Consolidation and Maintenance Therapy; Emerging Role of Minimal Residual Disease (MRD)

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Disclosures

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies, Amgen Inc, BeiGene, Celgene Corporation, Janssen Biotech Inc, Karyopharm Therapeutics, OncoPep, Takeda Oncology
Ownership Interest	OncoPep

Case Presentation: Dr Brenner

51-year-old man

- Presents with severe back pain, fevers, night sweats, hepatomegaly
- Diagnosis: R-ISS Stage III IgG-lambda myeloma, with 14;16 translocation, hyperdiploid

Case Presentation: Dr Lamar

77-year-old woman

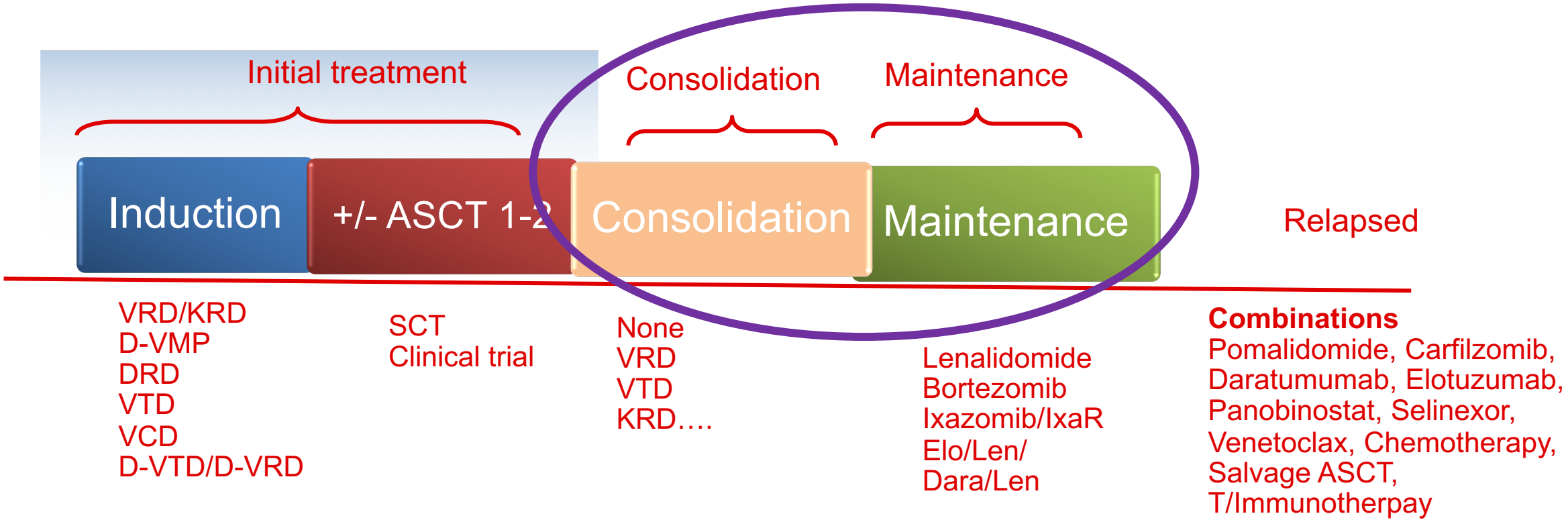
- Transferred from another hospital due to renal failure (Cr: 5)
- Diagnosis: IgM multiple myeloma
- CyBorD

Case Presentation: Dr Morganstein

82-year-old man

- Presents with elevated creatinine
- Diagnosis: Multiple myeloma (M-spike: 3, 60% plasma cells)
- CyBorD, with excellent response but limited travel → ixazomib/dexamethasone

Treatment Algorithm for Newly-Diagnosed Myeloma

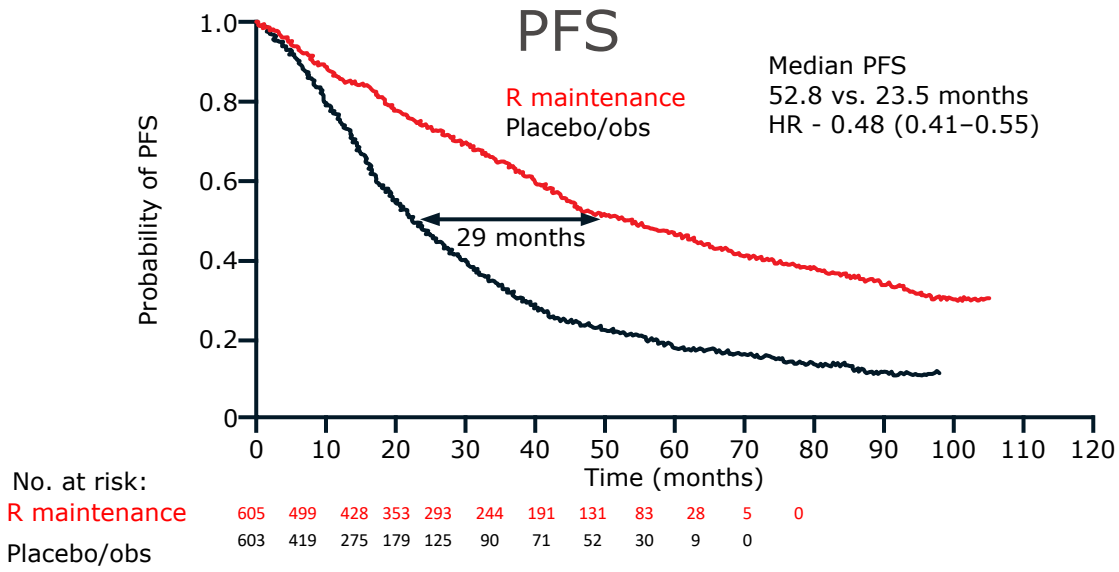


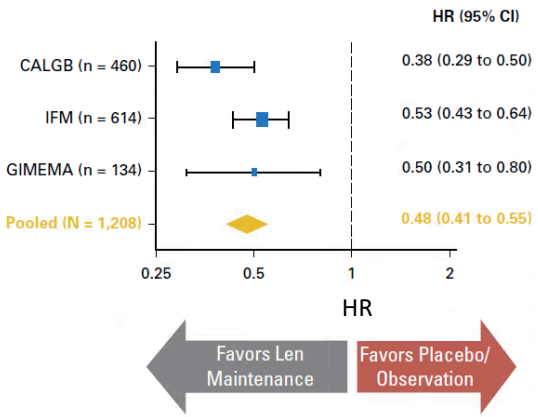
Role of Consolidation/Maintenance

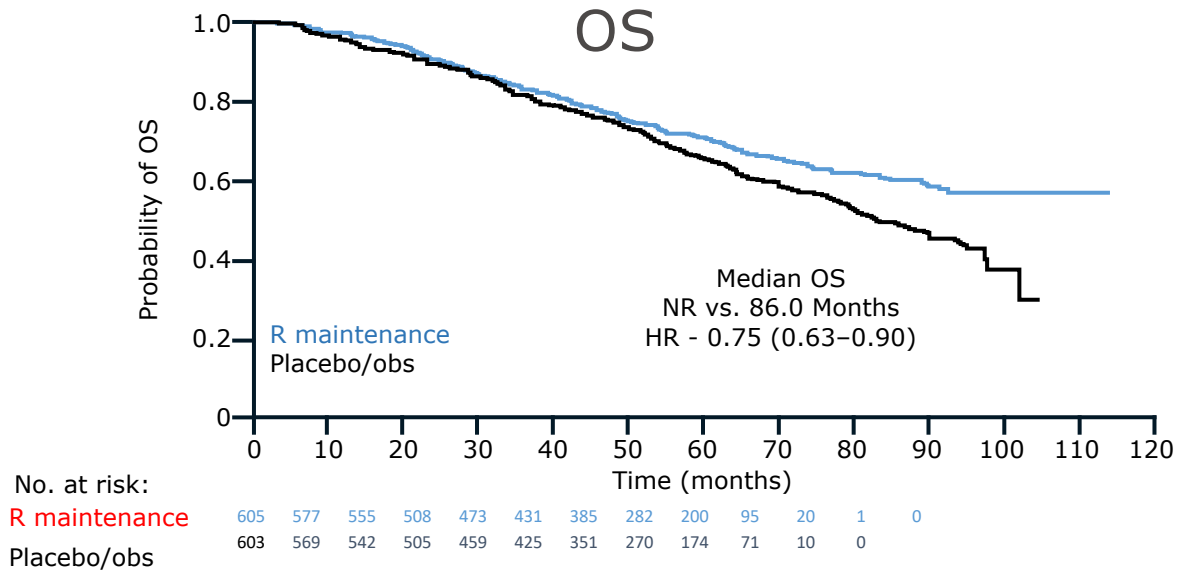
- Deepening of response
- Prevent recurrence (maintain remission)

Meta-analysis: Lenalidomide Maintenance Delays Disease Progression and Improved OS in post-ASCT NDMM

3 Phase III trials of R maintenance in NDMM patients after ASCT: GIMEMA RV-MM-PI-209, CALGB 100104, and IFM-2005-02







1. McCarthy PL, et al. *J Clin Oncol* 2017;35:3279–3289; 2. Palumbo A, et al. *N Engl J Med* 2014;371:895–905; 3. McCarthy PL, et al. *N Engl J Med* 2012;366:1770–1781; 4. Attal M, et al. *N Engl J Med* 2012;366:1782–1791.

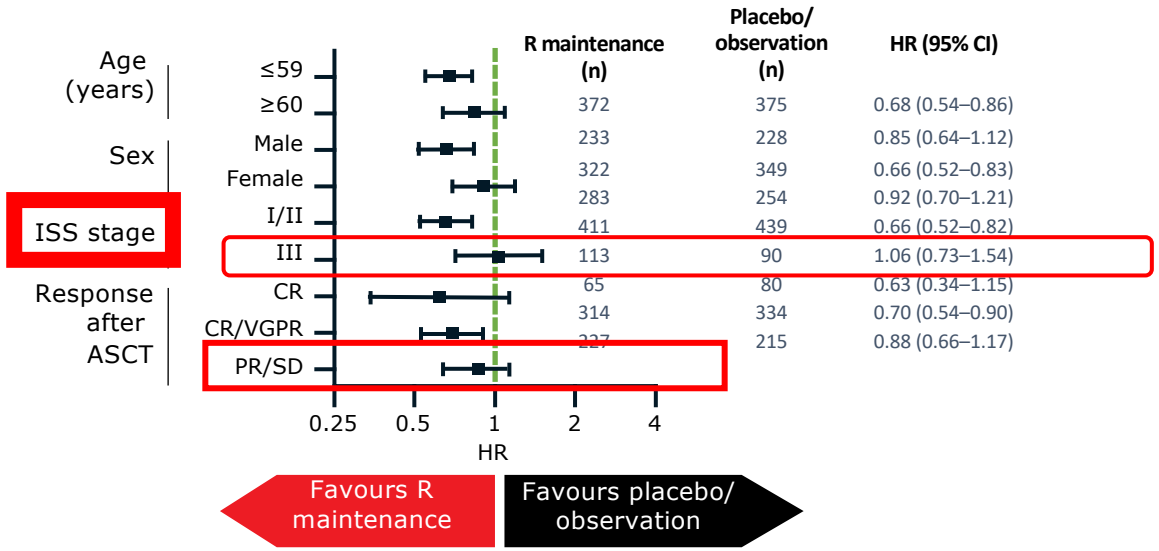
Important Considerations for Maintenance Therapy

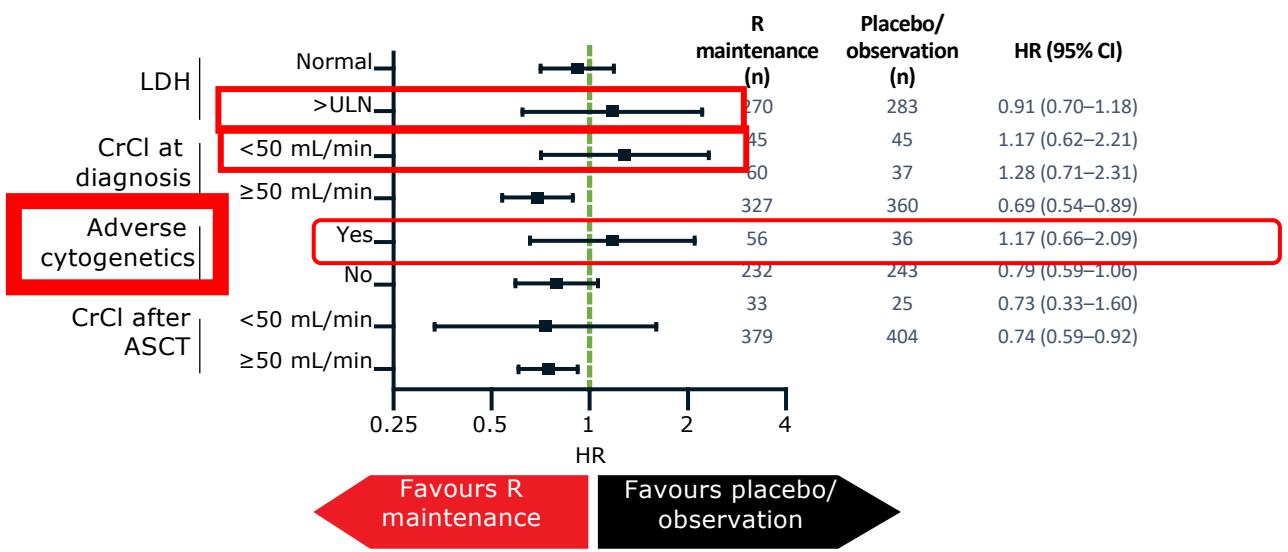
In addition to demonstrated efficacy, extended therapy should preferably include:

- **Tolerability/ Manageable Toxicity**
- **No cumulative toxicity**
- **Convenient administration**
- **Minimal impact on QoL**
- **No emergence of treatment-resistant clones**
- **Efficacy across subgroups**

Meta-analysis: Limited OS Benefit with Lenalidomide Maintenance in High-risk Subgroups

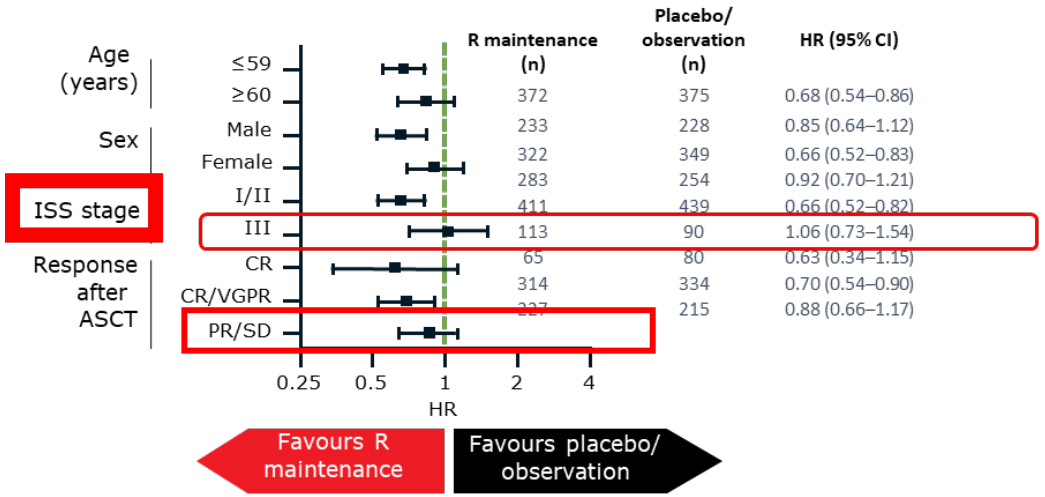
HR for OS by patient subgroup

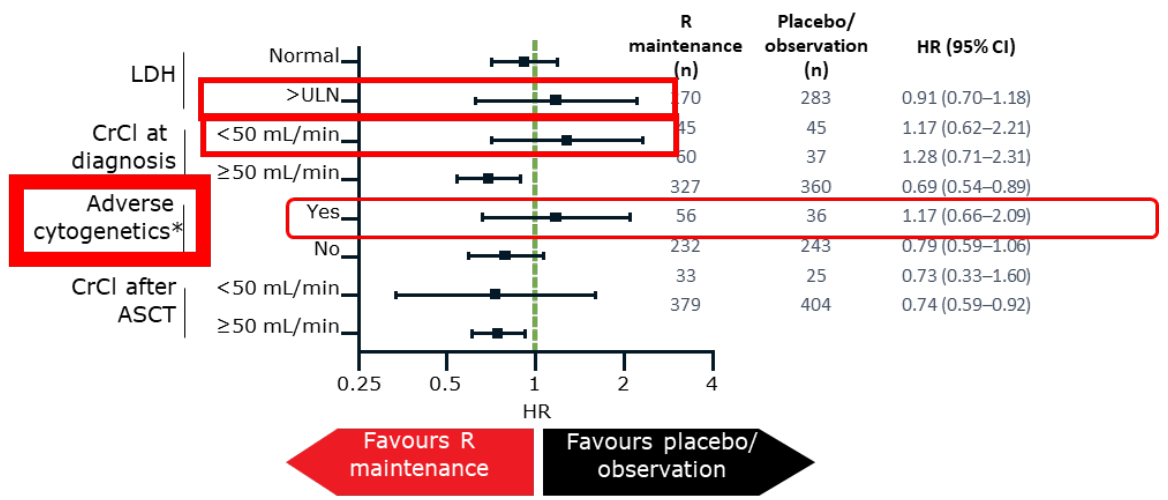




McCarthy PL, et al. *J Clin Oncol* 2017;35:3279–3289.

Consideration of Augmented Maintenance regimen





- **High-risk Myeloma – t(4;14); del17p; t(14;16) and may be amp1q**
- **High LDH disease**
- **Patients with Renal failure**
- **Inadequate response to Induction and/or post-ASCT**

Lenalidomide Maintenance: Toxicity and Quality of Life

Table 3. Discontinuations as a Result of TEAEs (safety population)

TEAE	No. of Patients (%)					
	CALGB		IFM*		Pooled	
	Len Maintenance (n = 224)	Placebo (n = 221)	Len Maintenance (n = 306)	Placebo (n = 302)	Len Maintenance (n = 530)†	Placebo (n = 523)†
≥ 1 TEAE leading to discontinuation	63 (28.1)	19 (8.6)	91 (29.7)	45 (14.9)	154 (29.1)	64 (12.2)
TEAEs leading to discontinuation (≥ 1% of all patients)‡						
Blood and lymphatic system disorder	11 (4.9)	4 (1.8)	12 (3.9)	7 (2.3)	23 (4.3)	11 (2.1)
Neutropenia	5 (2.2)	0	7 (2.3)	1 (0.3)	12 (2.3)	1 (0.2)
Thrombocytopenia	6 (2.7)	1 (0.5)	3 (1.0)	5 (1.7)	9 (1.7)	6 (1.1)
General disorders and administration site conditions	12 (5.4)	5 (2.3)	13 (4.2)	3 (1.0)	25 (4.7)	8 (1.5)
Adverse event not specified	10 (4.5)	4 (1.8)	0	0	10 (1.9)	4 (0.8)
Neoplasms: benign, malignant, and unspecified§	16 (7.1)	3 (1.4)	7 (2.3)	2 (0.7)	23 (4.3)	5 (1.0)
Skin and subcutaneous tissue disorders	6 (2.7)	1 (0.5)	12 (3.9)	9 (3.0)	18 (3.4)	10 (1.9)
Nervous system disorders	5 (2.2)	3 (1.4)	13 (4.2)	6 (2.0)	18 (3.4)	9 (1.7)
GI disorders	5 (2.2)	0	13 (4.2)	1 (0.3)	18 (3.4)	1 (0.2)
Diarrhea	5 (2.2)	0	6 (2.0)	0	11 (2.1)	0
Infections and infestations	4 (1.8)	0	5 (1.6)	4 (1.3)	9 (1.7)	4 (0.8)
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.5)	5 (1.6)	6 (2.0)	6 (1.1)	7 (1.3)

NOTE. Safety population includes patients who received at least one dose of study drug.
Abbreviations: CALGB, Cancer and Leukemia Group B; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; IFM, Intergroupe Francophone du Myélome; Len; lenalidomide; TEAE, treatment-emergent adverse event.

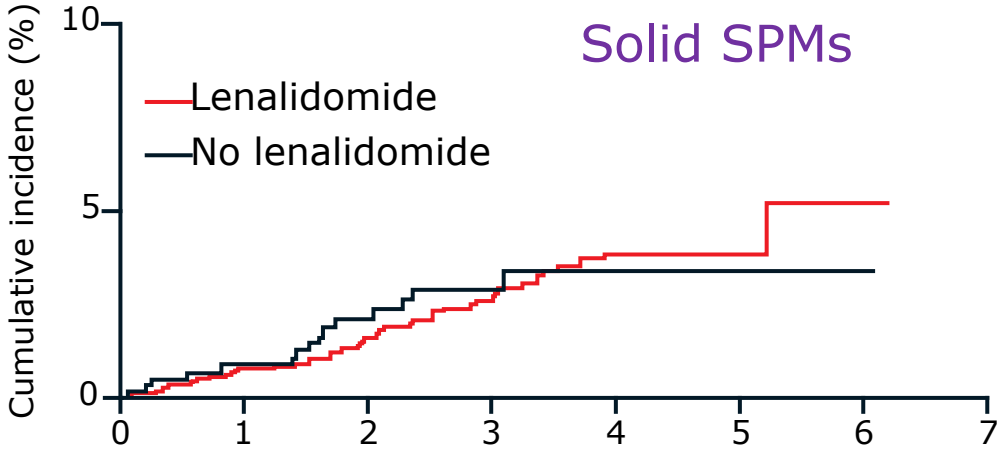
- **Increased risk of SPM, that start to be significant after 2 years of maintenance**

* In the IFM study, data from two cycles of lenalidomide consolidation are included.
† Data from the IFM and CALGB studies only.
‡ System organ class presented with preferred terms nested below.
§ Includes cysts and polyps.

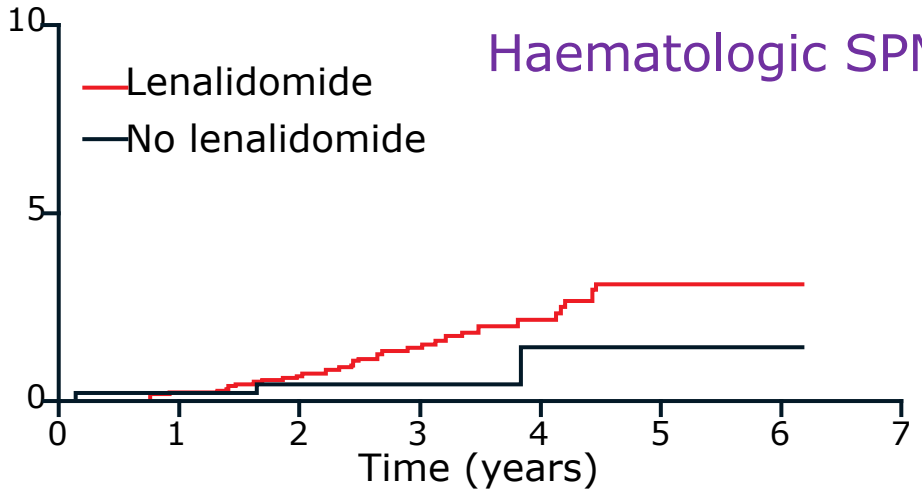
McCarthy et al. J Clin Oncol 2017

Lenalidomide Maintenance and Risk of Second Primary Malignancies

Meta-analysis of seven Phase III trials of R maintenance in NDMM patients (N=3,218)



Cumulative incidence (95% CI)	3 years	5 years
Lenalidomide	**2.6%** (1.8–3.3)	**3.8%** (2.7–4.9)
No lenalidomide	**2.9%** (1.4–4.4)	**3.4%** (1.6–5.2)



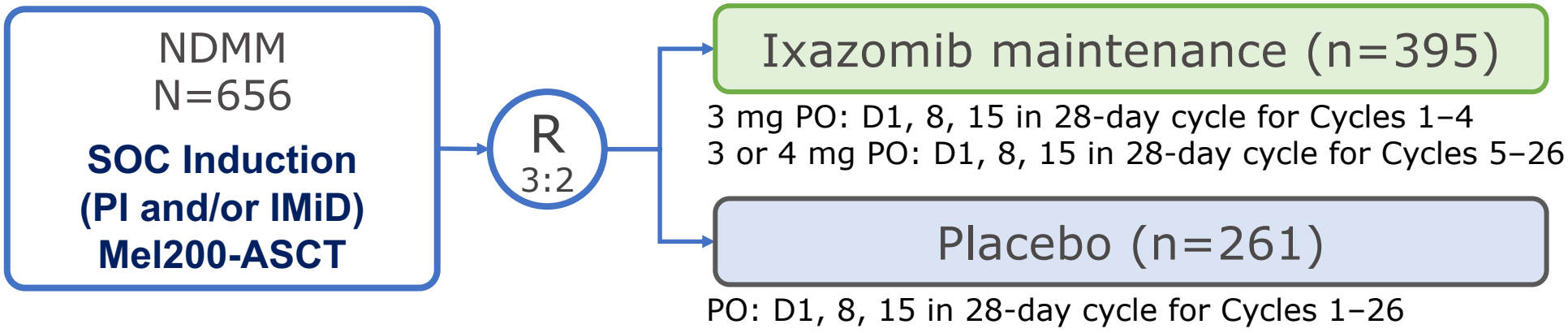
3 years	5 years
1.4% (0.8–2.0)	**3.1%** (1.9–4.3)
0.4% (0.0–0.9)	**1.4%** (0.0–3.6)

- **Significant increased risk of hematologic SPMs with lenalidomide maintenance versus no maintenance**
- **Primarily driven by co-exposure to lenalidomide and oral melphalan**

1. Palumbo A, et al. *Lancet Oncol* 2014;15:333–342.

Oral Ixazomib Maintenance After ASCT in NDMM TOURMALINE-MM3 Study:

- Phase III, randomised, placebo-controlled, double-blind study:



Primary endpoint:

- PFS

Key secondary:

- OS
- TTP
- PFS2
- HRQoL

Stratification - Prior induction treatment (PI and/or IMiD); Type of response to ASCT; ECOG PS 0–2

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Received SOC induction - a PI and/or IMiD • Received single Mel200 ASCT within 12 months of diagnosis • Documented response to ASCT (CR, VGPR, PR)	• Relapse from/or unresponsive to primary therapy • Double (tandem) ASCT • Post-ASCT consolidation therapy

Dimopoulous MA et al Lancet. 2019;393:253-264

Phase III TOURMALINE-MM4 Trial of Ixazomib as First-Line Maintenance Therapy Met Its Primary Endpoint

Press Release - November 7, 2019

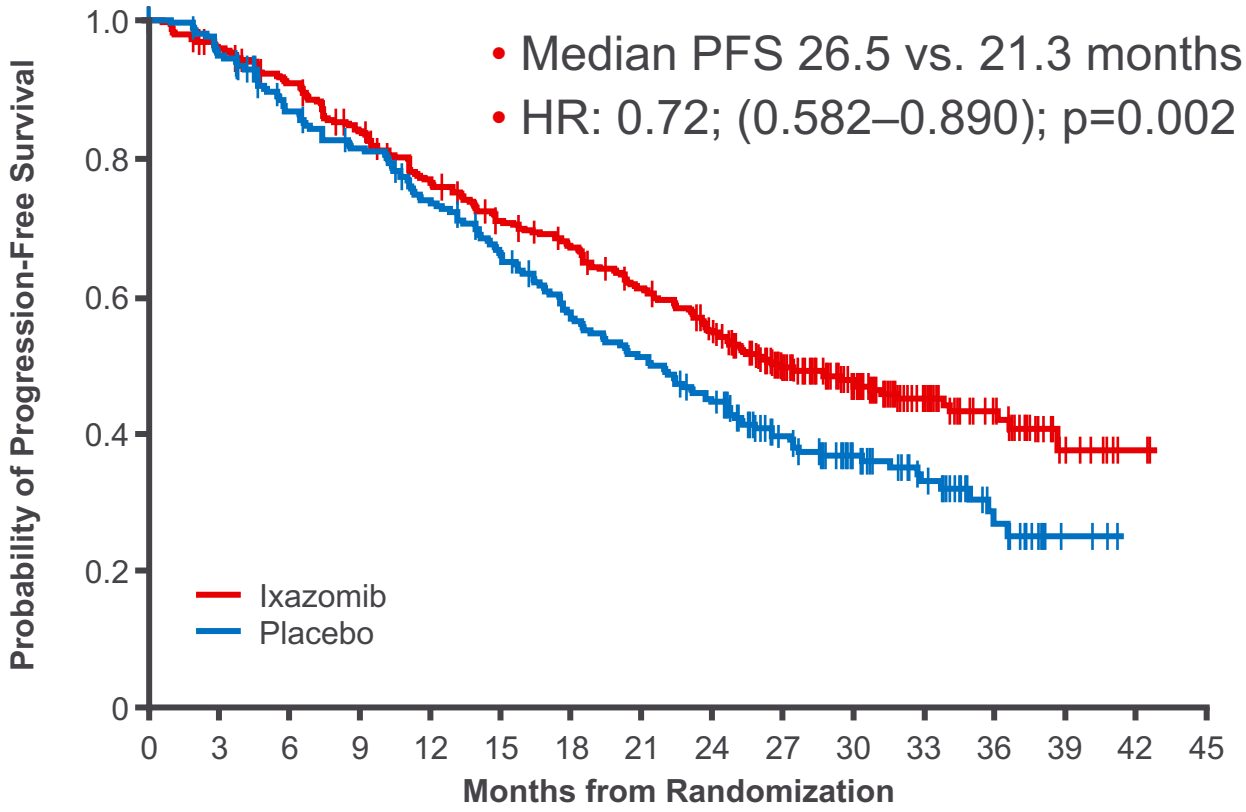
"The randomized, Phase 3 TOURMALINE-MM4 study met its primary endpoint of progression-free survival (PFS). The trial evaluated the effect of single-agent oral ixazomib as a first line maintenance therapy versus placebo in adult patients diagnosed with multiple myeloma not treated with stem cell transplantation. TOURMALINE-MM4 is the first industry sponsored Phase 3 trial to explore the concept of "switch" maintenance, the use of medicines not included in initial induction therapy, in this setting. Ixazomib is currently not approved for this specific use.

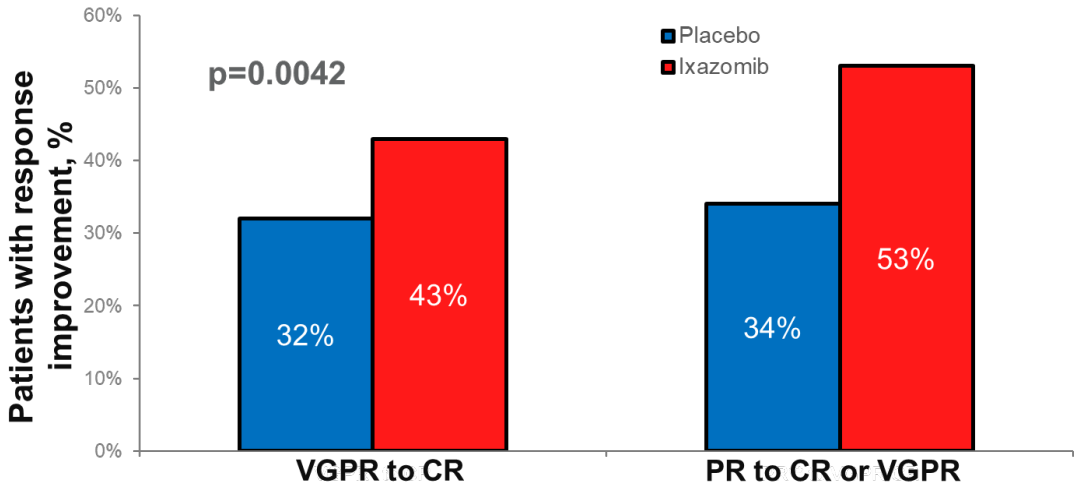
The safety profile of Ixazomib in the maintenance setting was consistent with previously reported results of single-agent ixazomib use, and there were no new safety signals identified in TOURMALINE-MM4."

https://www.businesswire.com/news/home/20191107005221/en/Phase-3-Trial-NINLAROTM-ixazomib-Line-Maintenance

Significant Improvement in PFS with Oral Ixazomib Maintenance After ASCT in NDMM: TOURMALINE-MM3 Study Results:

- 39% improvement in PFS
- Median OS not reached in either arm



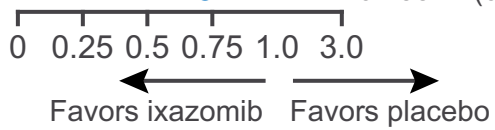


- 41% had improvement in response
- 139/302 (46%) on the ixazomib vs 60/187 (32%) on the placebo arm

Dimopoulous MA et al Lancet. 2019;393:253-264

PFS benefit observed broadly across patient subgroups

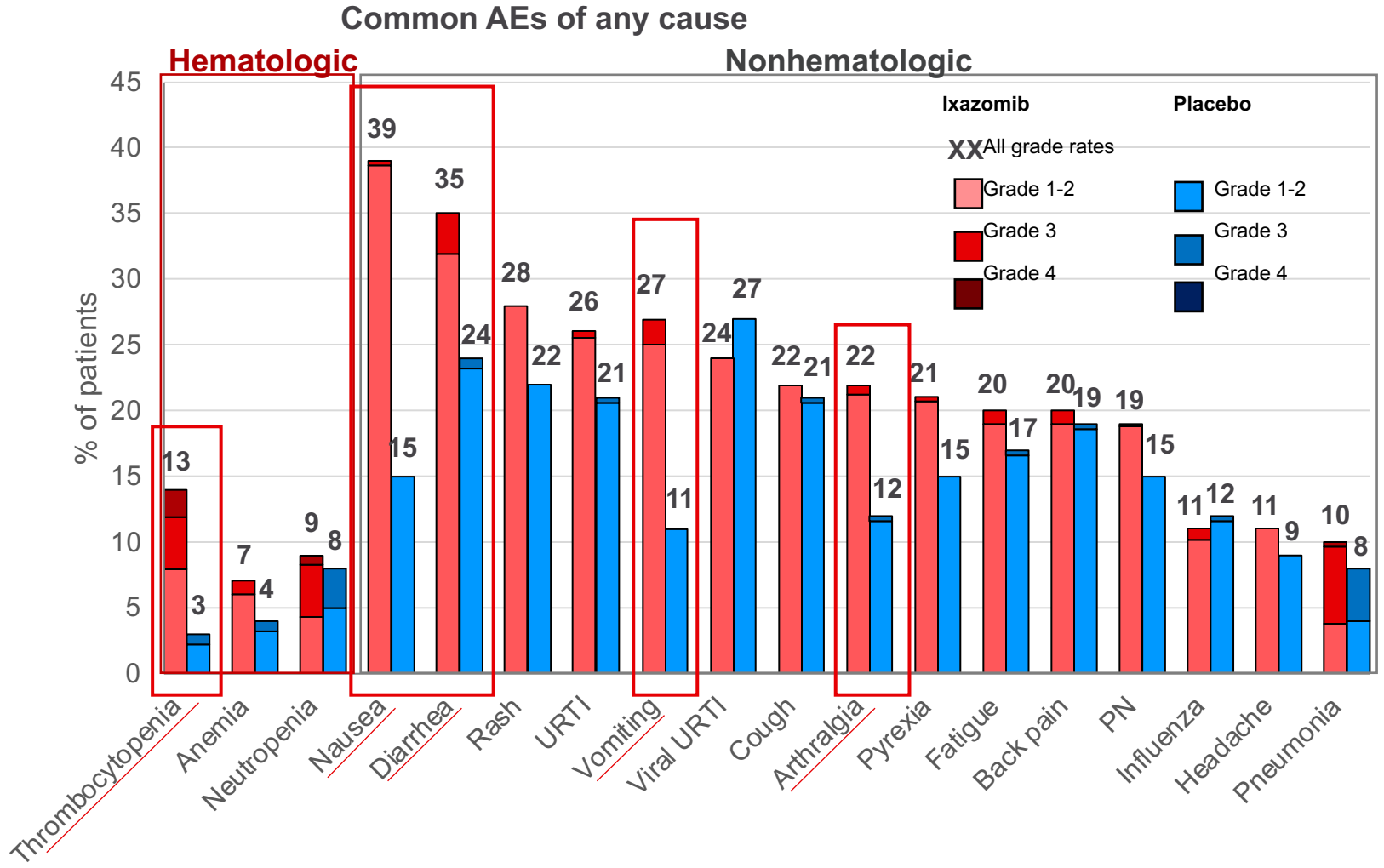
Variable	Subgroup	% of patients Ixazomib	% of patients Placebo	HR	95% CI
All subjects	All (n = 656)	100	100	0.720	(0.582, 0.890)
Induction regimen	PI exposed (n = 585)	89	89	0.750	(0.600, 0.938)
	PI without IMiD (n = 389)	59	59	0.667	(0.510, 0.874)
	PI with IMiD (n = 196)	30	30	0.966	(0.647, 1.442)
	PI + thalidomide* (n = 177)			0.993	(0.643, 1.532)
	PI + lenalidomide* (n = 24)			0.594	(0.132, 2.683)
	No PI; with IMiD (n = 71)	11	11	0.497	(0.254, 0.973)
Age	<60 years (n = 356)	58	49	0.835	(0.620, 1.125)
	≥60 years and <75 years (n = 300)	42	51	0.662	(0.480, 0.914)
Pre-induction ISS stage	I (n = 245)	38	36	0.678	(0.471, 0.975)
	II (n = 221)	33	35	0.876	(0.611, 1.256)
	III (n = 190)	29	29	0.661	(0.438, 0.998)
Response at study entry	CR (n = 225)	33	36	0.881	(0.593, 1.307)
	VGPR (n = 294)	45	44	0.686	(0.498, 0.945)
	PR (n = 137)	21	20	0.693	(0.440, 1.093)
Cytogenetic risk	High-risk (n = 115)	15	21	0.625	(0.383, 1.019)
	Standard-risk (n = 404)	64	58	0.648	(0.490, 0.857)
Renal function based on baseline creatinine clearance	30–<60 ml/min (n = 58)	10	8	0.708	(0.240, 2.090)
	≥60 ml/min (n = 595)	90	92	0.738	(0.592, 0.920)



*IMiD use reported by investigator

Dimopoulos MA et al. *Lancet* 2019;393(10168):253-64.

Ixazomib Maintenance Associated with Low Toxicity

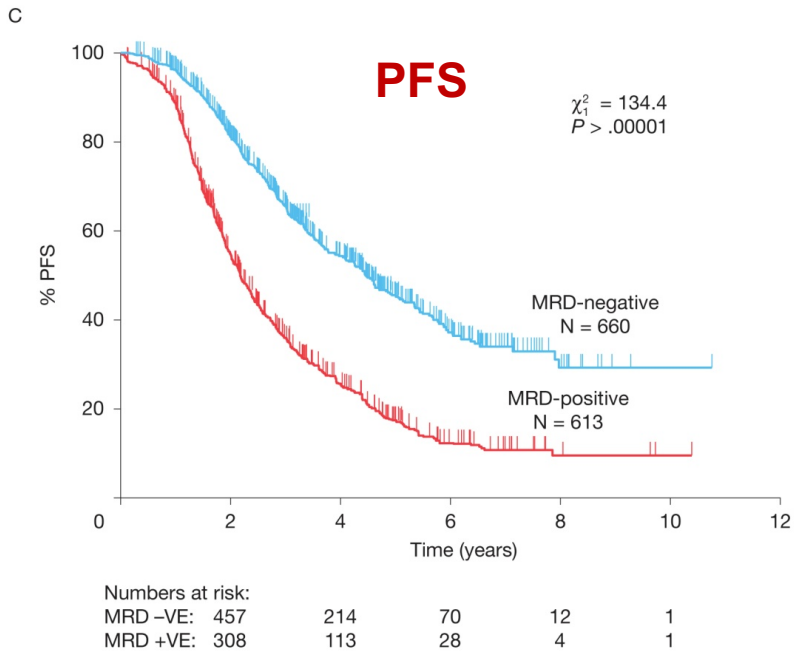


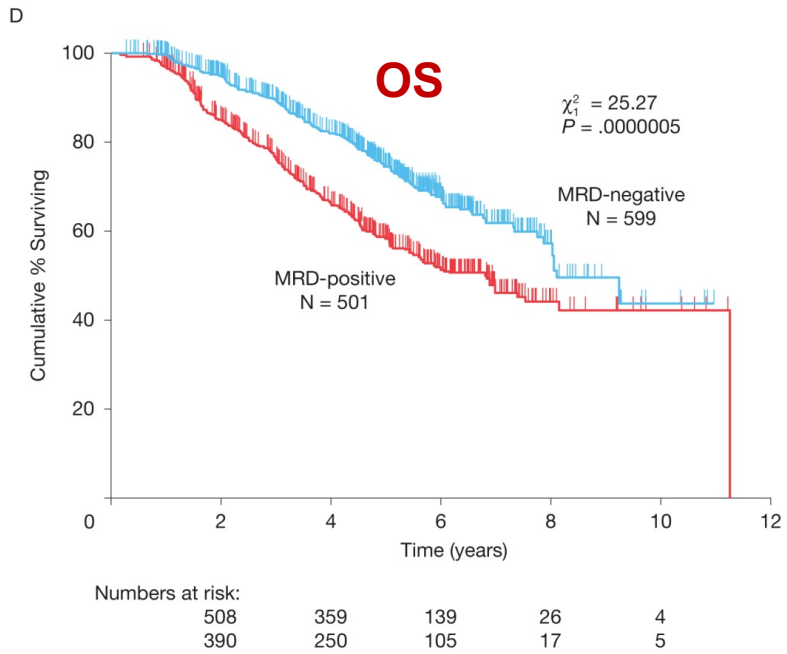
- No difference in the rate of new primary malignancy (3% versus 3%)
- AEs leading to study treatment discontinuation occurred in 7% (ixazomib) and 5% (placebo) of patients

PN, peripheral neuropathy; URTI, upper respiratory tract infection

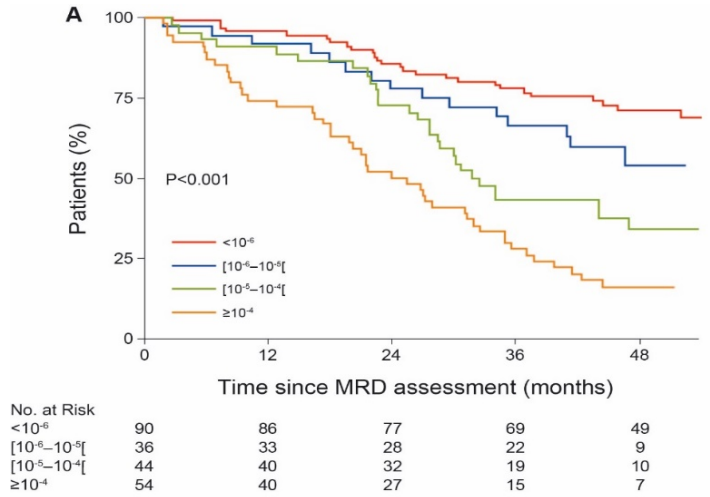
Dimopoulos MA et al. *Lancet* 2019;393(10168):253-64.

MRD Negativity, Measured by Either NGF or NGS Improves Both PFS and OS





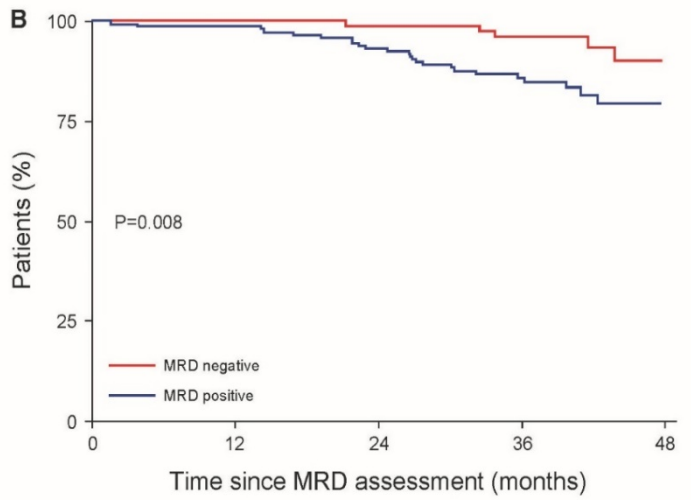
Sensitivity Matters: Superior PFS with Deeper Response



Munshi N et al., JAMA Oncol, 2017

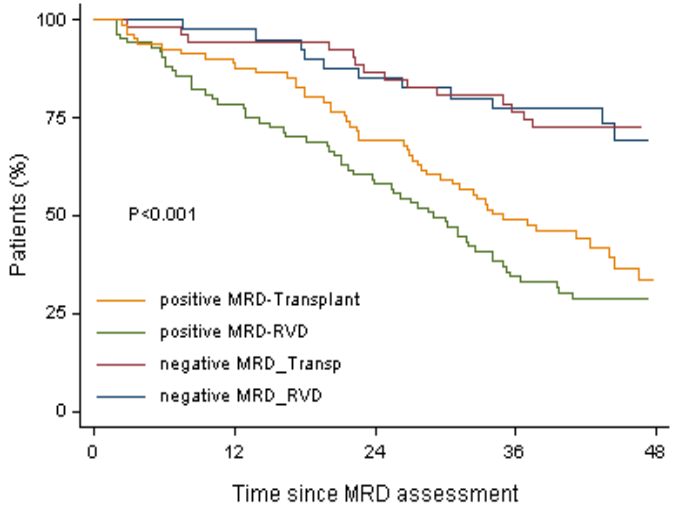
IFM/DFCI 2009 Study
Superior Survival with Minimal Residual Disease negative Status

Superior Overall Survival With MRD negativity



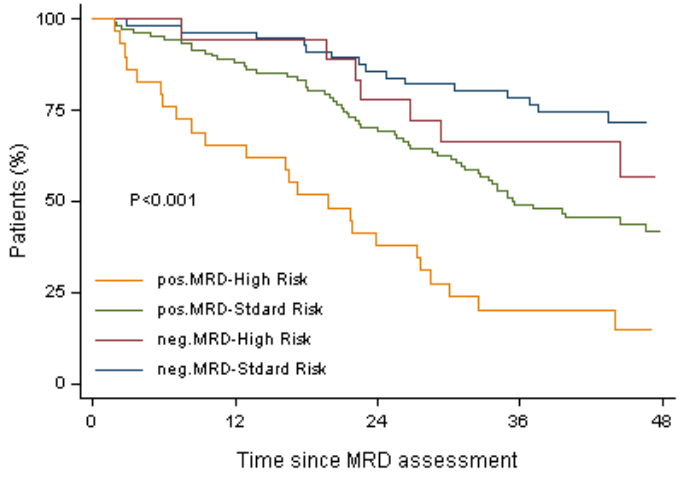
No. at Risk					
MRD negative	92	92	91	58	11
MRD positive	147	145	136	89	13

MRD- patients have improved outcome irrespective of therapy used



N at risk					
positive MRD-Transplant	81	72	56	35	9
positive MRD-RVD	84	65	48	26	8
negative MRD_Transp	52	49	45	37	17
negative MRD_RVD	40	39	34	31	10

MRD- Patients have improved outcome irrespective of risk category



N at risk					
pos.MRD-High Risk	29	19	11	5	0
pos.MRD-Stdard Risk	107	94	74	46	16
neg.MRD-High Risk	18	17	14	11	4
neg.MRD-Stdard Risk	56	54	48	42	18

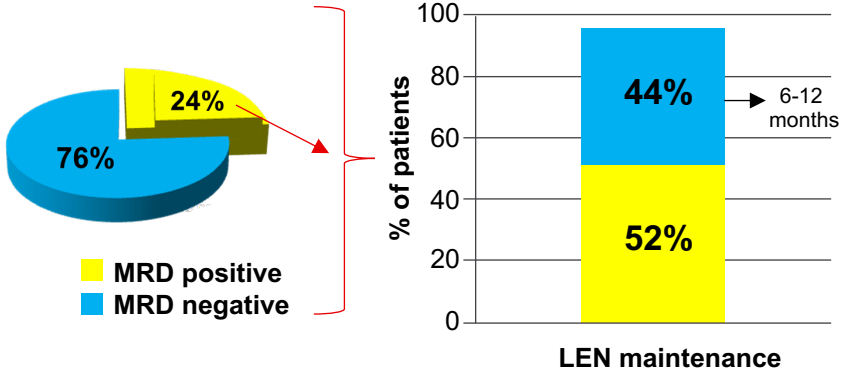
Perrot A et al Blood, 2018

Maintenance Therapy Achieves MRD Negativity

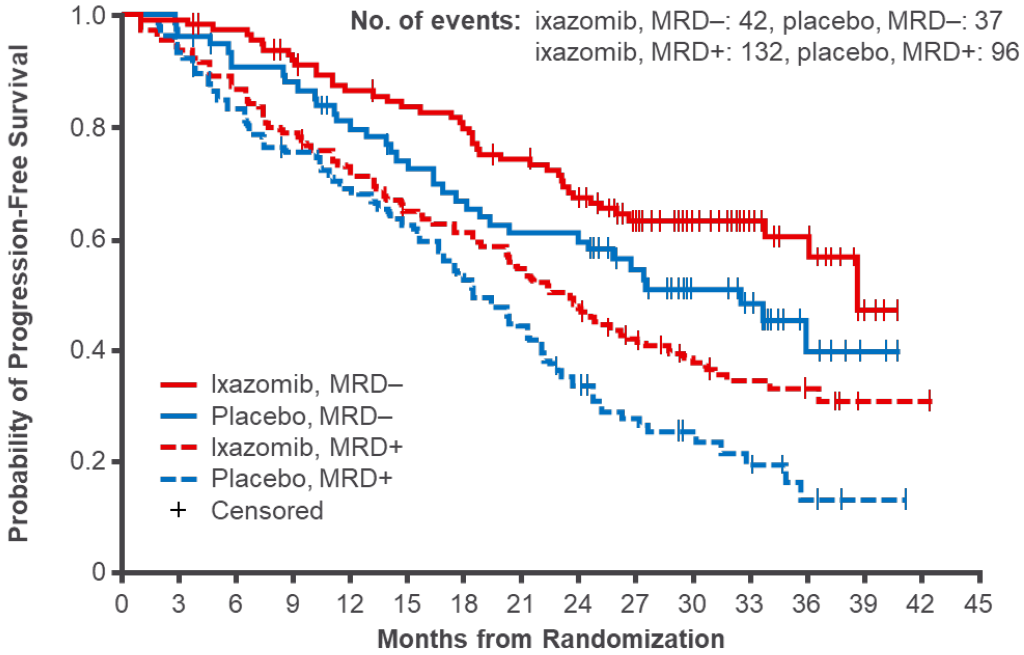
Deepening of response with Maintenance - IFM-DFCI 2009 Study

	Minimal Residual Disease Status	
	Negative	Positive
Response at the beginning of maintenance. (%)	24.6%	75.4%
Response after 12 months of maintenance. (%)	38.5%	61.5

MRD positive patients pre-maintenance achieve MRD negativity after >1 year of Lenalidomide maintenance EMN-02



A PFS benefit observed in the ixazomib group irrespective of MRD status at study entry



Clinical Application of MRD

- Judge prognosis pre-maintenance and during maintenance
- Inform the need for transplant as well as consolidation
- Contribute to determining the type and length of maintenance
- Identify early relapse for close follow up and may consider intervention – especially in high-risk patients
- Role in management of relapsed disease
- Measure real depth of the disease – in all patients who have achieved VGPR or better