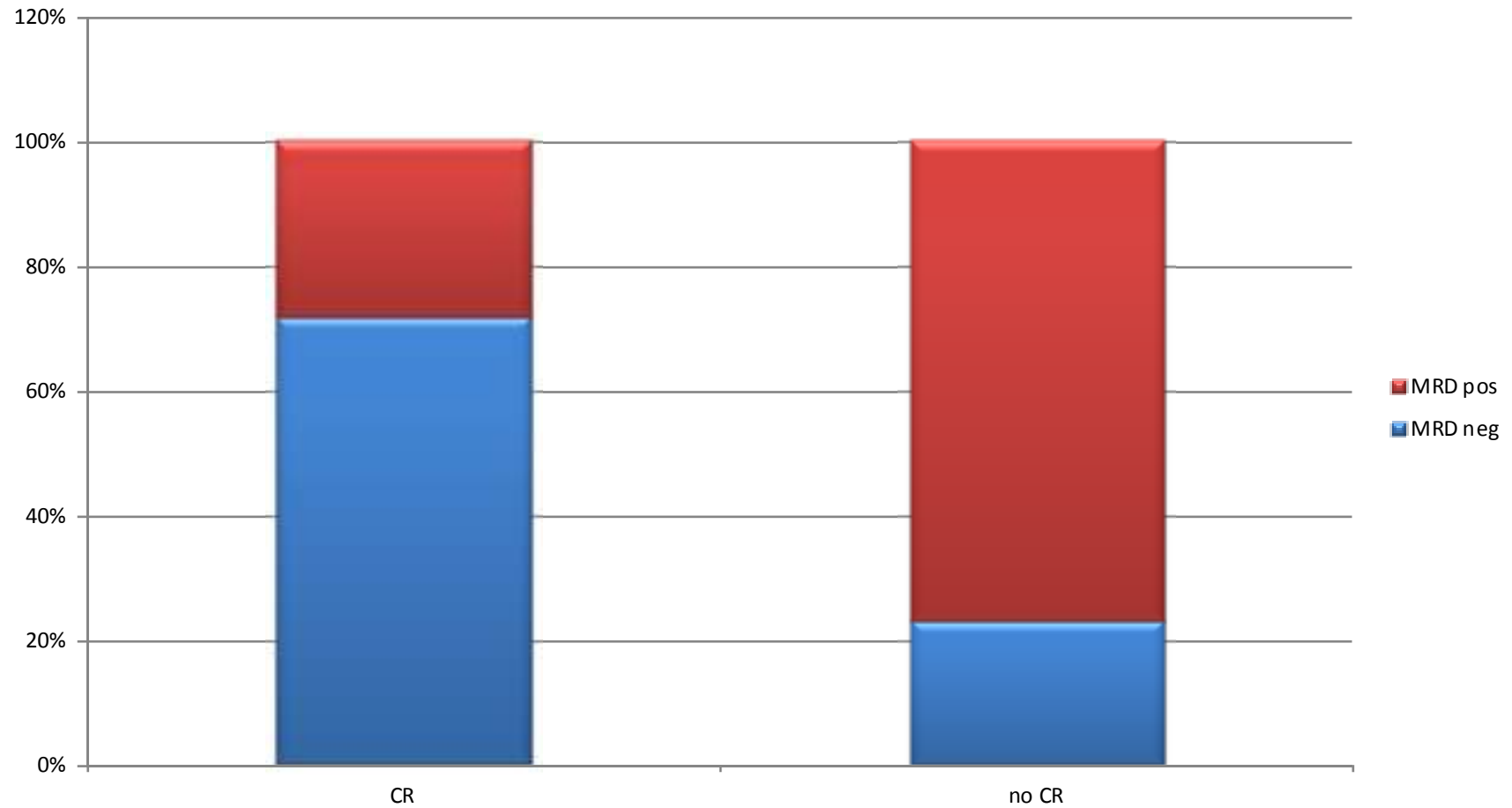


OS: Non-intensive pathway.

Overall survival by outcome at the end of induction chemotherapy for non-intensive pathway patients

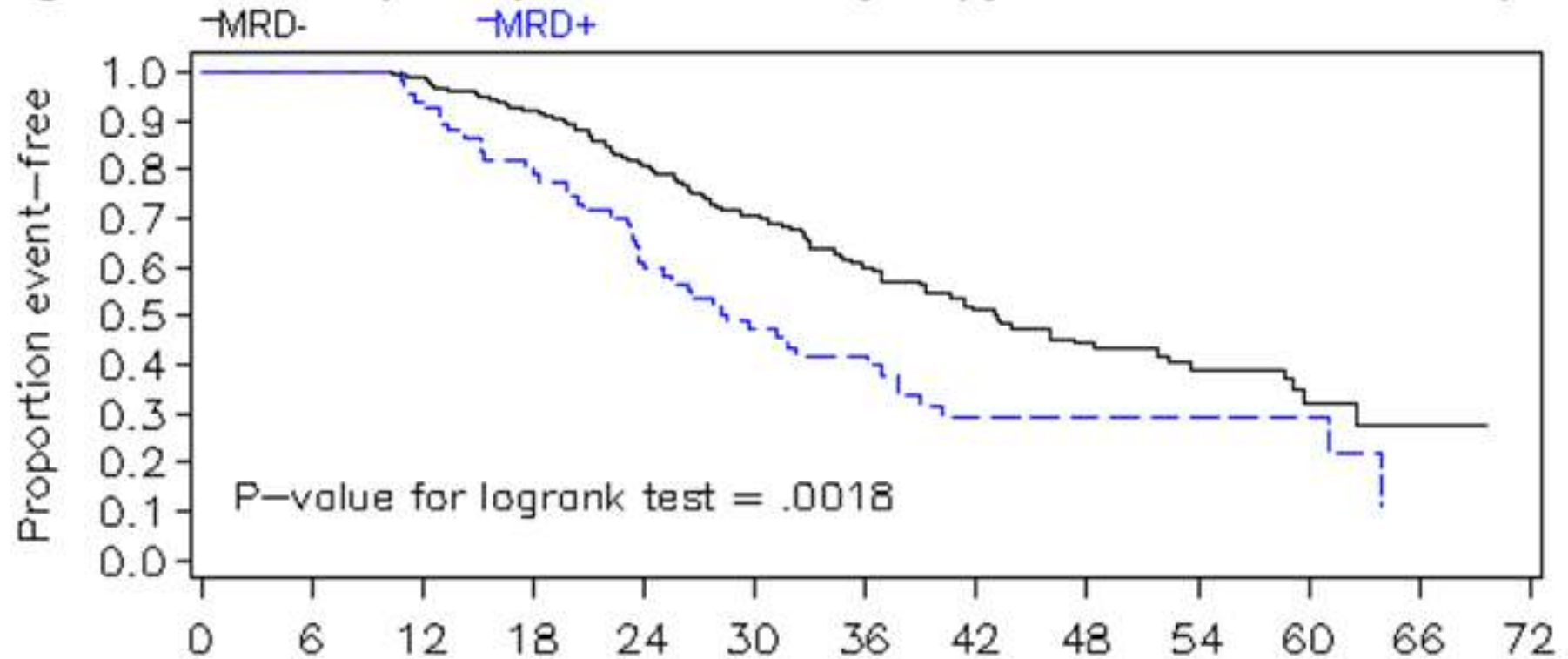


Comparison of MRD and paraprotein responses at Day 100 post HDM.



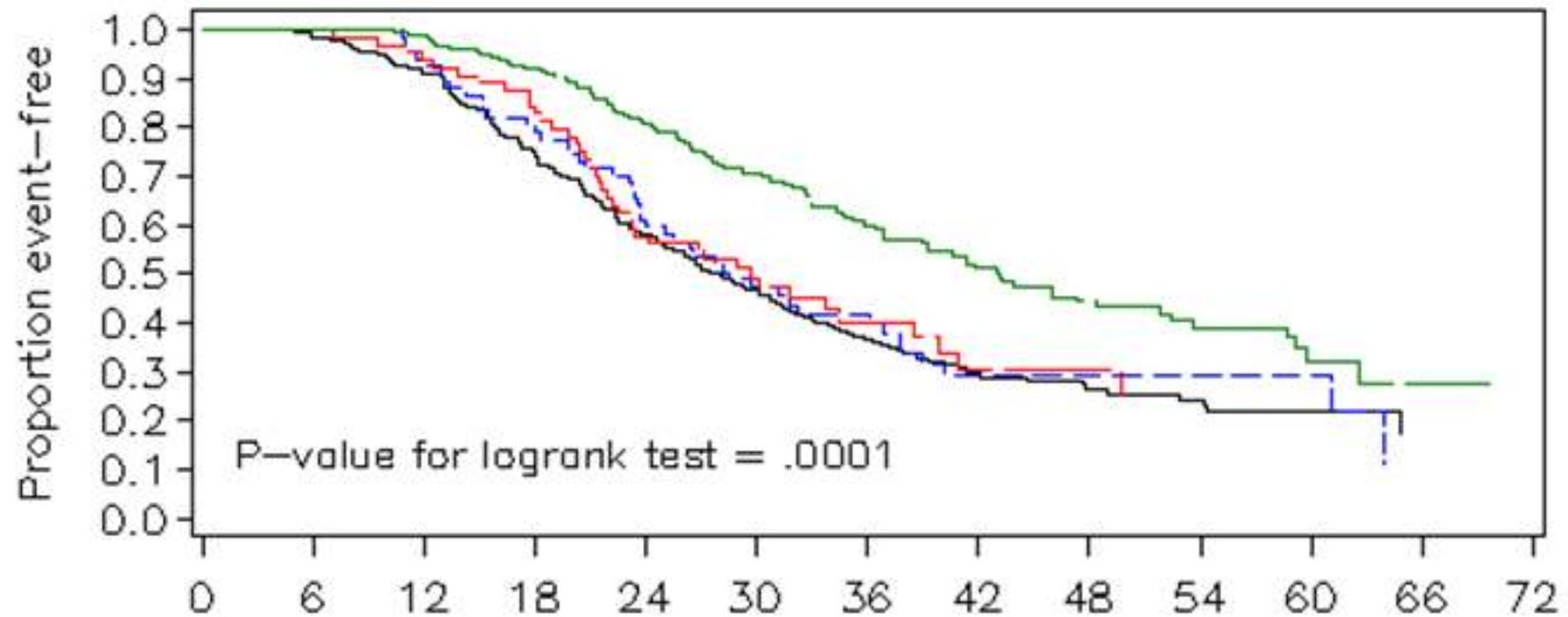
MRD predicts outcome in patients in CR.

Progression-free survival by 100-day outcome for intensive pathway patients who had achieved CR at day 100



Outcome according to MRD status and conventional response.

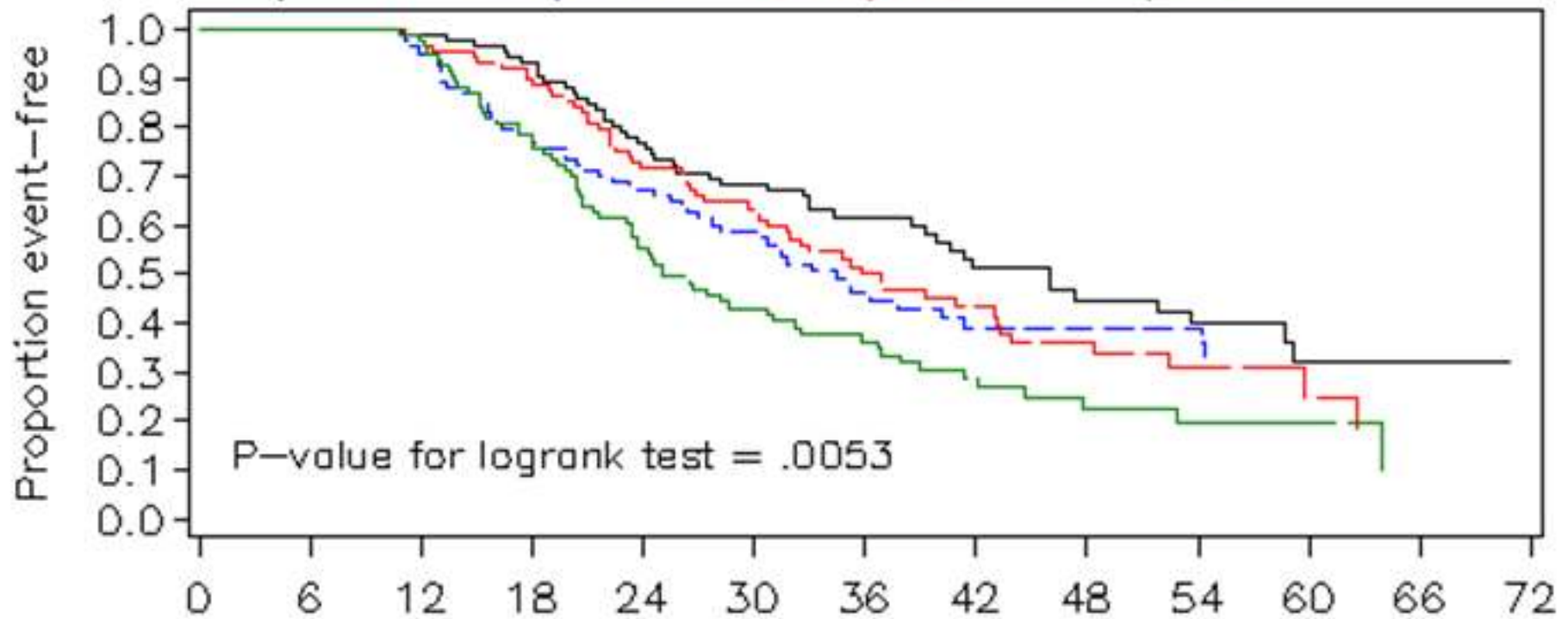
Progression-free survival by 100-day outcome for intensive pathway patients
-1:MRD+ not CR -2:MRD+CR -3:MRD- not CR -4:MRD-CR



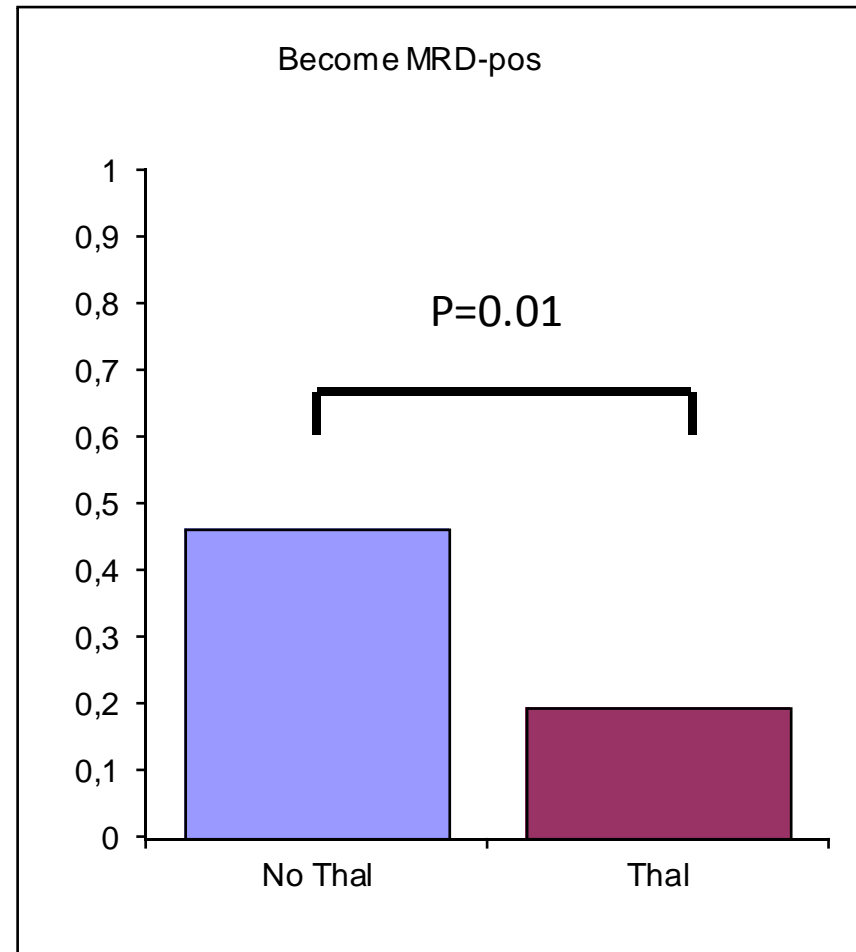
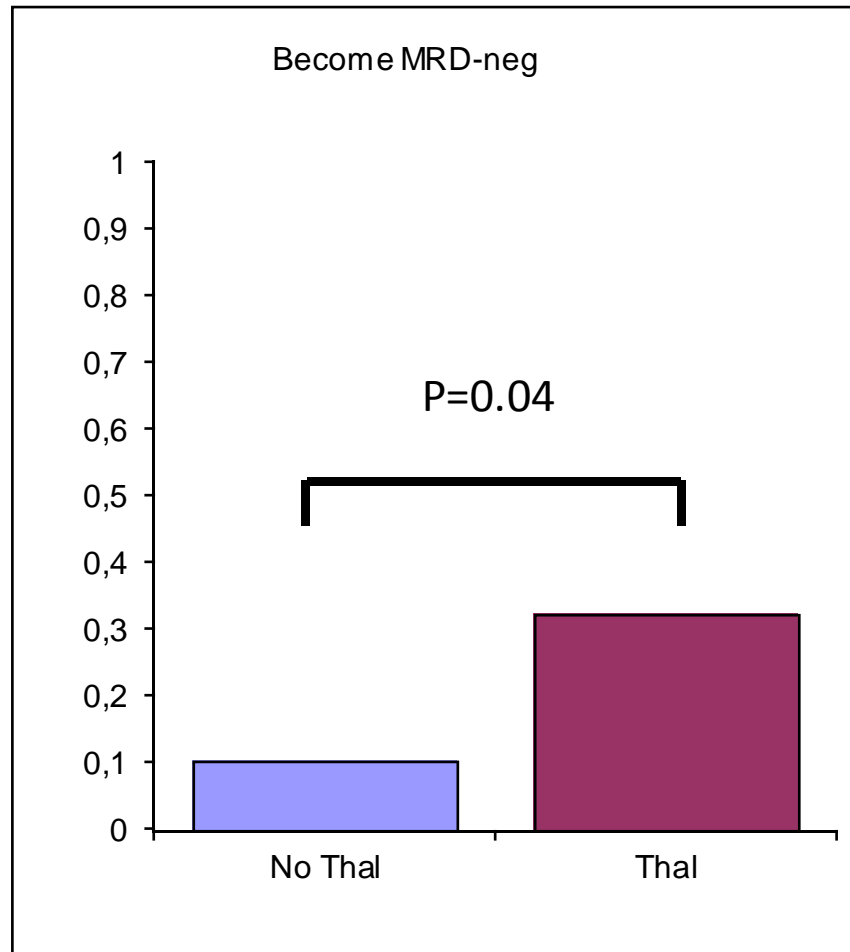
What about maintenance?

Progression-free survival by 100-day outcome assessed in all patients by MRD/maintenance. T: thalidomide; NM: no maintenance.

-1: T; MRD- -2: T; MRD+ -3: NM; MRD- -4: NM; MRD+

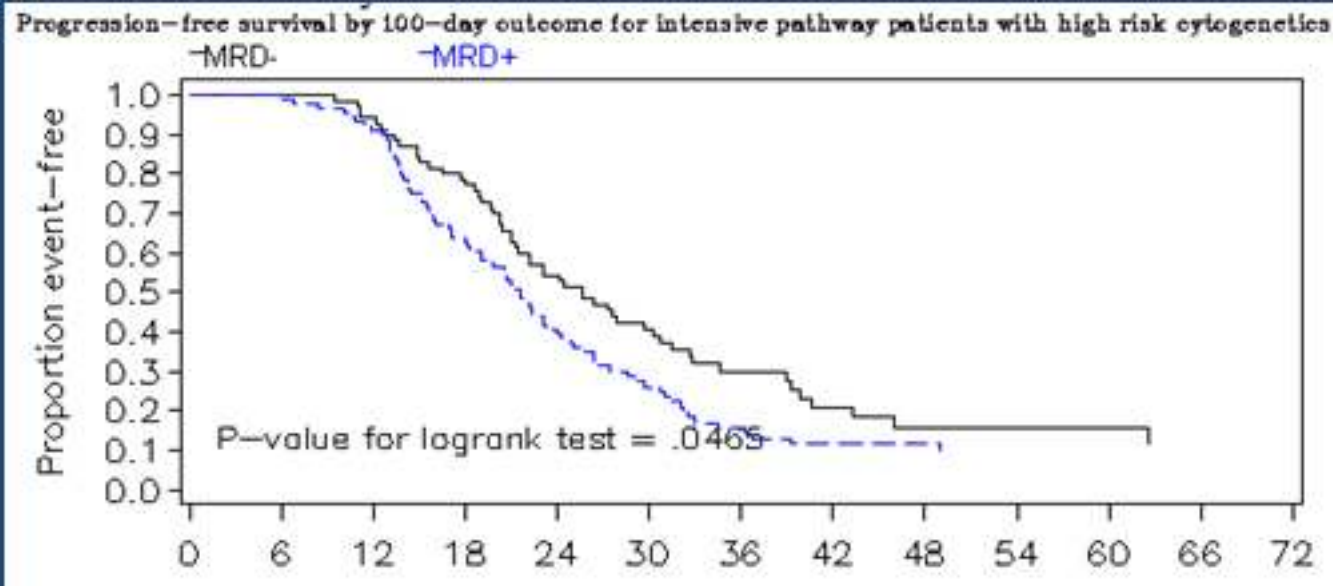
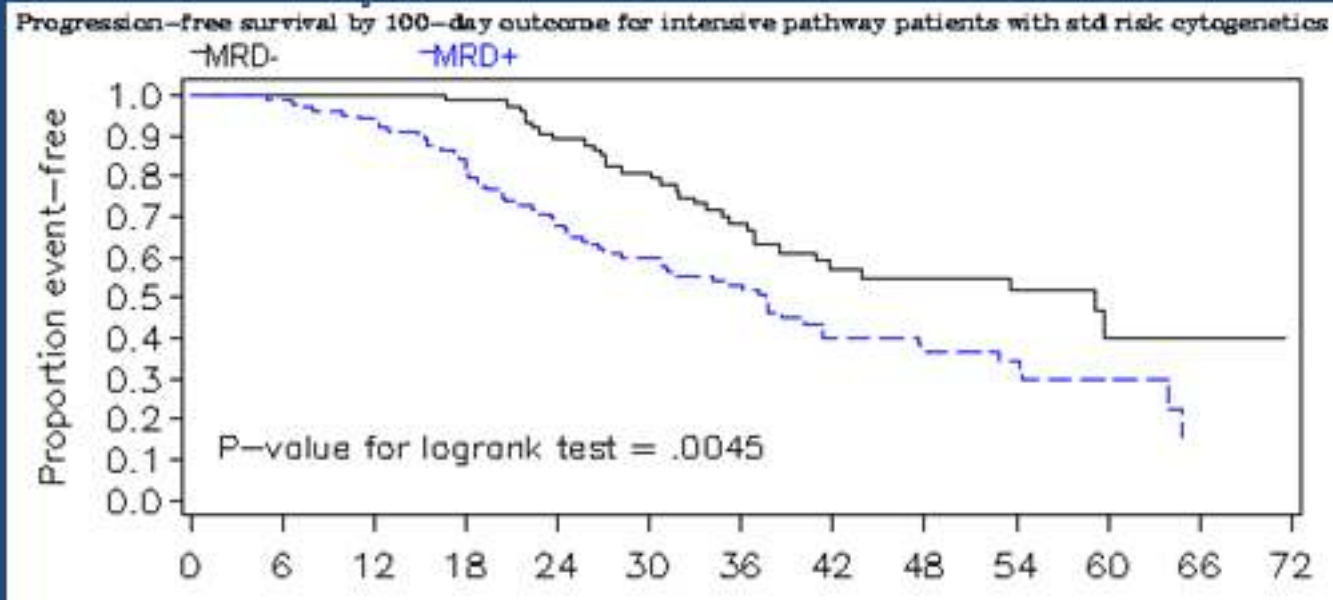


Maintenance or consolidation?



N=158

Effect of cytogenetics.



Conclusions.

- MRD assessment by flow cytometry is highly predictive of outcome
 - PFS and OS
 - intensive and non-intensive therapies
 - favourable and adverse cytogenetics
- Complimentary to conventional response assessment
- Assessment of individual components of multicomponent treatment schedules and maintenance strategies

Acknowledgements

Chief Investigators

JA Child

GJ Morgan

GH Jackson

CTRU, Leeds

K Cocks

W Gregory

A Szubert

S Bell

N Navarro Coy

F Heatley

P Best

J Carder

M Matouk

D Emsell

A Davies

D Phillips

A Gillman

L Flanagan

C Tyas and others

University of Birmingham

MT Drayson

K Walker

A Adkins

N Newnham

Wessex Regional Genetics Laboratory, Salisbury

F Ross

L Chieccio

LTHT, Leeds

G Cook

S Feyler

D Bowen

HMDS, Leeds

RG Owen

AC Rawstron

R de Tute

M Dewar

S Denman

ICR, London

FE Davies

M Jenner

B Walker

D Johnson

D Gonzalez

N Dickens

K Boyd

P Leone

L Brito

A Avridromou

MRC Leukaemia Trial Steering
Committee

MRC Leukaemia Data Monitoring and
Ethics Committee

NCRI Haematological Oncology
Clinical Studies Group

NIHR, through the National Cancer
Research Network

UK Myeloma Forum Clinical Trials
Committee

Myeloma UK

Funding

Medical Research Council

Pharmion

Novartis

Chugai Pharma

Bayer Schering Pharma

OrthoBiotech

Celgene

Kay Kendall Leukaemia Fund



Acknowledgements

Patients and staff from 121 participating institutions in the UK

Nottingham City Hospital
Leeds General Infirmary
Hull Royal Infirmary
Ninewells Hospital, Dundee
Addenbrooke's Hospital, Cambridge
St James's University Hospital, Leeds
Christie Hospital, Manchester
Blackpool Victoria Hospital
Glan Clwyd Hospital
James Paget Hospital, Great Yarmouth
The Great Western Hospital, Swindon
New Cross Hospital, Wolverhampton
Eastbourne District General Hospital
Hillingdon Hospital, Uxbridge
Kings Mill Hospital, Sutton-in-Ashfield
University Hospital Aintree, Liverpool
Western Infirmary, Glasgow
Glasgow Royal Infirmary
Stepping Hill Hospital, Stockport
Good Hope Hospital, Sutton Coldfield
Darlington Memorial Hospital
Diana Princess of Wales Hospital, Grimsby
Bradford Royal Infirmary
Manchester Royal Infirmary
Stoke Mandeville Hospital, Aylesbury
Scarborough General Hospital
Hope Hospital, Manchester
Poole Hospital
Barnsley District Hospital
Royal Alexandra Hospital, Paisley
City Hospital, Birmingham
Pilgrim Hospital, Boston
Royal Surrey County Hospital
Southport and Formby District General Hospital
Grantham and District Hospital
Doncaster Royal Infirmary
Queen Mary's Hospital, Sidcup
Royal Bolton Hospital
Arrowe Park Hospital
Mid Staffordshire General Hospital

Western General Hospital, Edinburgh
Birmingham Heartlands Hospital
Royal Liverpool University Hospital
University Hospital of Wales, Cardiff
Aberdeen Royal Infirmary
Russells Hall Hospital, Dudley
Royal Cornwall Hospital, Truro
James Cook University Hospital
Medway Maritime Hospital, Gillingham
Royal United Hospital, Bath
Gloucestershire Royal Hospital
Ysbyty Gwynedd, Bangor
Swanwell General Hospital
Lincoln County Hospital
Queen Elizabeth Hospital, Kings Lynn
St Bartholomew's Hospital, London
Southern General Hospital, Glasgow
Darent Valley Hospital
Trafford General Hospital, Manchester
St Richard's Hospital, Chichester
Pembury Hospital
Warwick Hospital
Southend General Hospital
Whiston Hospital, Prescot
Queen Elizabeth Hospital, Gateshead
Countess of Chester Hospital
Victoria Infirmary, Glasgow
Princess Royal University Hospital
North Devon District Hospital
Borders General Hospital
King George Hospital, Ilford
Dorset County Hospital
University Hospital of North Tees
North Tyneside General Hospital
Harrogate District Hospital
Royal Marsden Hospital, Sutton
Prince Charles Hospital, Merthyr Tydfil
Central Middlesex Hospital
Ipswich Hospital
Mayday Hospital

Royal Devon and Exeter Hospital
Royal Hallamshire Hospital, Sheffield
Mid Yorkshire NHS Trust
Torbay Hospital, Torquay
Worcester Royal Infirmary
Derbyshire Royal Infirmary
Southampton General Hospital
Colchester General Hospital
Norfolk and Norwich University Hospital
St Helier Hospital, Carshalton
Singleton Hospital, Swansea
Monklands General Hospital, Airdrie
Wycombe General Hospital
Chesterfield & N Derbyshire Royal
Kent and Canterbury Hospital
Cheltenham General Hospital
Hereford County Hospital
Salisbury District Hospital
Bristol Haematology & Oncology Centre
Oldchurch Hospital, Romford
Taunton and Somerset Hospital
Walsgrave Hospital
The Royal Bournemouth Hospital
Derriford Hospital
Worthing Hospital
Royal Victoria Infirmary, Newcastle
Rotherham General Hospital
Milton Keynes General Hospital
Kingston Hospital
Queen Elizabeth Hospital, Birmingham
Conquest Hospital, St Leonard's on Sea
Southmead Hospital, Bristol
George Eliot Hospital
Epsom General Hospital
Basildon Hospital
Nevill Hall Hospital, Abergavenny
Prince Philip Hospital
Northwick Park Hospital, Harrow
South Tyneside District Hospital
Forth Valley