

Highlights from IMS 20th meeting 2023

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**Terapia di mantenimento:
durata ottimale**

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BOLOGNA, Royal Hotel Carlton

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Honoraria
Sanofi							x
Amgen							x
GlaxoSmithKline							x

Lenalidomide Maintenance

- Maintenance with lenalidomide is considered the standard of care for all MM patients post-ASCT (EMA-approved until progression)

Trial	N pts	Dosing schedule	Control arm	Intended duration	Reported duration	TTP/PFS	OS
CALGB 100104 ¹⁻²	460	10 mg 28/28; up to 15 mg	Placebo	Until progression	31 mos (median)	57 vs 29 mos HR 0.57, p<0.0001	114 vs 84 mos p = 0.004
IFM 2005-02 ³	614	10 mg 28/28; up to 15 mg (2 cycles of cons. 25 mg 21/28)	Placebo	Until progression interrupted for SPM at 2ys (range 1-3 ys)	25 mos (mean)	41 vs 23 mos HR 0.5 , p<0.001	73 vs 75% at 4-ys (p=0.7)
RV-MM-209 ⁴	402	10 mg 21/28	Observ.	Until progression	35 mos (mean)	42 vs 22 mos HR 0.47, p<0.001	88 vs 79% at 3-ys (p=0.14)
Meta-analysis ⁵	1208	/	/	/	28 mos (mean)	53 vs 24 mos HR 0.48	62 vs 50% at 7-ys (p=0.001)
Myeloma XI ⁶⁻⁷	1248 (TE)	10 mg 21/28	Observ.	Until progression	28 cycles (median)	64 vs 32 mos HR 0.52, p<0.0001	88 vs 80% at 3-ys HR 0.69; p=0.014

- Broad consensus about survival benefit of len-maintenance outweighing side effects^{5,8}

1. McCarthy, et al. NEJM 2012;366:1770-81
 2. Holstein, et al. Lancet Haematol 2017;4:e431-442
 3. Attal, et al. NEJM 2012;366:1782-91
 4. Palumbo et al. NEJM 2014;371:895-905

5. McCarthy, et al. JCO 2017;35:3279-89
 6. Jackson, et al. Lancet Oncol 2019;20:57-73
 7. Pawlyn et al. Blood 2022;140(S1):1371-1372
 8. Palumbo, et al. Lancet Oncol 2014;3:333-42

Retrospective analysis / real world data

Prolonged survival with a longer duration of maintenance lenalidomide after autologous hematopoietic stem cell transplantation for multiple myeloma

Idrees Mian MD, Denai R. Milton MS, Nina Shah MD, Yago Nieto MD, PhD, Uday R. Popat MD, Partow Kebriaei MD, Simrit Parmar MD, Betul Oran MD, Jatin J. Shah MD, Elisabet E. Manasanch MD, Robert Z. Orlowski MD, PhD, Elizabeth J. Shpall MD, Richard E. Champlin MD, Muzaffar H. Qazilbash MD, Qaiser Bashir MD ✉

Cancer. 2016 December 15; 122(24): 3831–3837. doi:10.1002/cncr.30366

LEUKEMIA & LYMPHOMA

<https://doi.org/10.1080/10428194.2018.1473577>

LETTER TO THE EDITOR

Prolonged survival with increasing duration of lenalidomide maintenance after autologous transplant for multiple myeloma

Isabel G. Amsler^a, Barbara Jeker^a, Behrouz Mansouri Taleghani^b, Ulrike Bacher^b, Daniel Betticher^c, Thomas Egger^d, Thilo Zander^e, Jean-Marc Luethi^f, Urban Novak^a and Thomas Pabst^a

The Effect of Duration of Lenalidomide Maintenance and Outcomes of Different Salvage Regimens in Patients with Multiple Myeloma (MM)

Matthew Ho^{b,1,3}, Saurabh Zanwar^{b,1,2,3}, Prashant Kapoor^{b,2}, Morie Gertz^{b,2}, Martha Lacy², Angela Dispenzieri^{b,2}, Suzanne Hayman², David Dingli^{b,2}, Francis Baudi², Eli Muchtar², Nelson Leung^{b,2}, Taxiarchis Kourelis^{b,2}, Rahma Warsame², Amie Fonder², Lisa Hwa², Miriam Hobbs², Robert Kyle², S. Vincent Rajkumar^{b,2} and Shaji Kumar^{b,2,3}

Blood Cancer Journal (2021)11:158; doi:10.1038/s41408-021-00548-7

Early versus Late Discontinuation of Maintenance Therapy in Multiple Myeloma

Jordan Nunnelee^{1,2}, Francesca Cottini³, QiuHong Zhao³, Muhammad Salman Faisal^{3,4}, Patrick Elder³, Ashley Rosko³, Naresh Bumma³, Abdullah Khan³, Elvira Umyarova³, Srinivas Devarakonda³, Don M. Benson³, Yvonne A. Efebera^{3,5} and Nidhi Sharma^{3,*}

J. Clin. Med. 2022, 11, 5794. <https://doi.org/10.3390/jcm11195794>

- Small size, monocentric cohorts of patients, pre antiCD38+ drugs era
- Lenalidomide dose ranging from 5 to 15 mg/day, median duration of maintenance ranging from 1 to 3 years
- Different timepoints chosen for comparison analysis
- Significant improvement in PFS and OS for patients on longer maintenance treatment

Predictors of lenalidomide maintenance duration after autologous stem cell transplant in patients with multiple myeloma

- Retrospective, multi-center cohort study including MM pts treated with auto-SCT + len-maintenance (jan12-feb21)
- Median duration of maintenance lenalidomide therapy 1.3 years (range 0.3-8.6)
- 21% of pts stopped therapy due to disease progression, 19% intolerable toxicities, 11% alternative reasons.
- Most common “intolerable” toxicities were cytopenias (35%), fatigue (14%), rash (14%), and diarrhea (10%)

Multivariate linear regression analysis of predictors of lenalidomide maintenance duration

Duration of Maintenance (Total Population, N = 299)		Duration of Maintenance (Patients without Disease Progression, N = 232)	
Variable	P-value §	Variable	P-value §
ECOG	0.0008	ECOG	0.0289
Age at transplant	0.7858	Age at transplant	0.8847
Lenalidomide dose	0.2178	Lenalidomide dose	0.0567
Creatinine clearance	0.8450	Creatinine clearance	0.7103
Combination maintenance therapy	0.1293	Combination maintenance therapy	0.1270
Cytogenetic risk	0.2347	Cytogenetic risk	0.5531
BMI	0.2022	BMI	0.2111

EVIDENCES FROM AVAILABLE TRIALS

IFM2009

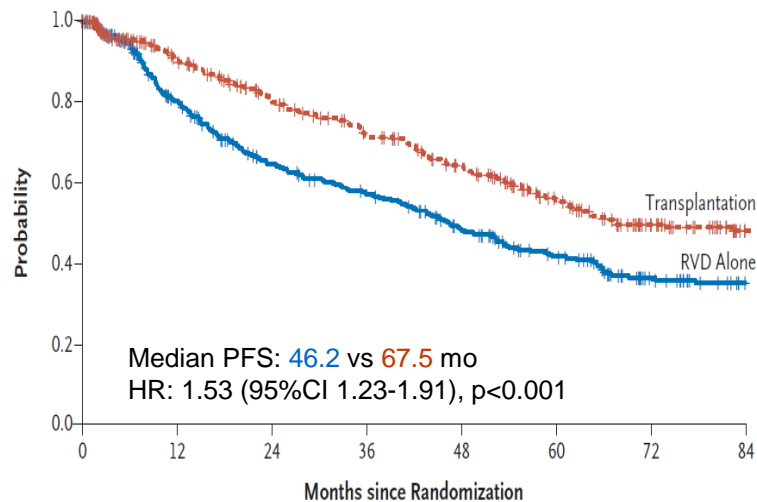
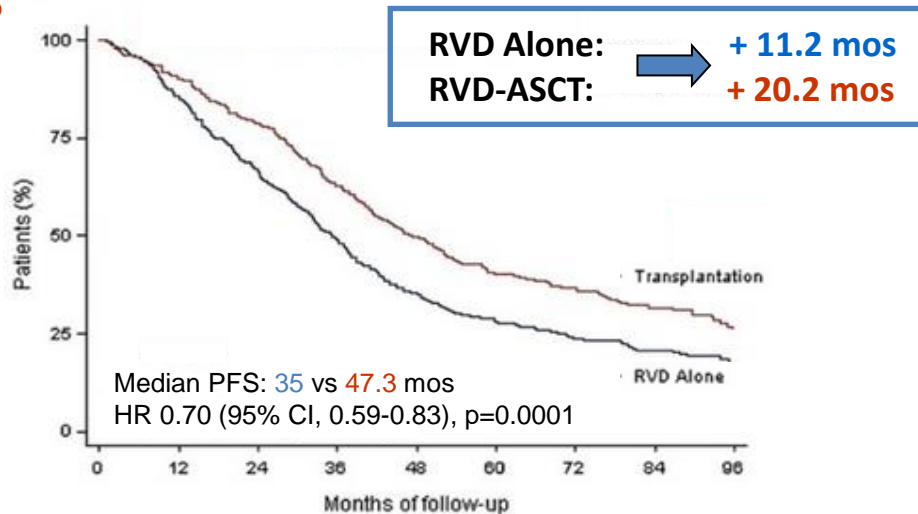
1year len-maintenance



DETERMINATION

len-maintenance until PD

PFS



OS

4-year: 82 vs 81%, ns

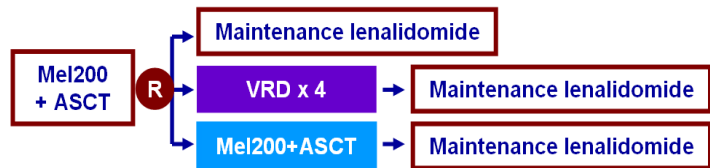
8-year: 60 vs 62%, ns

77% relapsed pts in RVD-alone received salvage ASCT

5-year: 81 vs 79%, ns

28% relapsed pts in RVD-alone received salvage ASCT

BMT CTN 0702 ph.2 trial (STaMINA)



2014 amendment



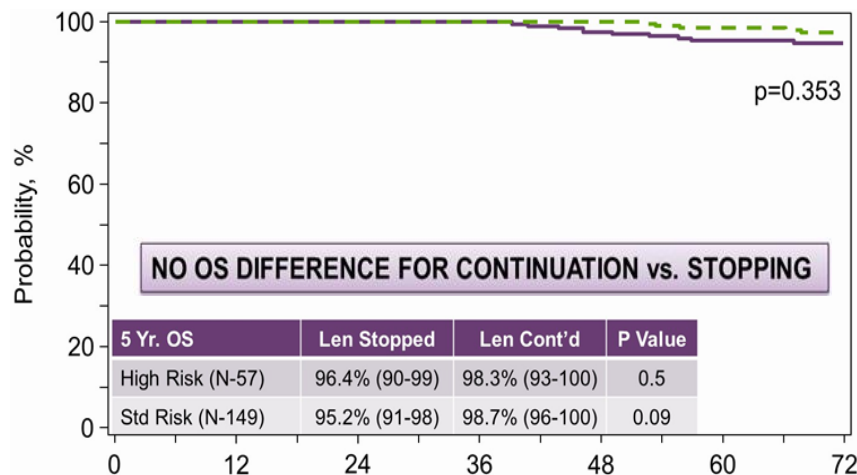
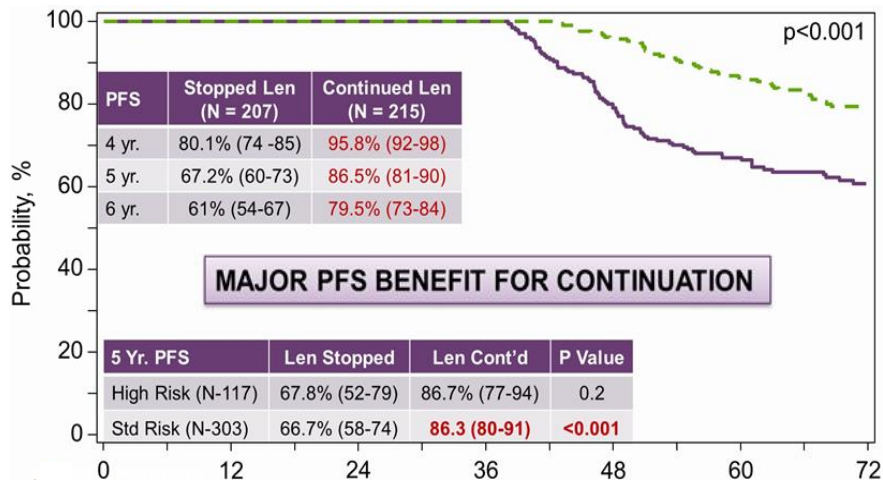
Pts progression-free at 38mo on len-maintenance

BMT CTN 07LT trial

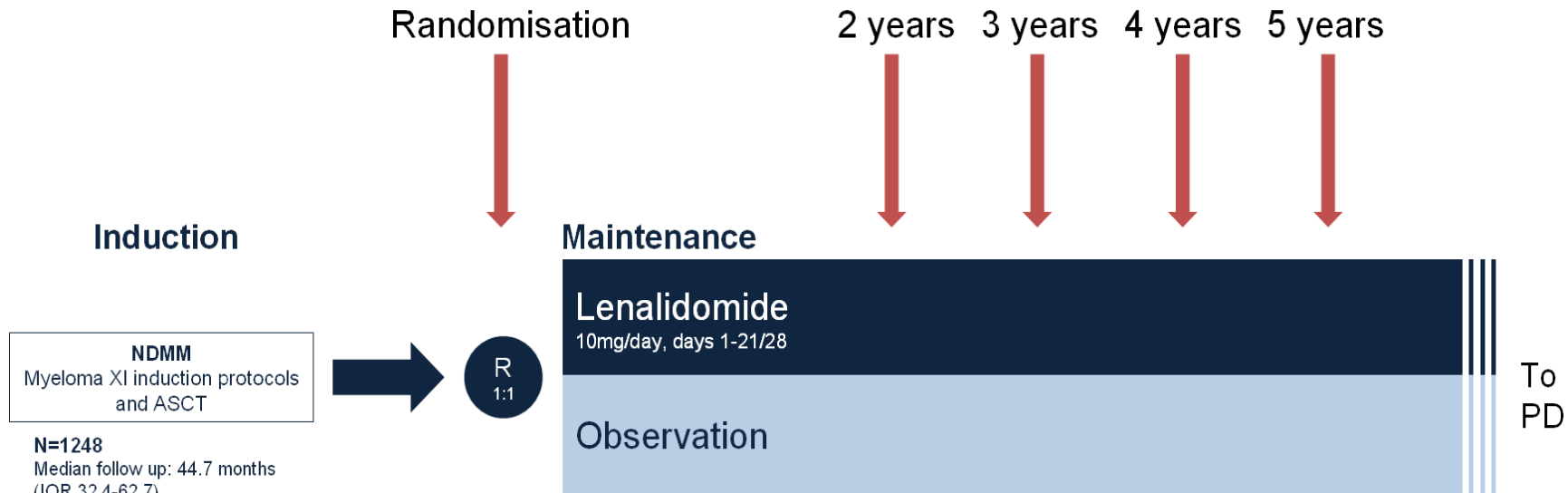
Len-maintenance until PD
(N=215)

STOP maintenance
(N=207)

Landmark analysis: Len continued beyond 38 mo vs Not



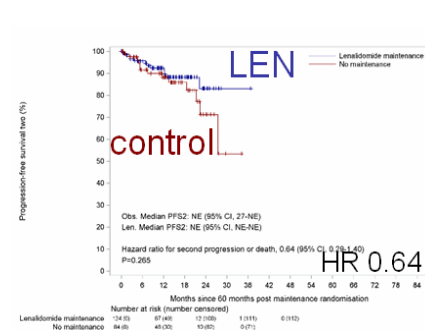
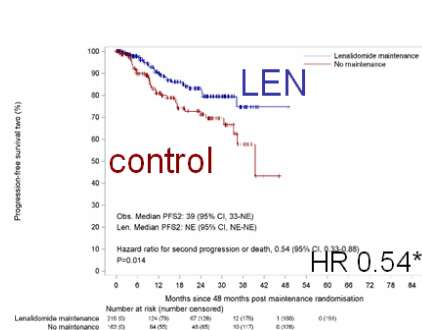
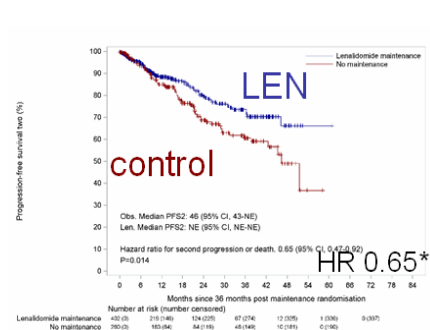
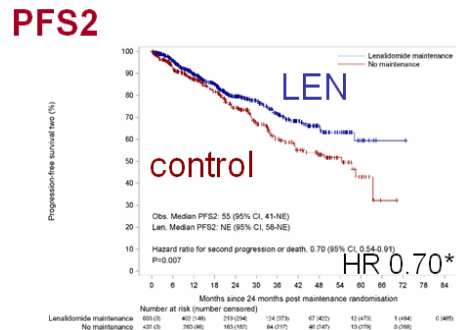
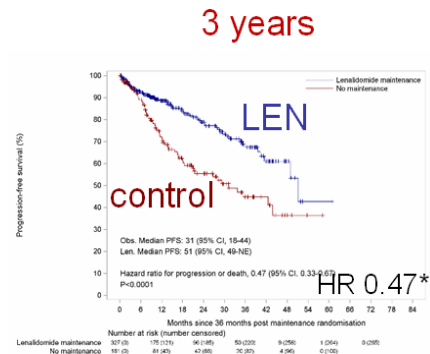
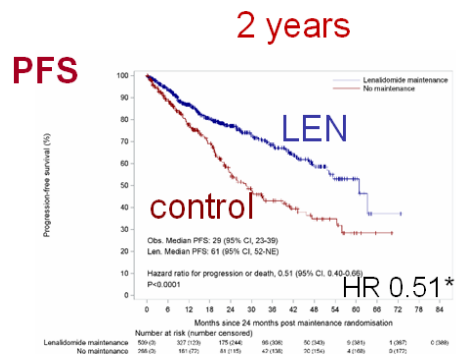
Multiple landmark analyses



Median duration of lenalidomide therapy 28 cycles (range 1-96)

•Patients still on therapy 330/730 (45%)

Outcomes in the overall population



Ongoing PFS benefit associated with continuing lenalidomide maintenance beyond at least 4-5 years in the overall patient population

*p<0.05

Outcomes by cytogenetic risk

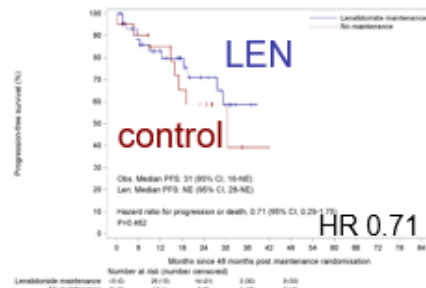
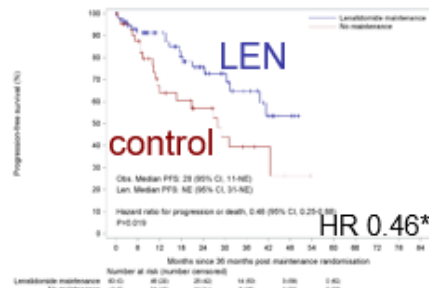
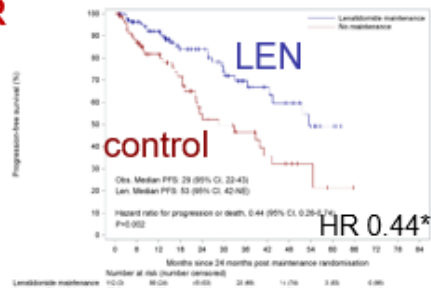
SR

2 years

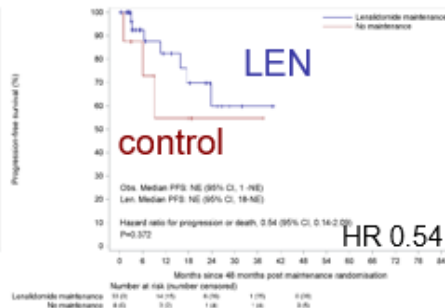
3 years

4 years

5 years



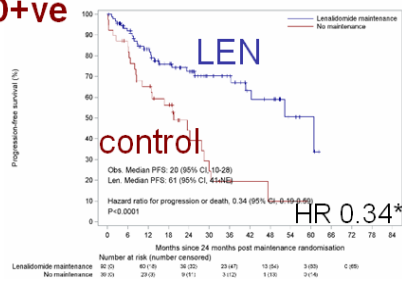
HR/UHR



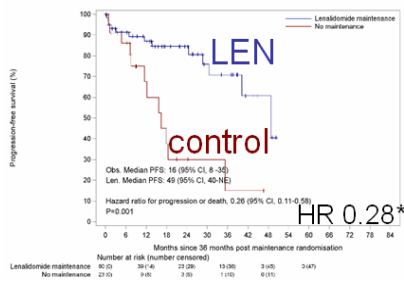
Outcomes by MRD status

2 years

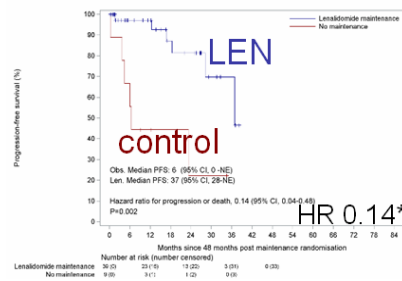
MRD+ve



3 years



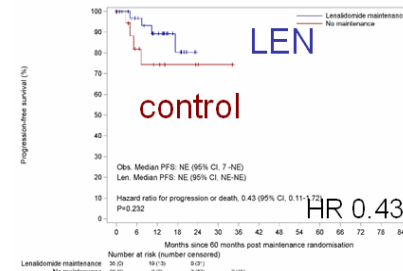
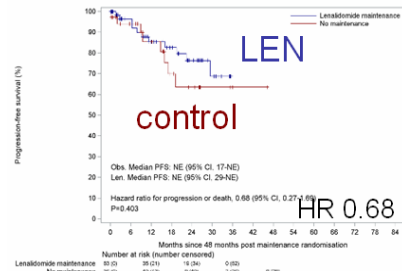
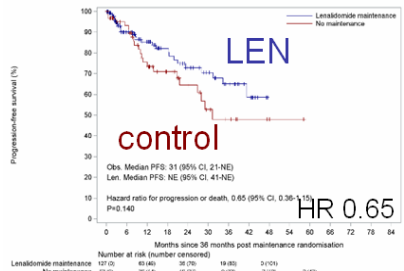
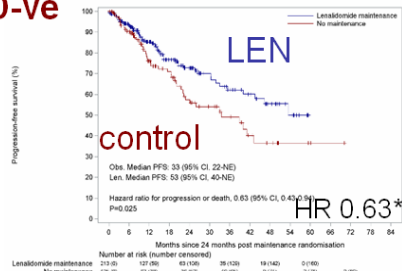
4 years



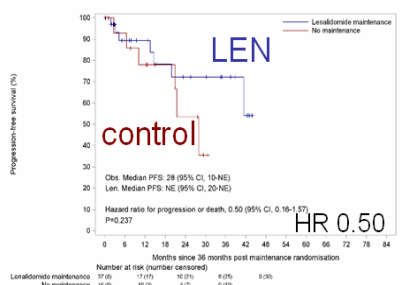
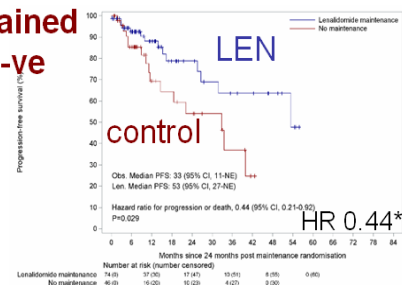
5 years

No data at 5-ys for pts MRD+ve: too few pts reaching this time point in control arm

MRD-ve



Sustained MRD-ve

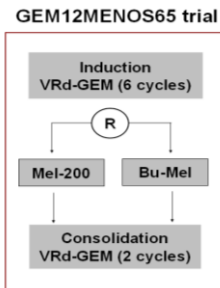


- Suggestion to continue lenalidomide until disease progression in MRD+ve patients
- Benefit from continuing lenalidomide maintenance for at least 3 years in total even in patients with sustained MRD negativity

*sustained MRD-ve for 6 mos from start of therapy

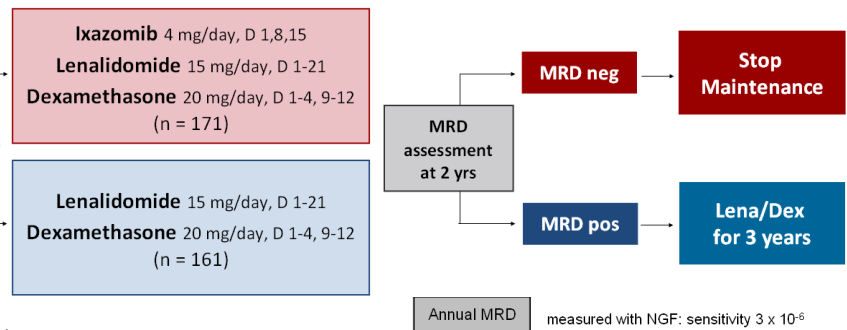
GEM2014MAIN trial

Primary endpoint PFS:
 6-year rate: 61% / 56% for RD / IRD
 HR 1.14; 95%CI 0.81-1.60; p 0.46
 median FUP 69 mos

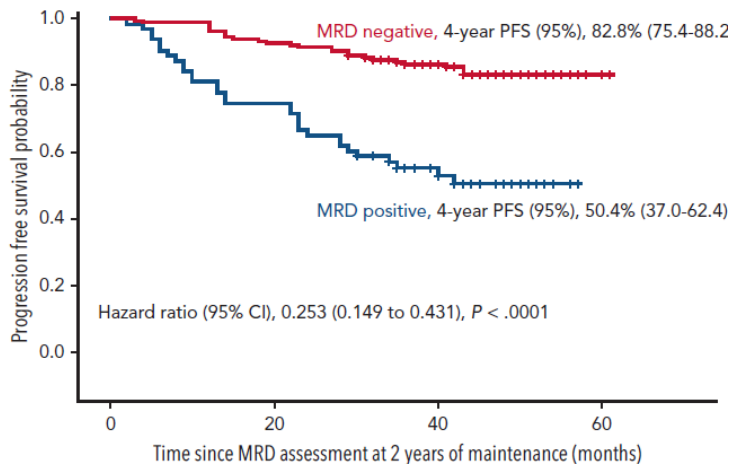


≥ SD

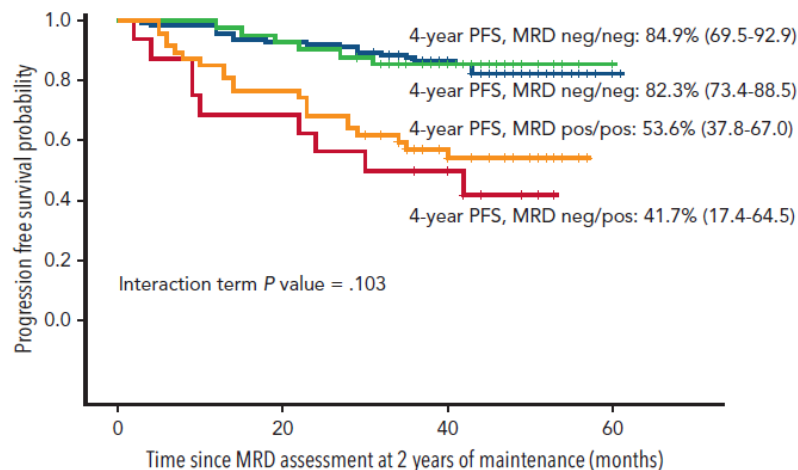
(R)

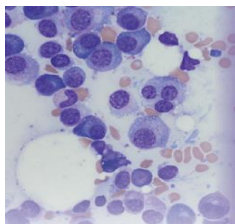


PFS based on MRD status after 2 years of maintenance in the overall series



PFS according to the kinetics of MRD from randomization to 2-ys of maintenance





IMS 20th Annual Meeting and Exposition

ATHENS, GREECE | SEPTEMBER 27-30, 2023



Wednesday, September 27



HELLENIC REPUBLIC
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EST. 1837



20th IMS Annual Meeting

September 27 - 30, 2023 - Athens, Greece



Persistent bone marrow and imaging MRD negativity may guide the duration of lenalidomide maintenance following ASCT in patients with multiple myeloma

Panagiotis Malandrakis¹, Ioannis Ntanasis-Stathopoulos¹, Ioannis V Kostopoulos², Maria Gavriatopoulou¹, Foteini Theodorakakou¹, Despina Fotiou¹, Magdalini Migkou¹, Maria Roussou¹, Vassiliki Spiliopoulou¹, Nikoletta-Aikaterini Kokkali¹, Rodanthi-Eleni Syrigou¹, Evangelos Eleutherakis-Papaiakovou¹, Efsthios Kastritis¹, Ourania E Tsitsilonis², Meletios A. Dimopoulos¹, Evangelos Terpos¹

¹Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece;

²Section of Animal and Human Physiology, Department of Biology, School of Sciences, National and Kapodistrian University of Athens, Athens, Greece

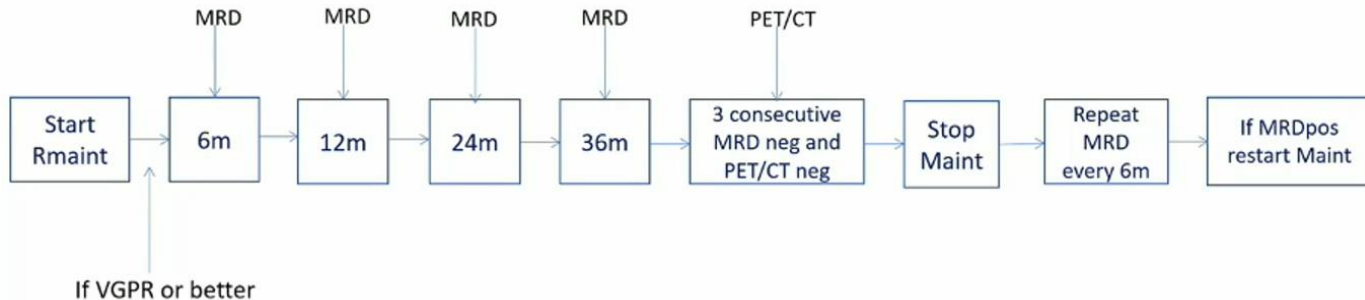
Study design

151 NDMM pts who underwent ASCT and len-maintenance from 1jan16 to 31dec19

140 started maintenance
107 pts without survival events after a median fup of 70mo from ASCT

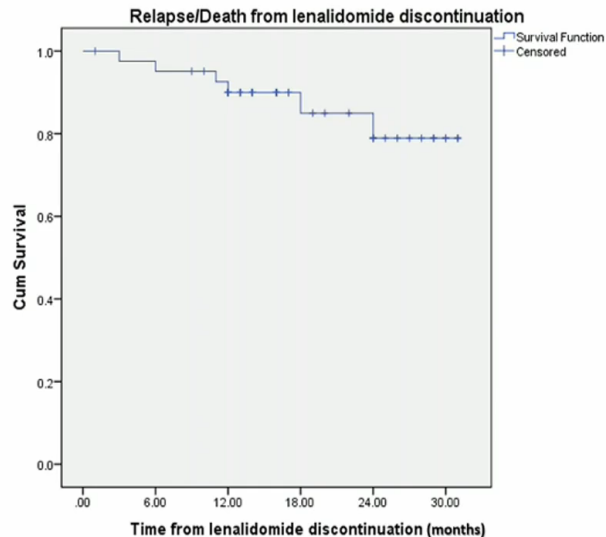
42 pts with sustained BM MRD negativity (NGF) + imaging after 3years of len-maintenance

STOP maintenance



MRD neg after 6 months: 39/41
MRD neg after 12 months: 36/38
MRD neg after 18 months: 18/18
MRD neg after 24 months: 13/14
MRD neg after 30 months: 4/4

5 pts converted to MRD pos, and restarted lenalidomide, (RISS1:3 pts, RISS2: 2 pts)
1 pt progressed (RISS2, high-risk cytogenetics) and 1 died (not MM related/second primary malignancy)



At risk	42	41	38	18	14	4
MRD negative	42	39	36	18	13	4

Median fup from len-start: 53 mos
Median fup from len-stop: 16 mos

SAFETY ISSUES QUALITY OF LIFE

Safety profile of len-maintenance

Discontinuations as a Result of TEAEs

TEAE	Pooled	
	Len Maintenance (n = 530)†	Placebo (n = 523)†
≥ 1 TEAE leading to discontinuation	154 (29.1)	64 (12.2)
TEAEs leading to discontinuation (≥ 1% of all patients)‡		
Blood and lymphatic system disorder	23 (4.3)	11 (2.1)
Neutropenia	12 (2.3)	1 (0.2)
Thrombocytopenia	9 (1.7)	6 (1.1)
General disorders and administration site conditions	25 (4.7)	8 (1.5)
Adverse event not specified	10 (1.9)	4 (0.8)
Neoplasms: benign, malignant, and unspecified§	23 (4.3)	5 (1.0)
Skin and subcutaneous tissue disorders	18 (3.4)	10 (1.9)
Nervous system disorders	18 (3.4)	9 (1.7)
GI disorders	18 (3.4)	1 (0.2)
Diarrhea	11 (2.1)	0
Infections and infestations	9 (1.7)	4 (0.8)
Musculoskeletal and connective tissue disorders	6 (1.1)	7 (1.3)

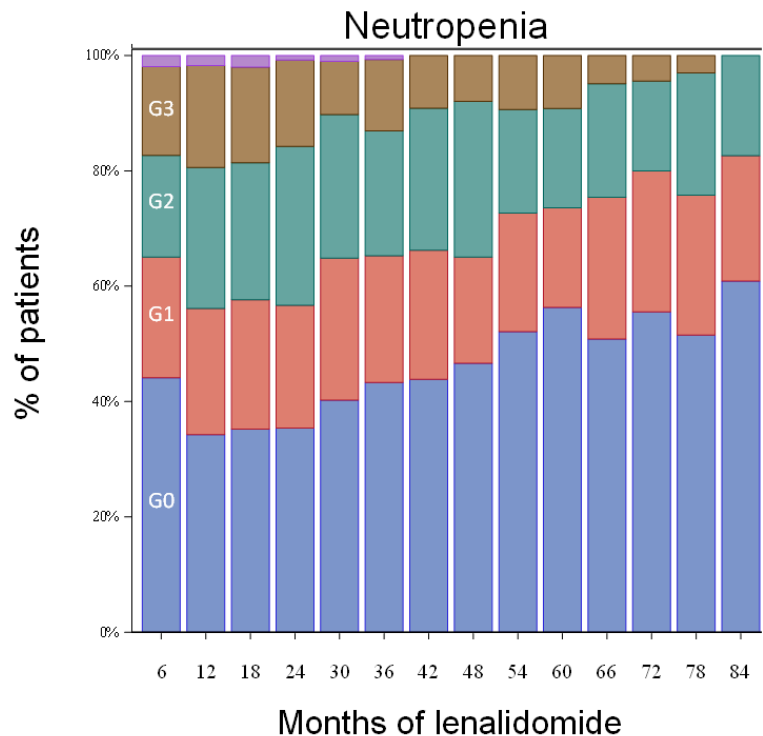
Data from the IFM and CALGB studies only

AEs in len-maintenance (Myeloma XI)

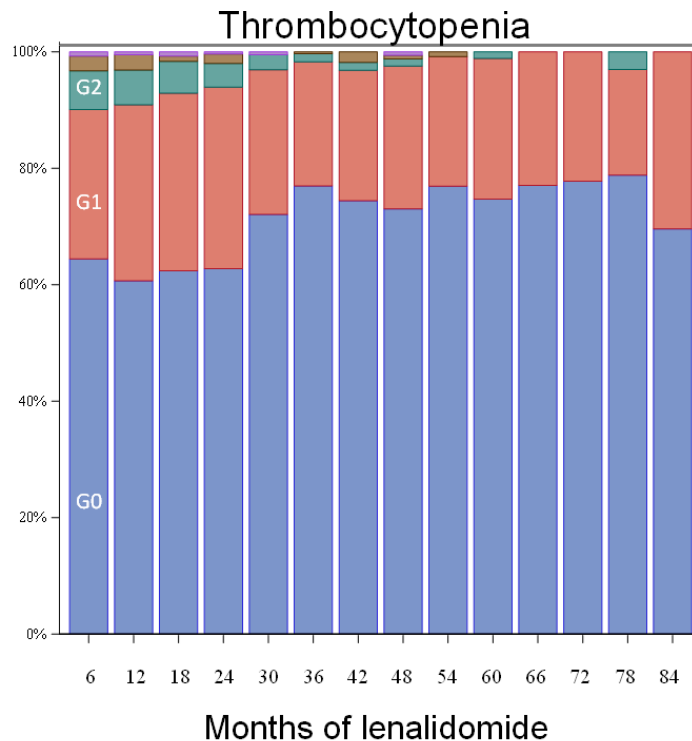
	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Haematological				
Neutropenia	419 (38%)	308 (28%)	54 (5%)	0
Anaemia	657 (60%)	40 (4%)	2 (<1%)	0
Thrombocytopenia	489 (45%)	49 (4%)	23 (2%)	0
Infections				
Lower or upper respiratory infection	261 (24%)	89 (8%)	4 (<1%)	4 (<1%)
Sepsis	1 (<1%)	12 (1%)	6 (1%)	2 (<1%)
Other infections and infestations	104 (9%)	23 (2%)	0	0
Neurological				
Peripheral sensory neuropathy	319 (29%)	9 (1%)	0	0
Gastroenterological				
Constipation	312 (28%)	1 (<1%)	0	0
Nausea	140 (13%)	2 (<1%)	0	0
Other				
Fatigue or lethargy	363 (33%)	15 (1%)	0	0
Back pain	171 (16%)	5 (<1%)	0	0
Rash	155 (14%)	8 (1%)	1 (<1%)	0
Cough	137 (13%)	3 (<1%)	0	0
Myalgia	128 (12%)	0	2 (<1%)	0
Arthralgia	115 (10%)	5 (<1%)	0	0
Cardiac disorder	0	0	0	1 (<1%)

The table includes gr. 1-2 AEs occurring in at least 10% of pts and gr. 3-4 events in at least 1% of pts

Patients continuing lenalidomide maintenance long term did not experience worsening bone marrow suppression

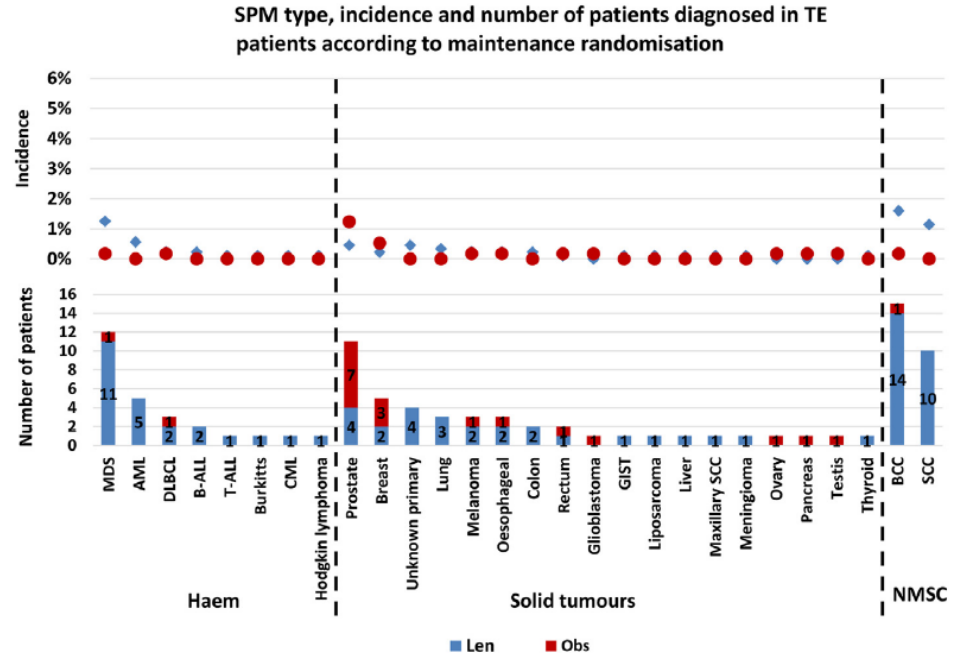
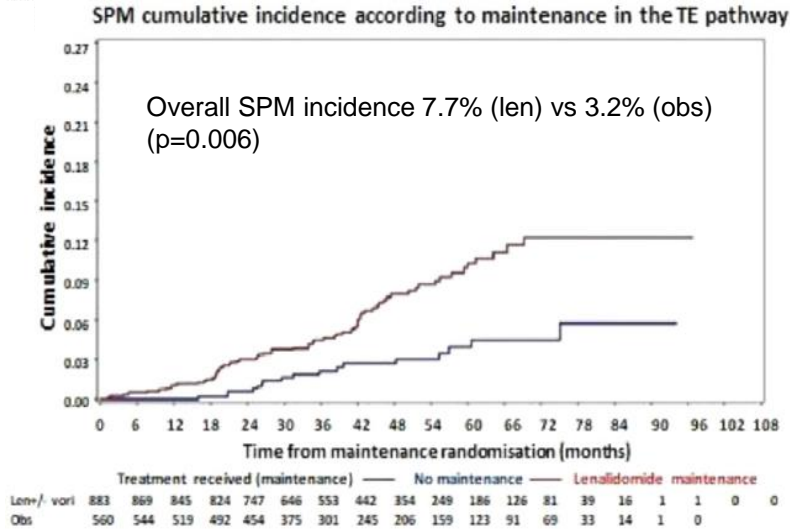


Number at risk: 675 572 548 494 390 291 219 163 117 87 61 45 33 23



675 572 548 494 390 291 219 163 117 87 61 45 33 23

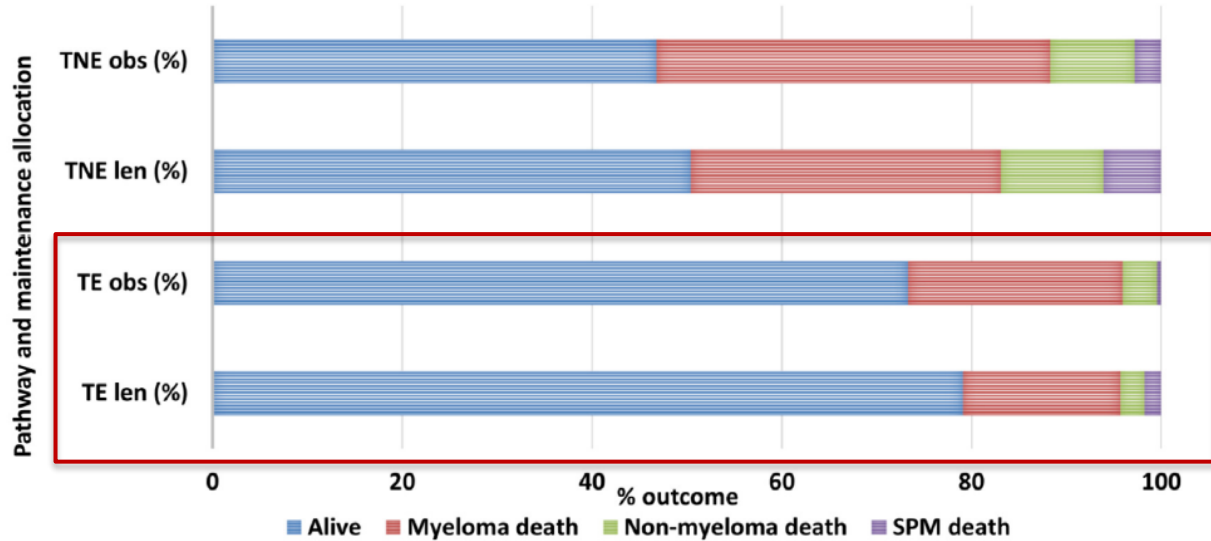
Maintenance lenalidomide in newly diagnosed transplant eligible and non-eligible myeloma patients; profiling second primary malignancies in 4358 patients treated in the Myeloma XI Trial



SPM incidence in pts being observed was 2.1%, 4.1% and 5.8% at 3, 5 and 7 years. In pts randomised to lenalidomide ± vorinostat the incidence was 4.5%, 10.5% and 12.2% (Pepe–Mori p=0.006)

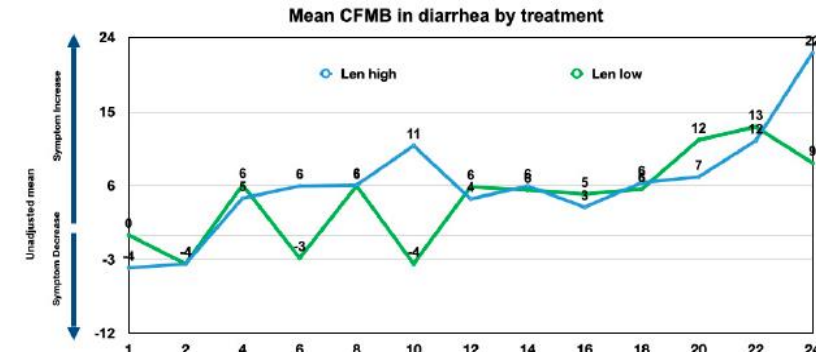
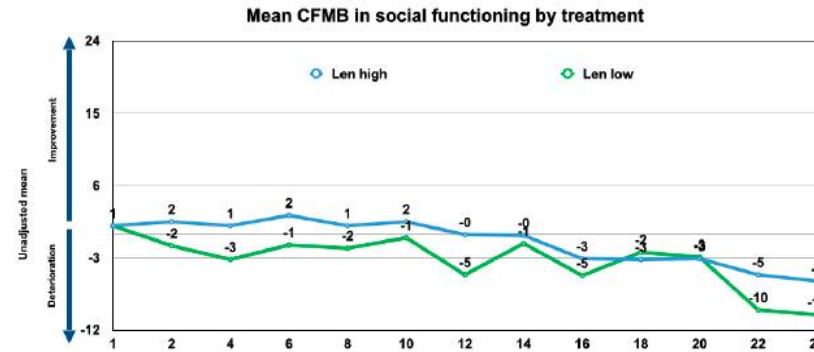
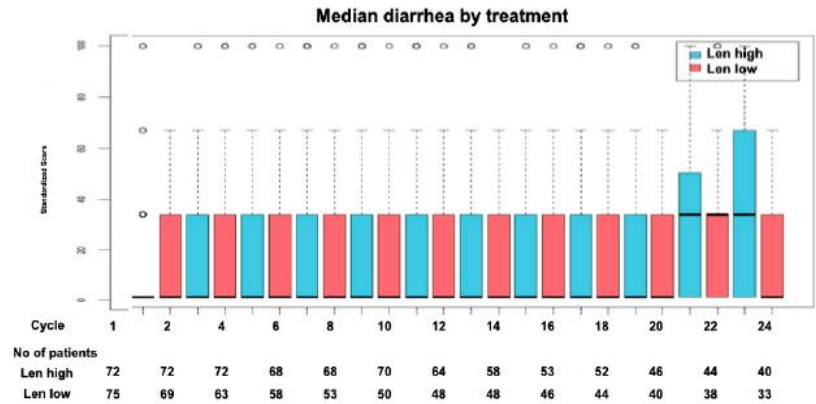
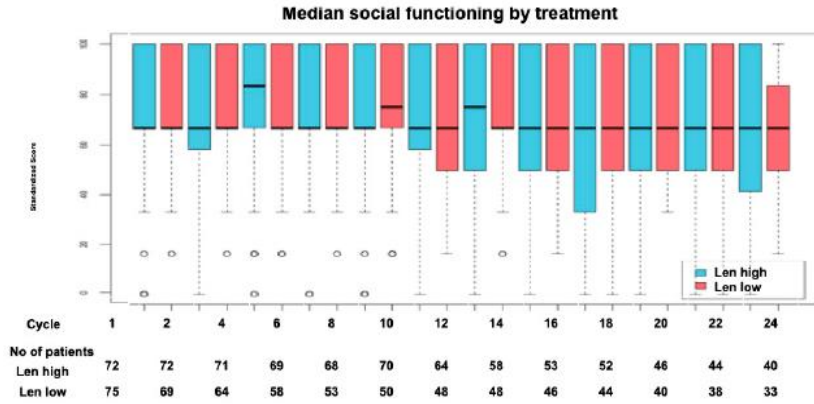
Haematological SPM: incidence 1.4% (36 pts)
Solid SPM: incidence 3% (76 pts)

Outcome of patients treated in the TE and TNE pathway according to maintenance randomisation



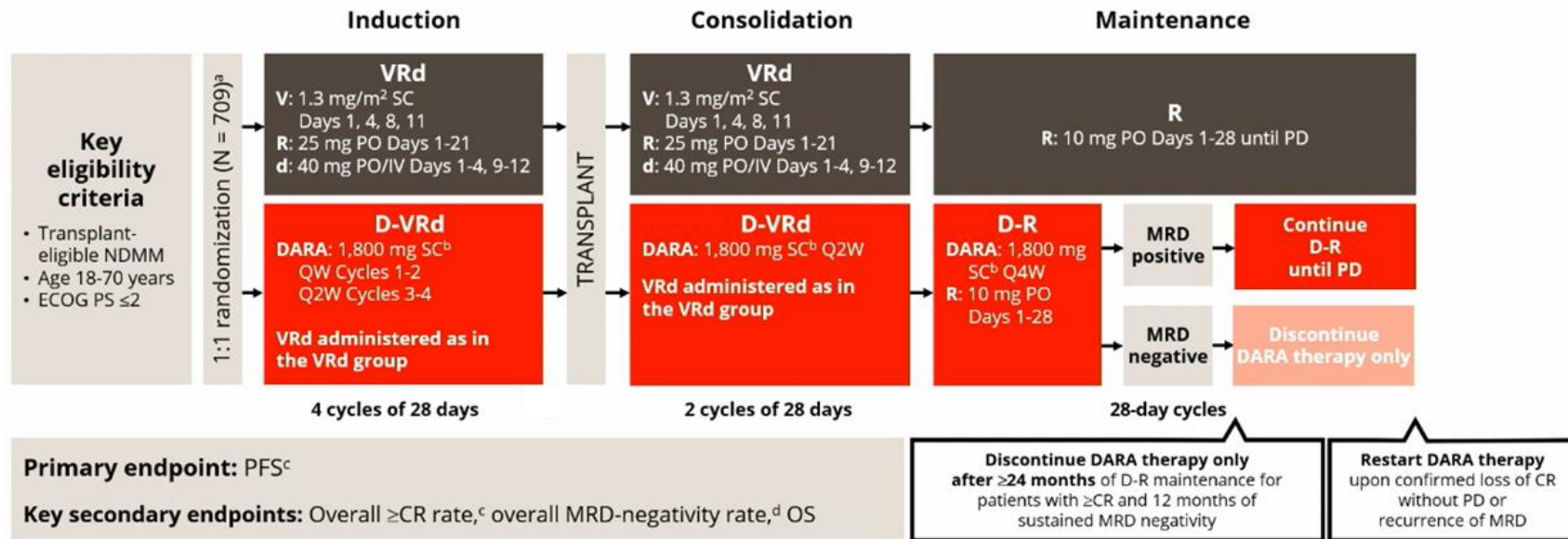
Outcome	Pathway and maintenance randomization			
	Transplant eligible (%)		Transplant non-eligible (%)	
	Lenalidomide	Observation	Lenalidomide	Observation
- Alive	79.1	73.3	50.4	46.8
- Progressive myeloma	16.6	22.6	32.7	41.5
- Non-myeloma	2.5	3.7	10.8	8.9
- SPM	1.8	0.4	6.1	2.8

Health-Related Quality of Life in Multiple Myeloma Patients Treated with High- or Low-Dose Lenalidomide Maintenance Therapy after Autologous Stem Cell Transplantation—Results from the **LenaMain Trial** (NCT00891384)



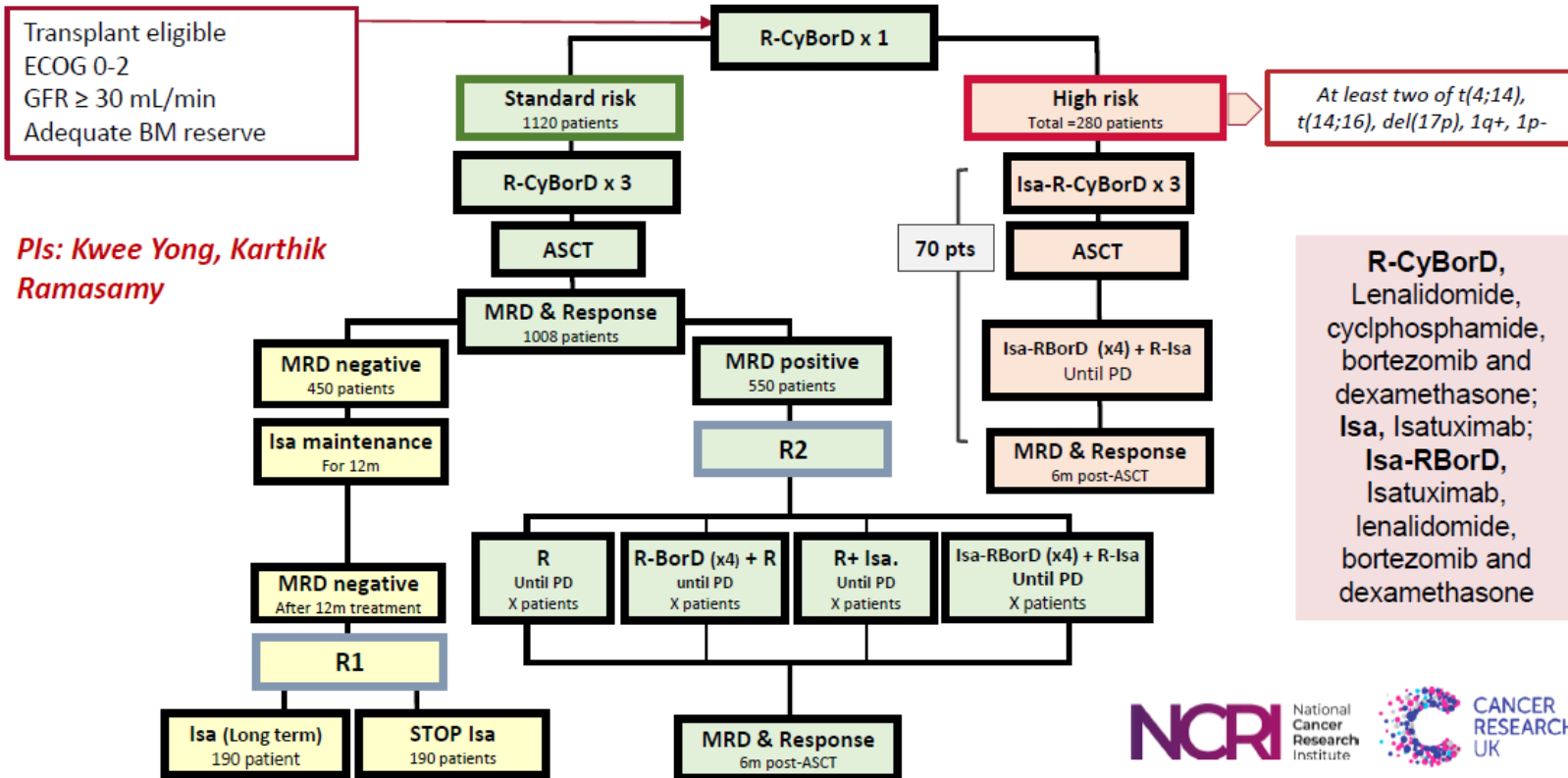
ONGOING CLINICAL TRIALS

PERSEUS (NCT03710603)



- Deep and durable MRD negativity was achieved with D-VRd
 - Rates of MRD negativity improved during maintenance
- 64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol^d

Risk-Adapted therapy Directed According to Response (RADAR)



All patients are tested for MRD at 12 and 24 months

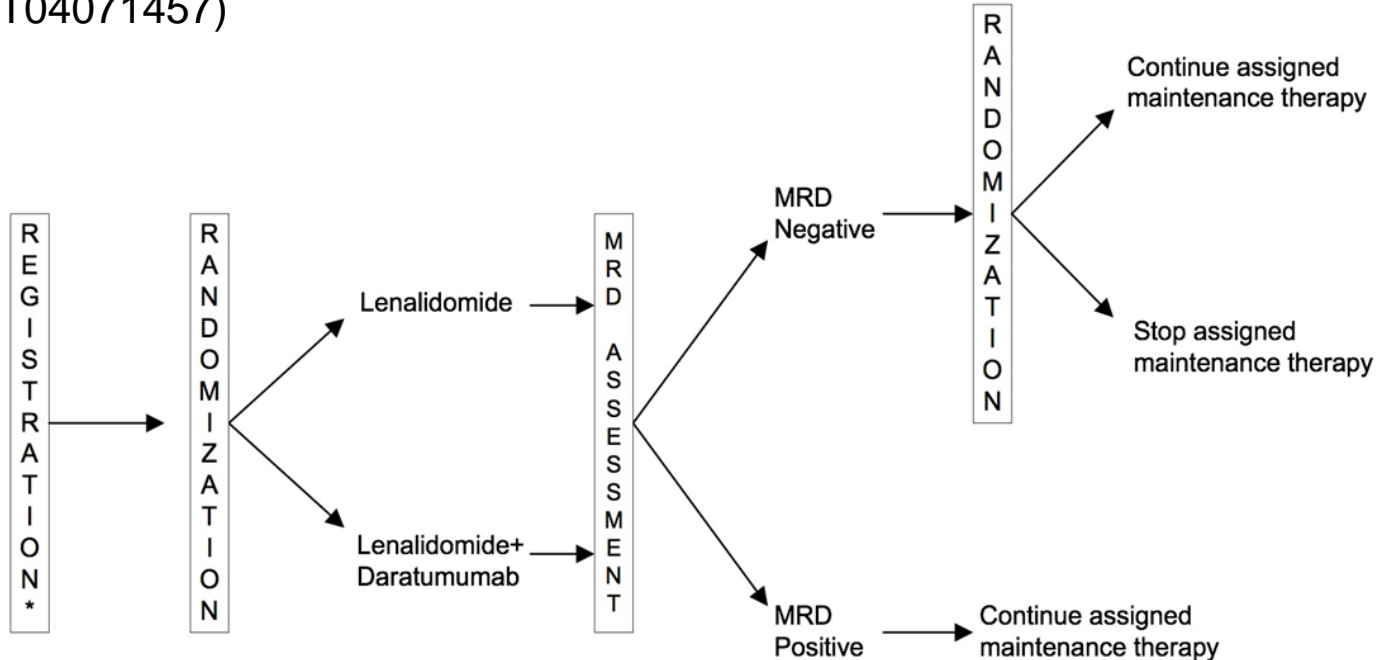
NCRI
National
Cancer
Research
Institute

CANCER
RESEARCH
UK

DRAMMATIC study (SWOG s1803):

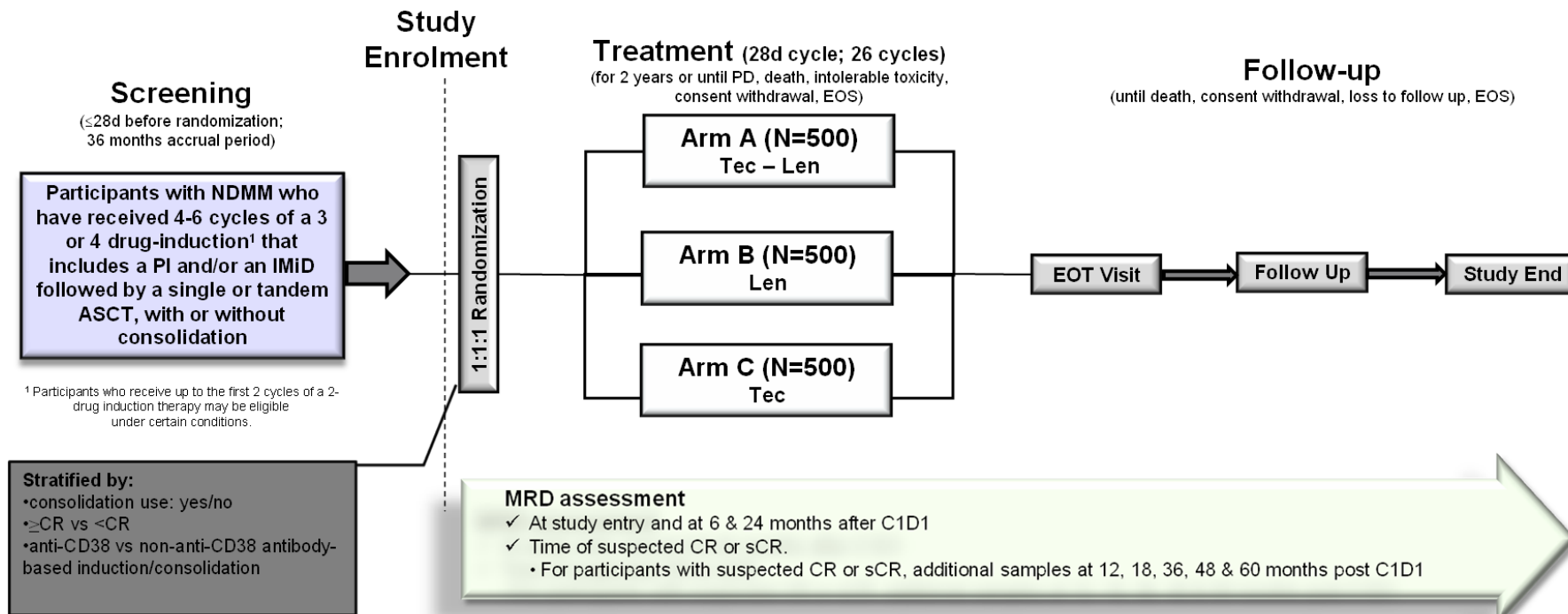
Phase III Study of Daratumumab/rhuph20 (nsc-810307) + Lenalidomide or Lenalidomide As Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) Using Minimal Residual Disease To Direct Therapy Duration

(NCT04071457)



EMN30

STUDY SCHEMA: RANDOMIZED PORTION



CONCLUSIONS

- Lenalidomide (EMA-approved until PD) as standard of care maintenance treatment post-ASCT, with broad consensus about survival benefit outweighing side effects
- **The optimal treatment duration remains to be determined**
- Retrospective and post hoc analysis demonstrated a prolonged survival with longer duration of len-maintenance, but no data are yet available from randomized trials
- The use of MRD status to drive treatment decisions is under investigation: results of several ongoing trials could enable personalization of maintenance therapy, allowing certain subgroups of patients to safely stop treatment