Disclosures for Francesca Gay, MD, PhD

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Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Amgen, BMS, Celgene, Janssen, Takeda
Scientific Advisory Board	Amgen, BMS, Celgene, Janssen, Roche, Takeda

Presentation includes discussion of the off-label use of a drug or drugs

La terapia di mantenimento: La medesima per tutti i pazienti, e con uno o più farmaci?

Francesca Gay, MD, PhD
Divisione di Ematologia 1
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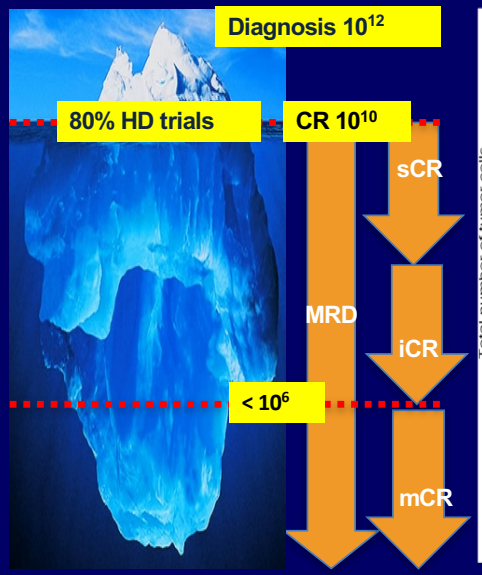
University of Torino, Italy, EU

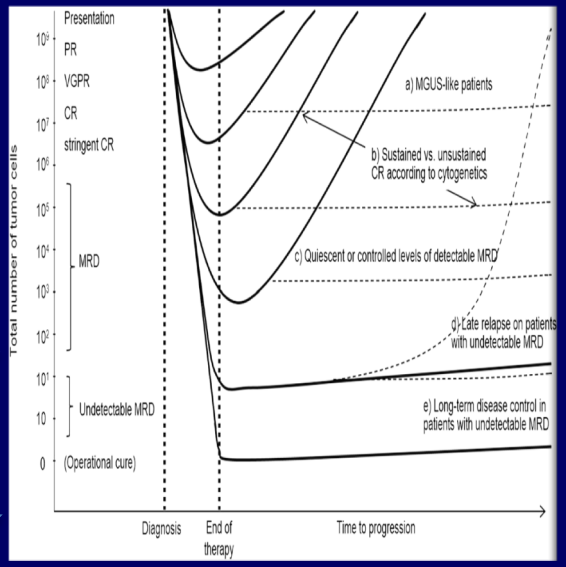
Newly diagnosed myeloma

Treatment objectives

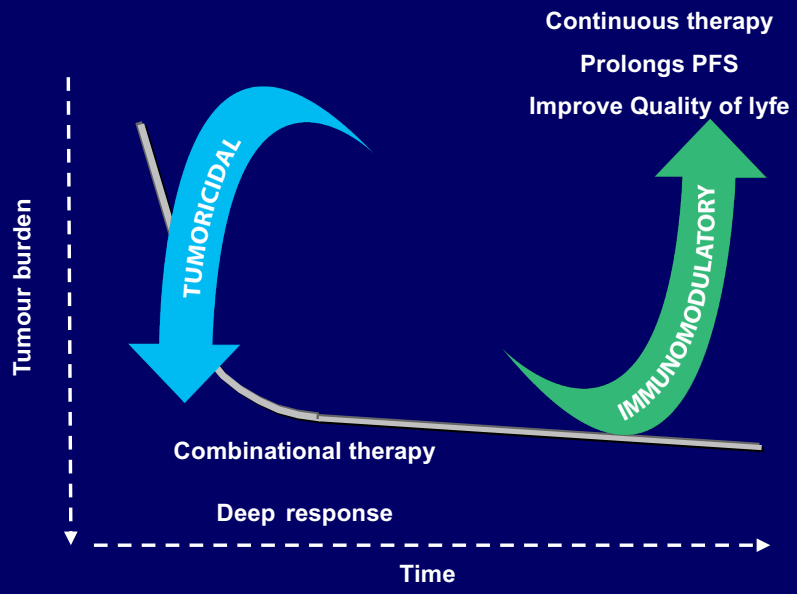
Depth of Response



Duration of Response



Treatment strategy



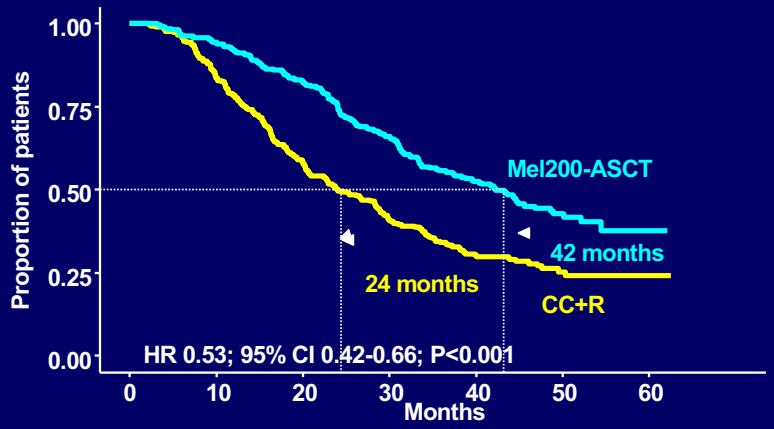
Paiva B, et al. Blood 2015;125(20):3059-68.

Why should we use maintenance post transplant?

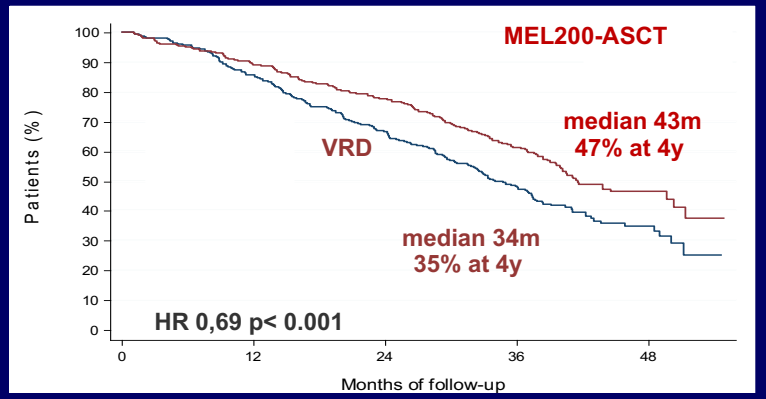
Improvement in PFS with ASCT vs no ASCT

...but no plateau phase → Residual disease is still present!

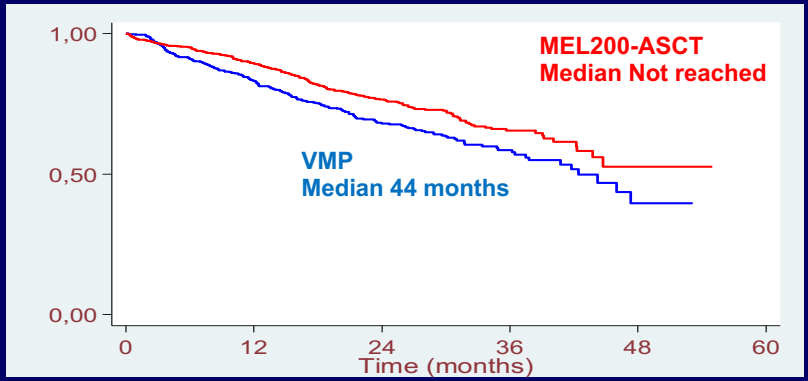
GIMEMA-EMN



IFM/DFCI



EMN-02

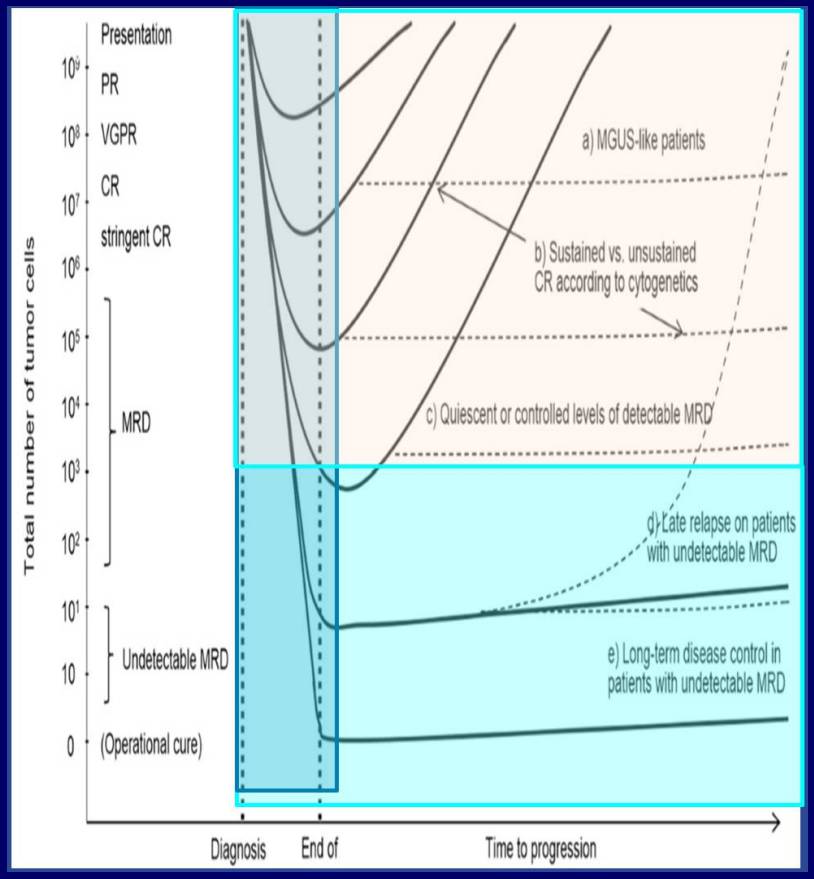


Mel200–ASCT, melphalan 200 mg/m2 followed by autologous stem cell transplantation; CC+R, conventional chemotherapy + lenalidomide; PFS, progression-free survival; VMP, bortezomib-melphalan-prednisone; VRD, bortezomib lenalidomide prednisone.

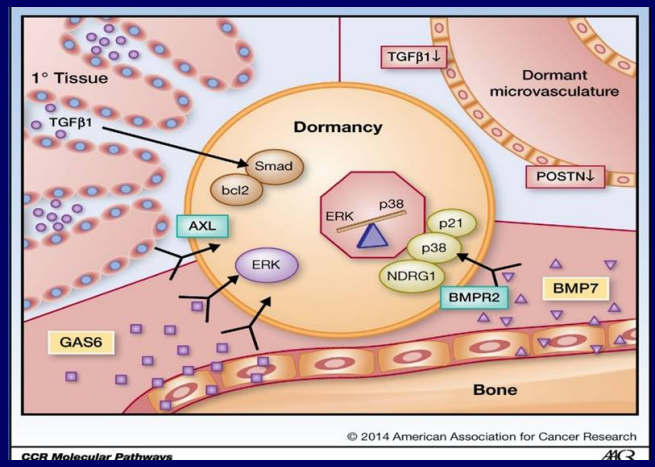
Gay F et al , EHA 2016; Attal M et al, ASH 2015; Cavo M et al; ASCO 2016

Treatment objective: maintain disease under control

Prolonged PFS as a surrogate endpoint for OS



Tumor dormancy, the ultimate objective for "cure"

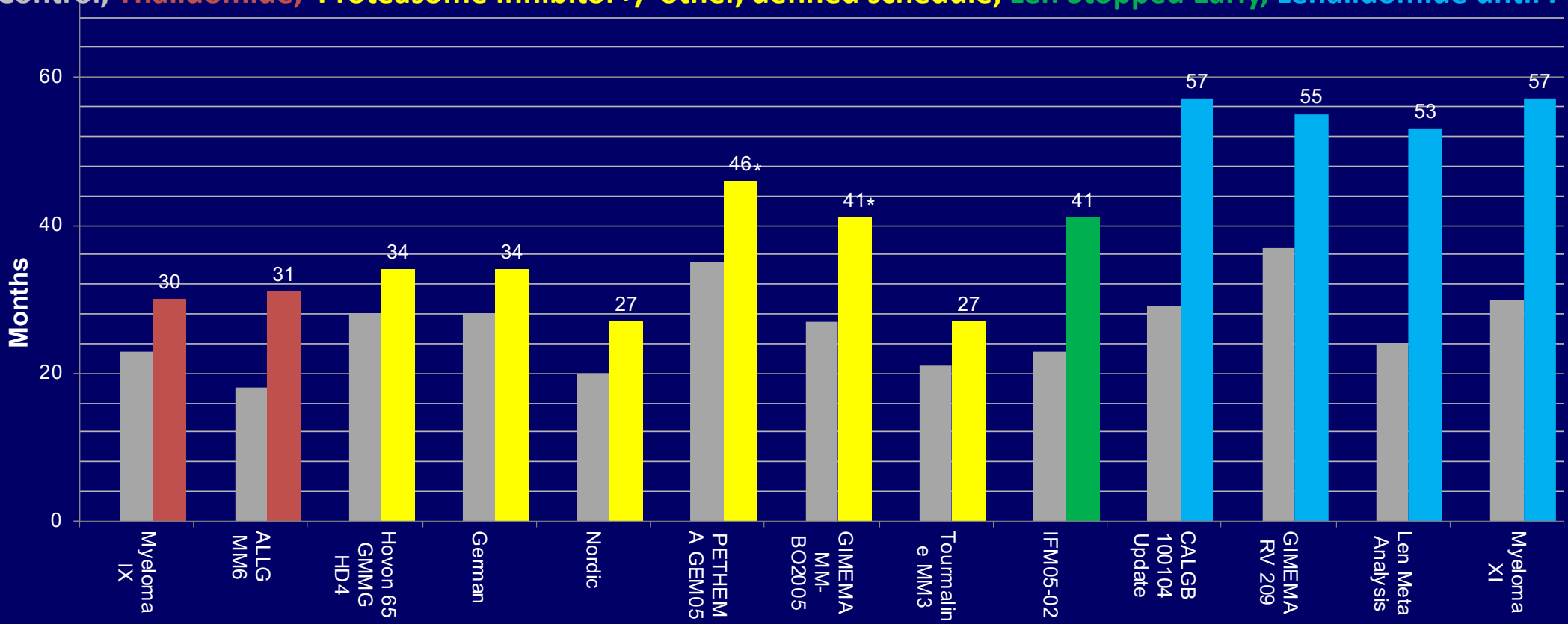


Paiva B, et al. Blood 2015;125(20):3059-68.

Current Evidence

Phase 3 Consolidation/Maintenance Regimens and PFS in TE-NDMM Patients

Control, Thalidomide, Proteasome Inhibitor+/-other, defined schedule, Len Stopped Early, Lenalidomide until PD

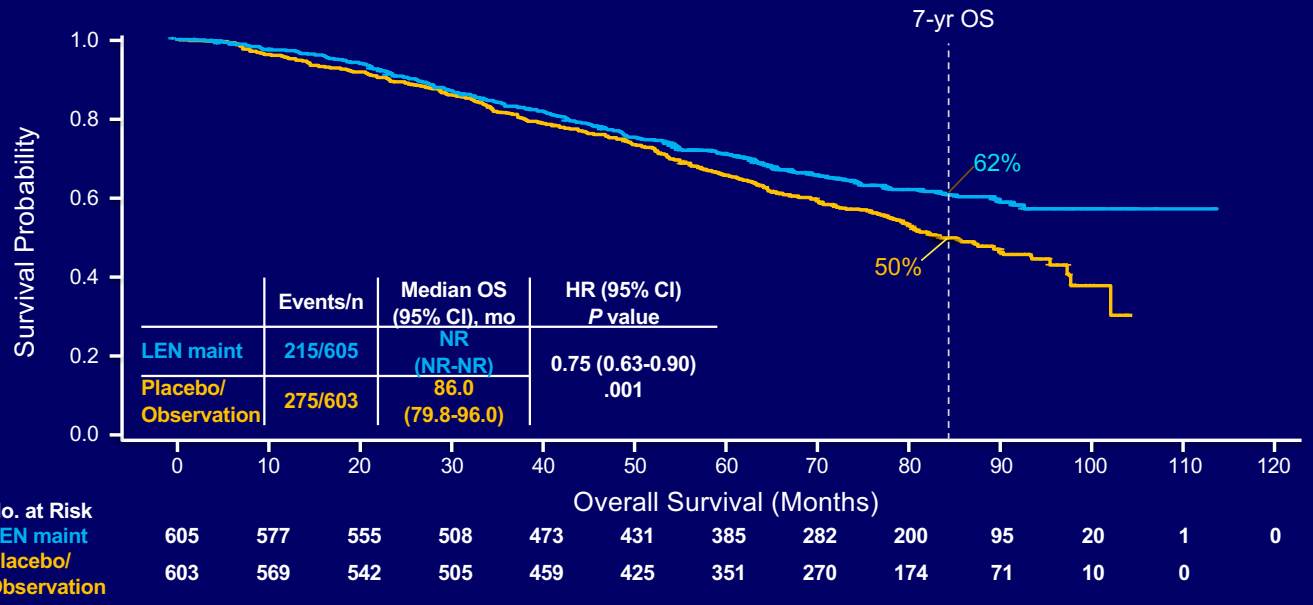


Myeloma IX, No Rx vs T until PD: Morgan et al Blood 2012; ALLGMM6, P vs TP until PD: Spencer et al JCO 2009; Hovon 65 GMMG HD4, T vs V 2 yrs: Sonneveld et al JCO 2012; German, No Rx vs V: Einsele et al Leukemia 2017; Nordic No Rx vs V: Mellqvist et al Blood 2013; PETHEMA GEM05, T vs VT 3yrs *assuming 5 mo for induction & SCT: Rosinol et al Leukemia 2017; GIMEMA MM-BO2005: ASCT x2 TD vs VTD D until PD *assuming 5 mo for induction & SCT: Cavo et al Blood 2012; Tourmaline, Pbo vs Ixa 2 yrs: Dimopoulos et al Lancet 2019; IFM 05-02, Pbo vs Len until PD (stopped early): Attal et al NEJM 2012; CALGB 100104 Update, Pbo vs Len: Holstein et al Lancet Haem 2017; GIMEMA Rv 209, No Rx vs Len: Palumbo et al NEJM 2014; Len Meta Analysis: Pbo vs Len: McCarthy et al JCO 2017; Myeloma XI No Rx vs Len: Jackson G et al Lancet Oncology 2019.

Courtesy of Mc Carthy P, presented at IMWG 2019.

Metaanalysis of 3 lenalidomide maintenance trials
Overall Survival: Median Follow-Up of 80 Months

There is a 25% reduction in risk of death, representing an estimated 2.4-year increase in median survival[a]

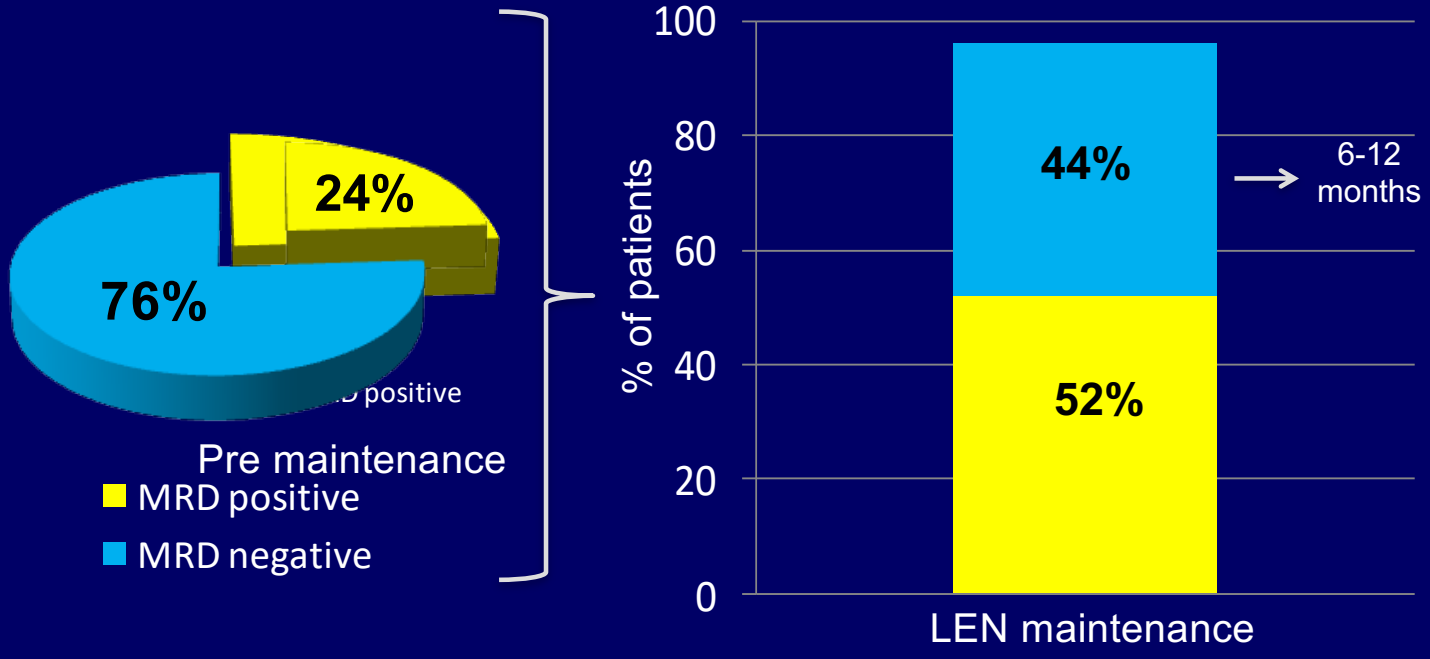


[a] Log-rank test and Cox model stratified by study to assess impact of lenalidomide maintenance on overall survival. Median for lenalidomide treatment arm was extrapolated to be 115 months based on median of the control arm and HR (median, 86 months; HR = 0.75).
HR, hazard ratio; maint, maintenance; NR, not reached; OS, overall survival.

Mc Carthy P et al. IMW Delhi 2017

EMN02: MRD Analysis

Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



Oliva S et al. EHA 2017

EMN02: MRD Analysis

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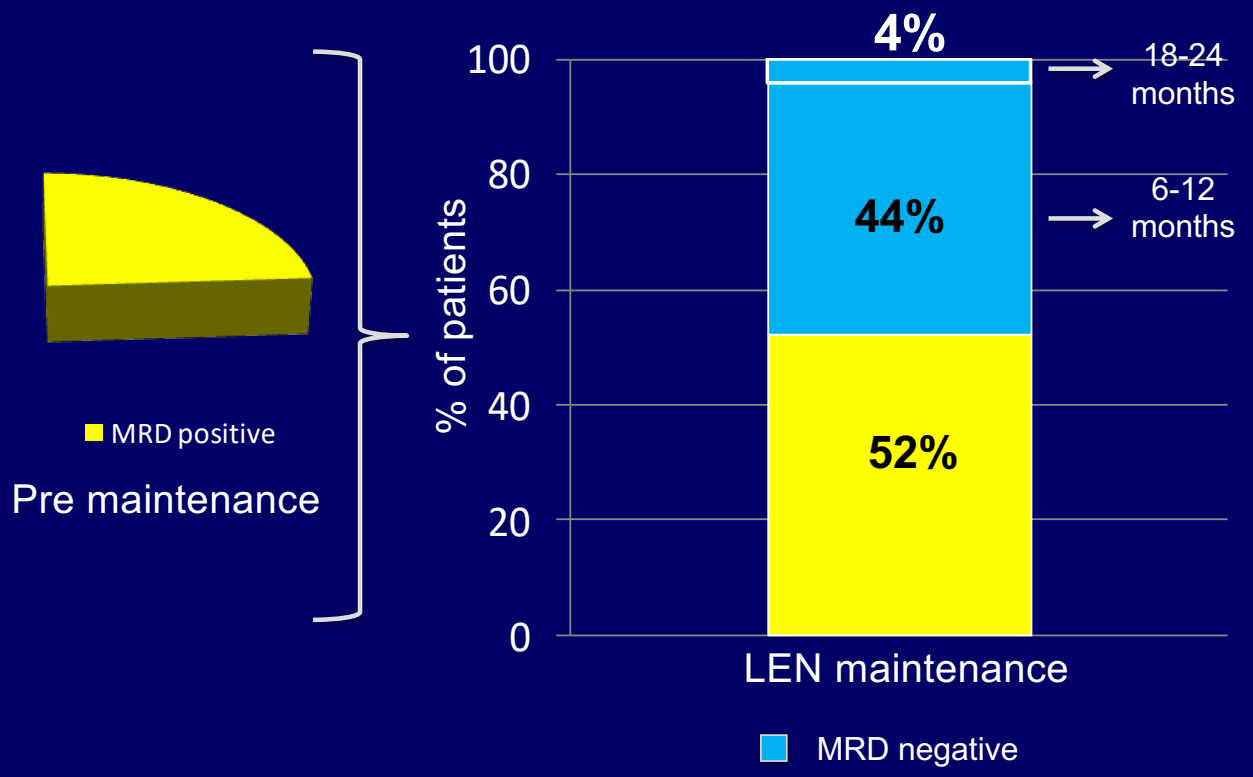


Oliva S et al. EHA 2017

Open Issues

Open issues

- Optimal duration
- Optimal drug
- Do we need combinations?

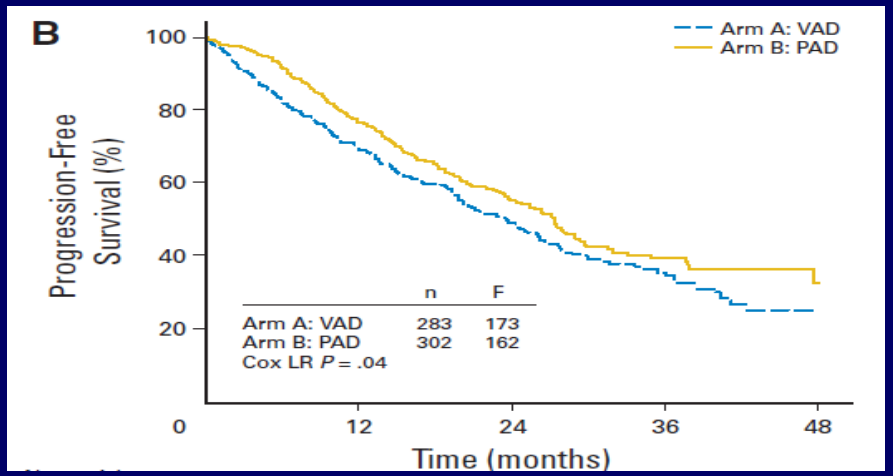
Open issues

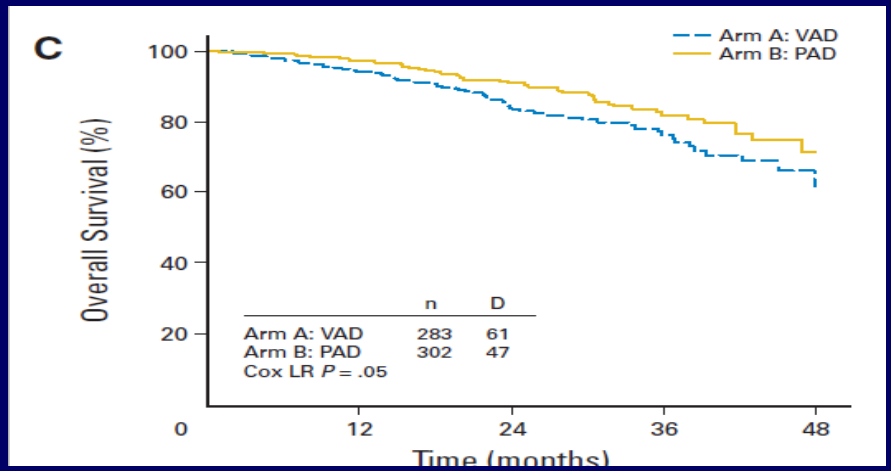
- Optimal duration
- Optimal drug
- Do we need combinations?

- Tolerability
- Patient risk
- Previous induction therapy

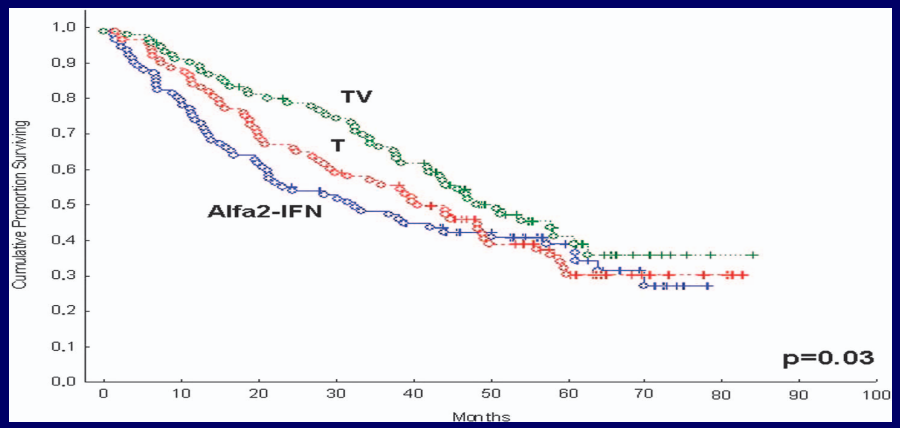
Bortezomib-based maintenance after ASCT

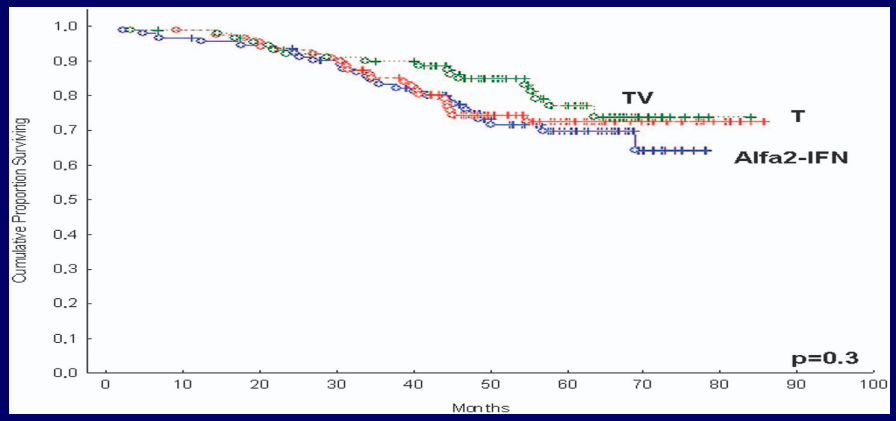
Bortezomib vs Thalidomide





Bortezomib-Thalidomide vs Thalidomide vs Interferon



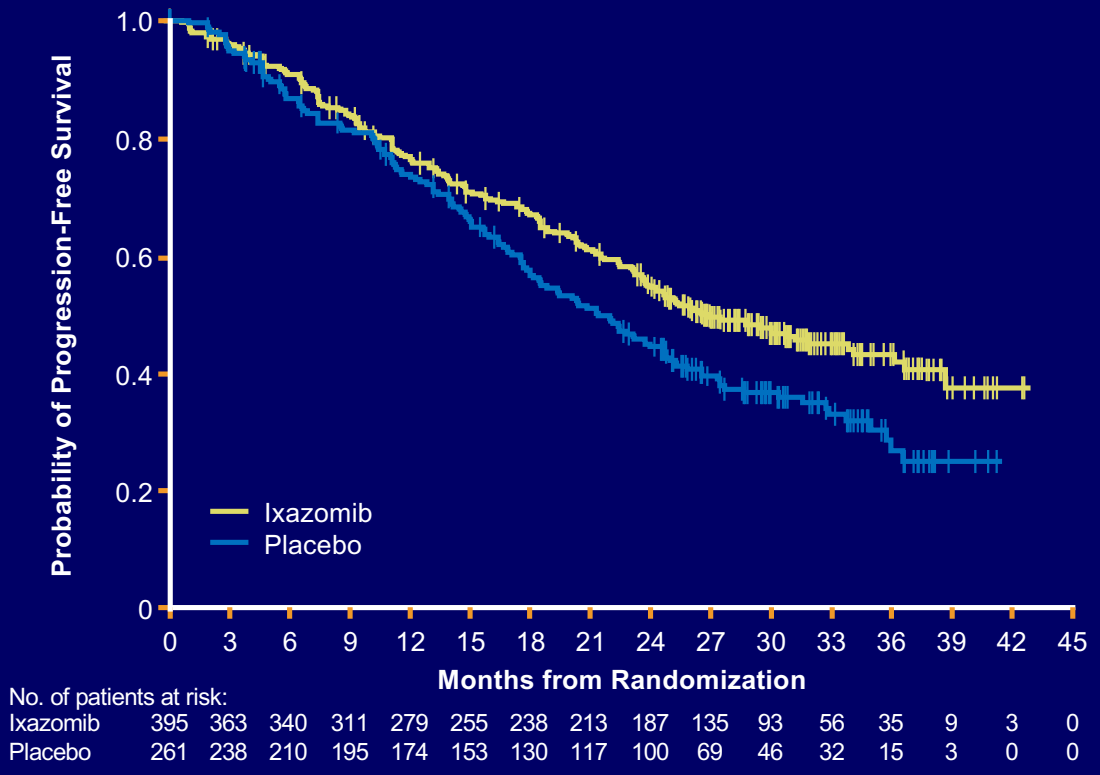


Sonneveld P et al. JCO 2012

Rosignol et al. Leukemia 2017

Ixazomib vs. placebo maintenance post ASCT: PFS

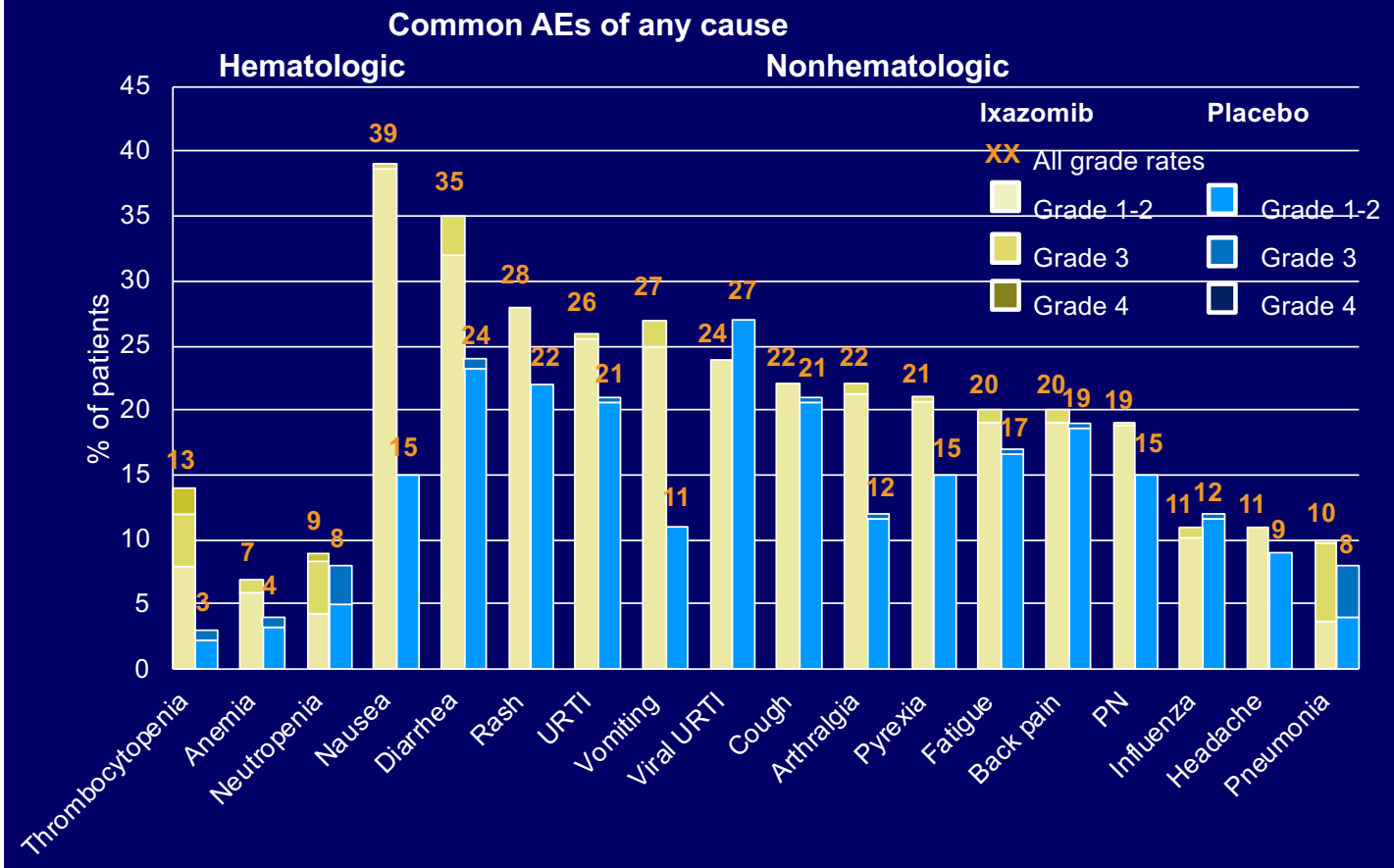
- There was a significant 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs. placebo maintenance:
  - HR: 0.72; 95% CI: 0.582–0.890
  - p=0.002
  - Median 26.5 months vs. 21.3 months
- With only 14% of deaths reported, at a median follow-up of 31 months, median OS has not been reached in either treatment arm and follow up continues



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Dimopoulus M et al ASH 2018.

Ixazomib vs placebo maintenance: Adverse events



- There was no increase in hepatic, cardiac, or renal AEs
- At the current follow-up, there was no difference in the rate of new primary malignancy (3% versus 3%)
- The number of on-study deaths was very low in both groups (1 versus 0 patients)

PN, peripheral neuropathy; URTI, upper respiratory tract infection.

Dimopoulus M et al ASH 2018.

Maintenance Toxicities

Grade 3-4 AEs	Lenalidomide	Placebo	Ixazomib
Neutropenia	23%-51%	0%*-18%	5%
Thrombocytopenia	4%-14%	0%*-7%	5%
Febrile neutropenia	4%-5%	<1%-2%	-
Infections	6%-13%	2%*-5%	15%
Skin	4%-7%	0%*-4%	2%
Diarrhea	2%-5%	<1%-2%	3%
Vascular	1%-4%	3%	-

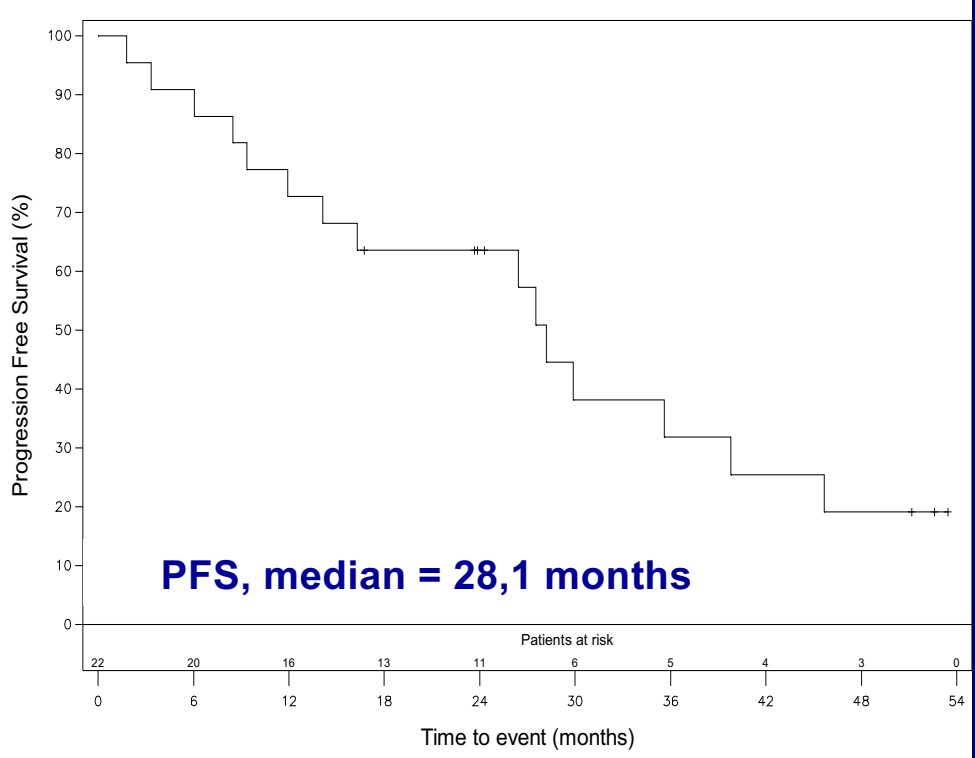
**from GIMEMA trial, where no placebo was given*

Attal M, et al. NEJM 2012;366:1782, McCarthy PL, et al. NEJM. 2012;366:1770, Palumbo A, et al. NEJM 2014;371:10 , Graham J et al. ASH 2016. Dimopoulus Lancet 2019

Carfilzomib Maintenance

Ph I IFM 2012-03 study ELDERLY PATIENTS, NON TRANSPLANT ELIGIBLE

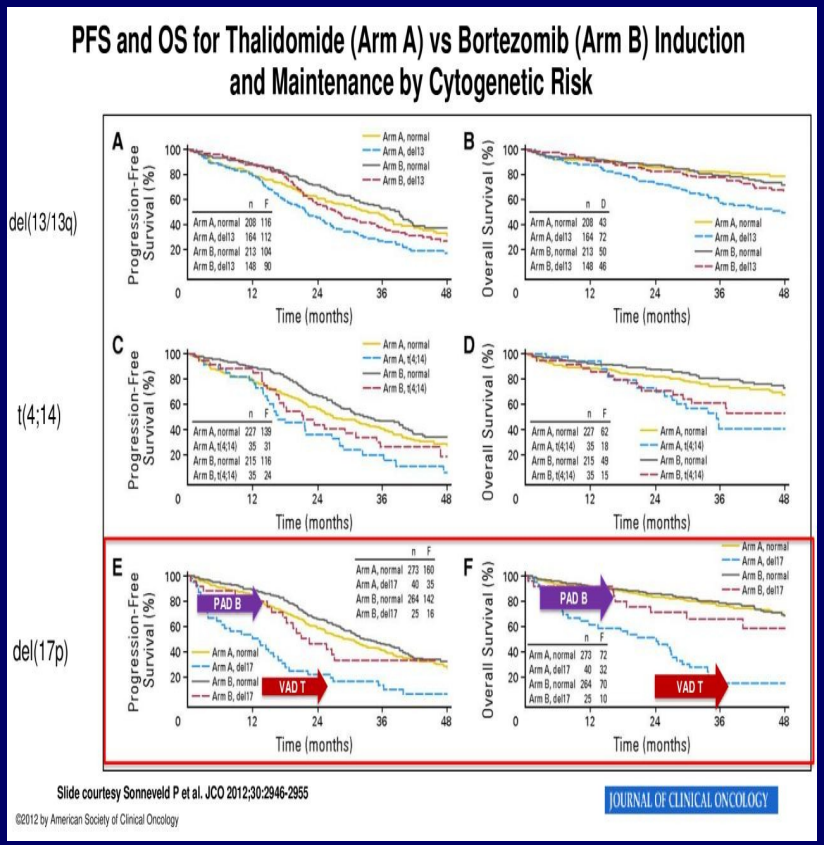
PFS from maintenance

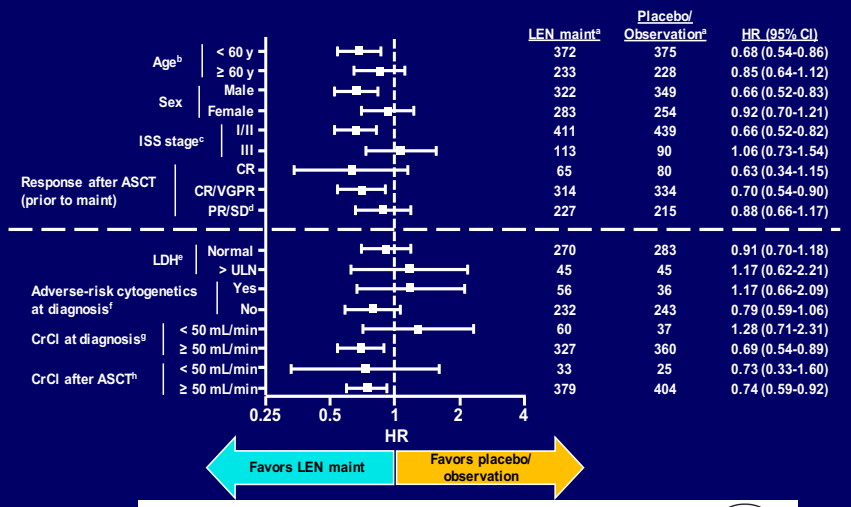


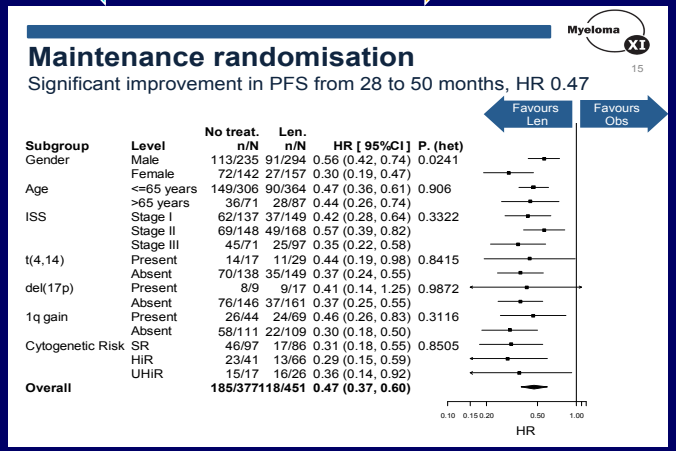
AEs, n (%)	Any grade	Grade 3-4
Blood and lymphatic system disorders		
Anemia	0 (0)	0 (0)
Lymphopenia	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)
Thrombocytopenia	0 (0)	0 (0)
Gastrointestinal disorders		
Diarrhea	0 (0)	0 (0)
Nausea	8 (36.4)	0 (0)
Vomiting	8 (36.4)	0 (0)
General disorders and administration site conditions		
Asthenia	3 (13.6)	0 (0)
Edema limbs	0 (0)	0 (0)
Fever	0 (0)	0 (0)
Infections and infestations		
Bronchitis	4 (18.2)	0 (0)
Urinary infection	0 (0)	0 (0)
Weight loss	0 (0)	0 (0)
Musculoskeletal disorders: Bone pain	0 (0)	0 (0)
Renal and urinary disorders : Acute renal failure	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Cough	0 (0)	0 (0)
Dyspnea	0 (0)	0 (0)
Vascular disorders : Hypertension	4 (18.2)	0 (0)
Neurological toxicities : Sensitive neuropathy	0 (0)	0 (0)

Leleu X et al IMWG 2019.

High vs standard-risk patients: is lenalidomide the best treatment for all patients?



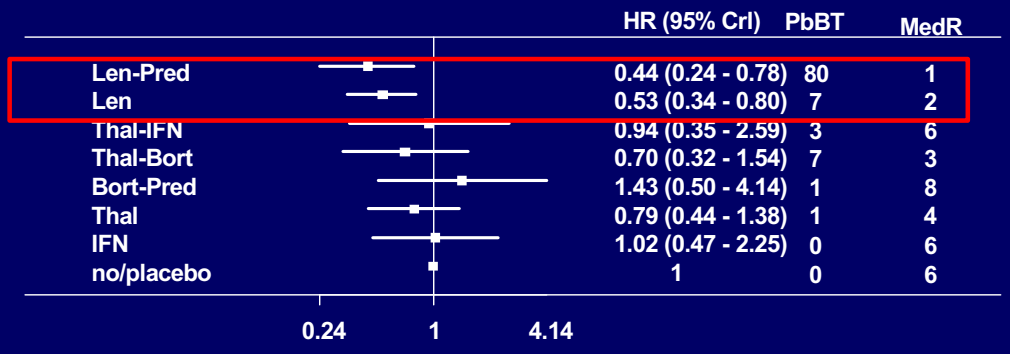




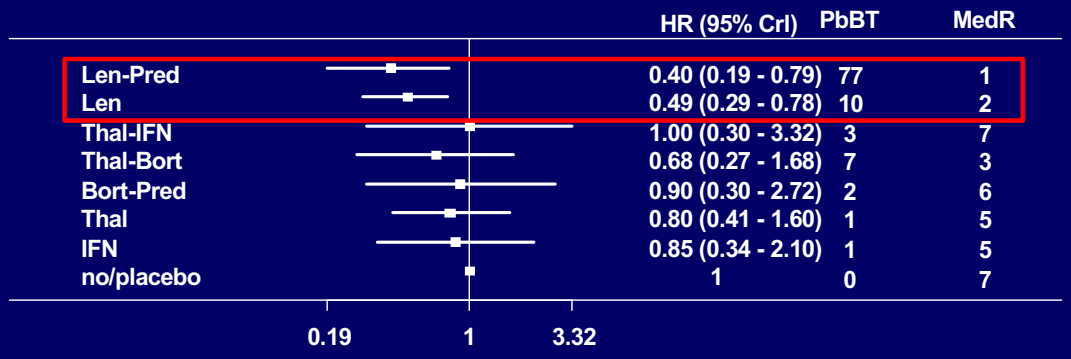
Attal M, et al. NEJM 2012;366:1782, McCarthy PL, et al. NEJM. 2012;366:1770; Palumbo A, et al. NEJM 2014;371:10 , Graham J et al. ASH 2016.

Network metaanalysis of maintenance strategies: Subgroup according to prognostic features

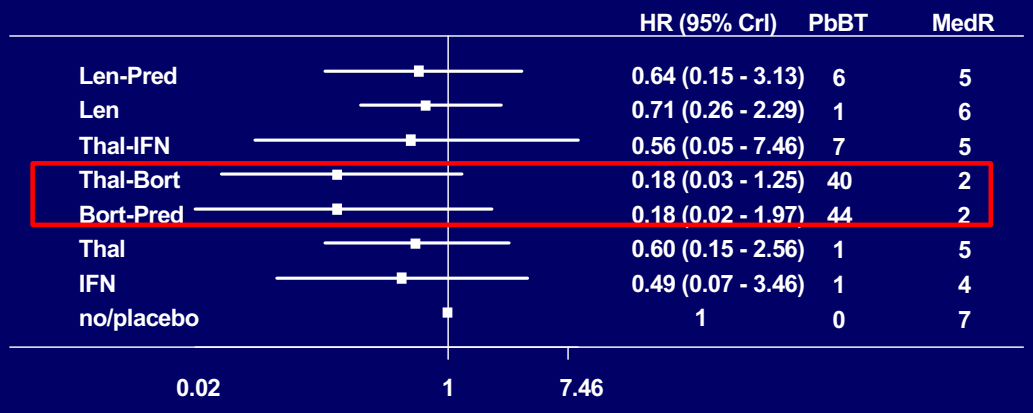
ISS stage I/II



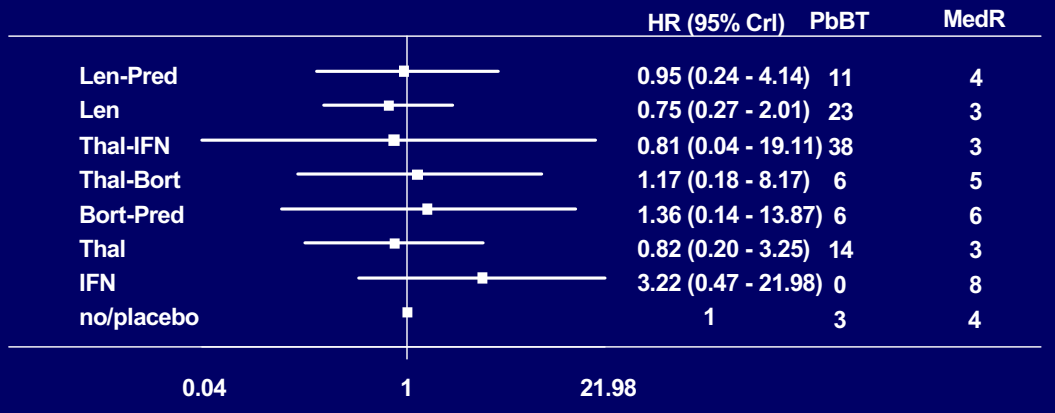
Standard-risk chromosomal abnormalities



ISS stage III



High-risk chromosomal abnormalities



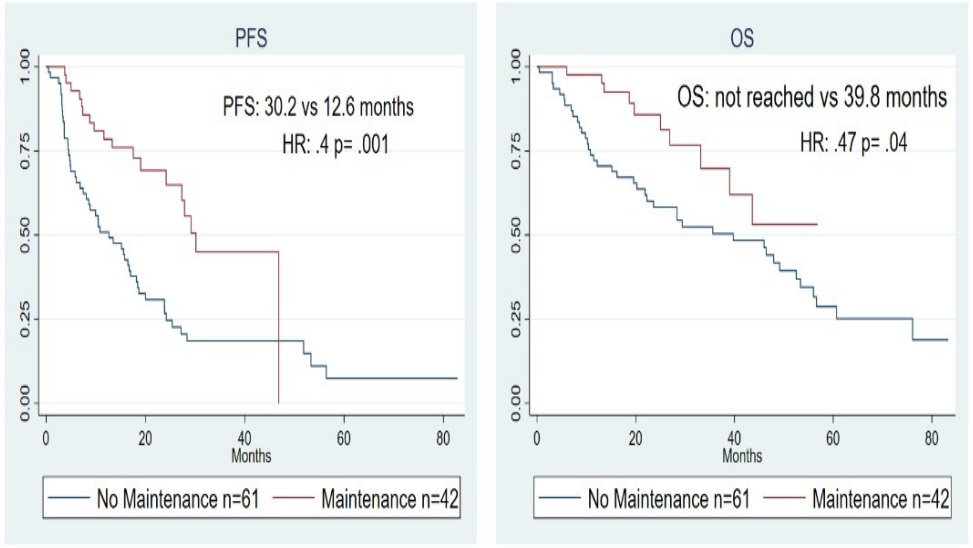
Gay F. et al, Jama Oncol 2018

Bortezomib vs Lenalidomide maintenance: retrospective data

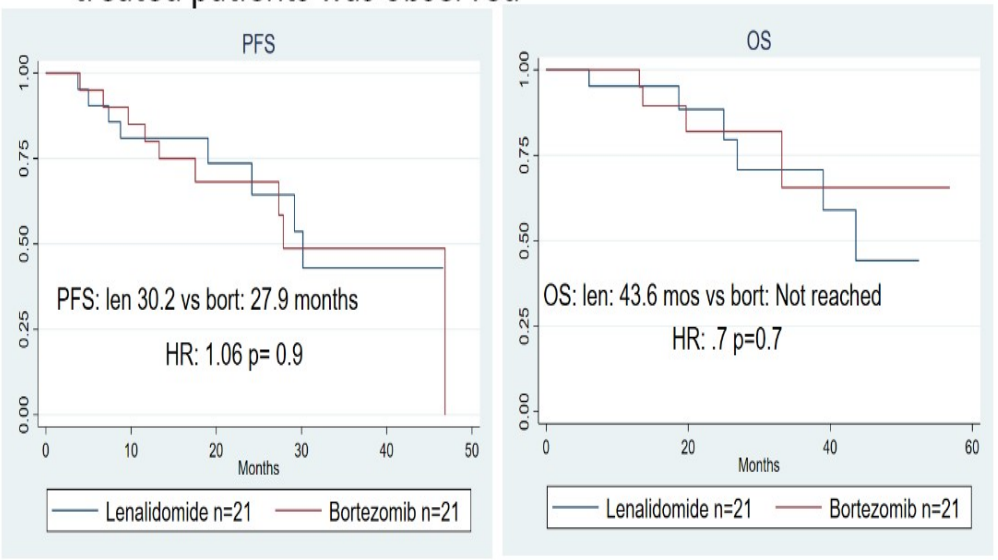
N=103 del17p (51pts) or t(4;14) or t(14;16)

Maintenance, N=42

Maintenance post autologous SCT improves PFS and OS in high risk patients



In HRC patients no difference between the PFS and OS outcome of lenalidomide as compared to bortezomib treated patients was observed

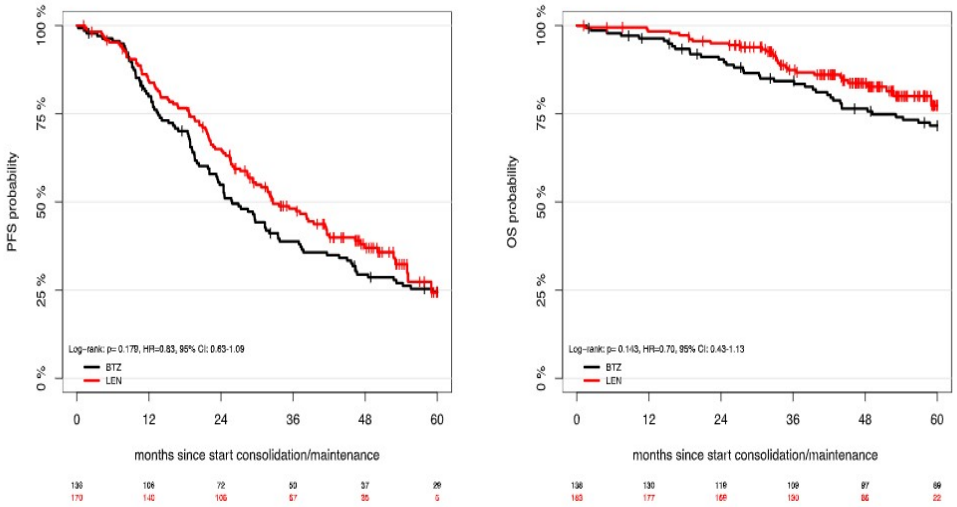


Halahwal A et al IMWG 2019

Bortezomib vs Lenalidomide maintenance: retrospective data

GMMG-HD4 & MM5 trials
Bortezomib based induction
N=321

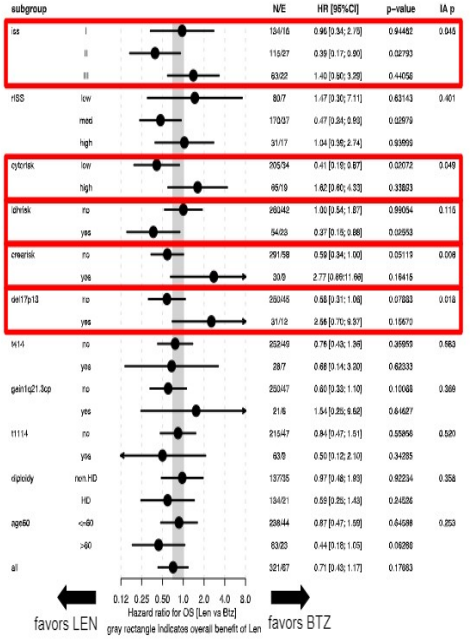
Progression-free and overall survival



- neither PFS (p=0.18) nor OS differed significantly (p=0.14) in the overall cohort
- median PFS was LEN: 32.7 vs. BTZ: 25.9 months, median OS not reached

Response-adjusted analyses on OS

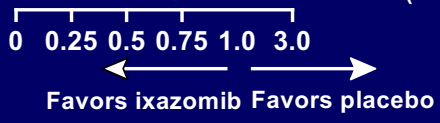
- multivariate model adjusted for response status prior to start of consolidation / maintenance (CR/nCR vs. <nCR)
- significant OS benefit for LEN in ISS stage II, no HR cytogenetics, increased LDH and no RI
- trend towards OS benefit for BTZ in del17p and RI
- no differences in OS from first disease progression between LEN and BTZ cohort (p=0.25, not shown)



Mai EK et al IMWG 2019

Ixazomib vs placebo maintenance: subgroups analysis of PFS

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)



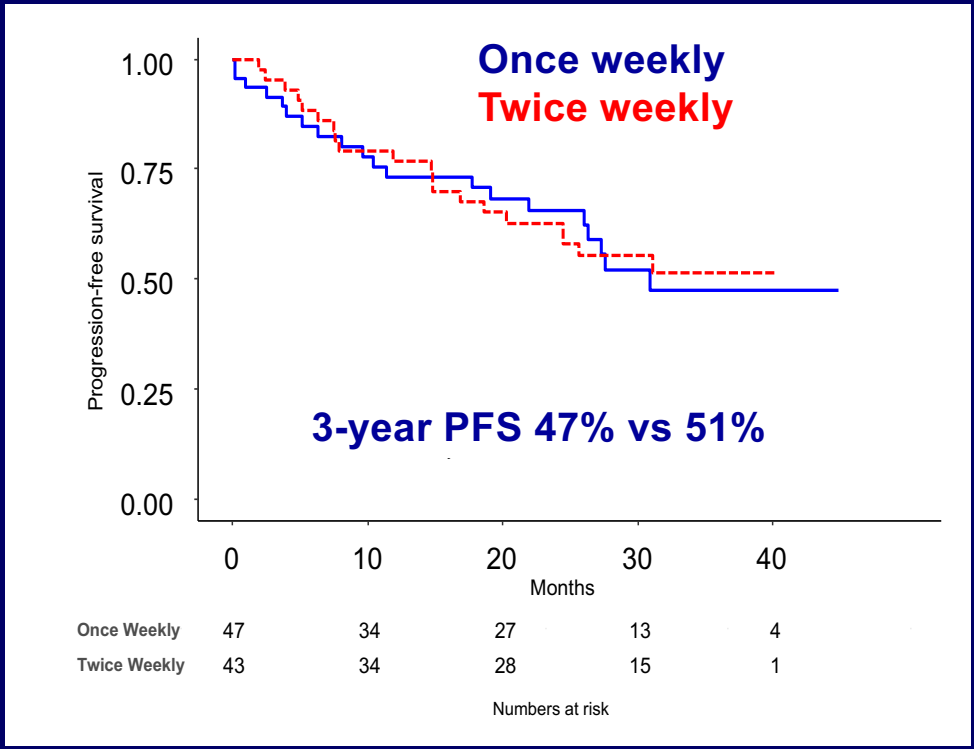
*IMiD use reported by investigator

Dimopoulus M et al ASH 2018.

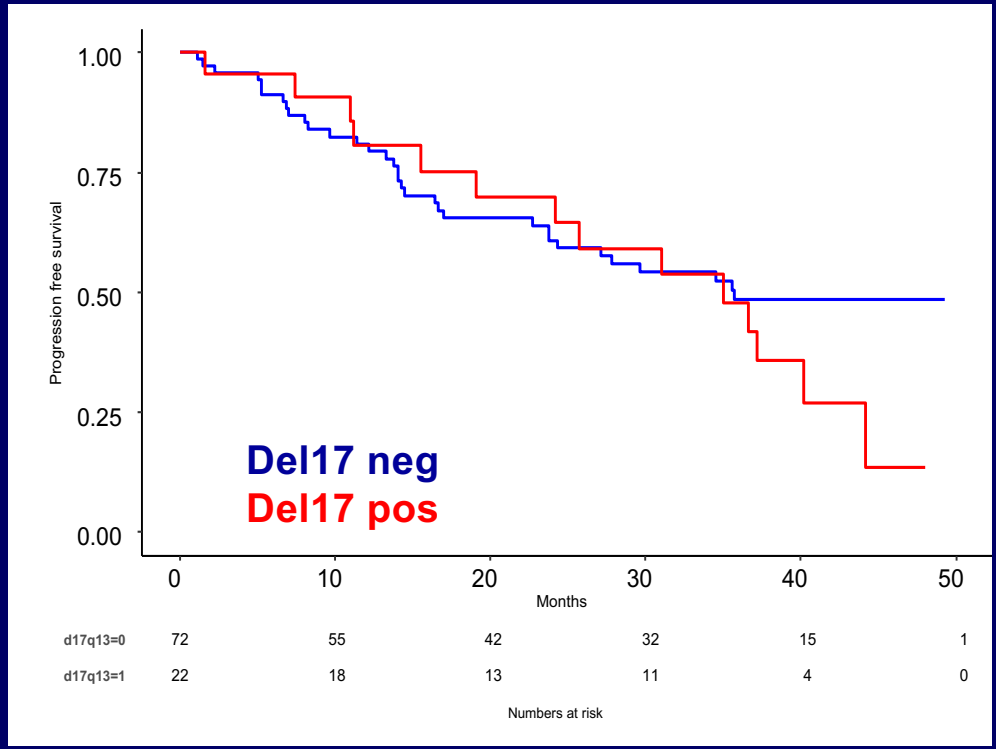
Carfilzomib Maintenance

Pooled analysis ELDERLY PATIENTS, NON TRANSPLANT ELIGIBLE

PFS from maintenance



Subgroup analysis



Bringhen S Hematologica 2019, Mina R et al, ASH 2018

High-risk patients

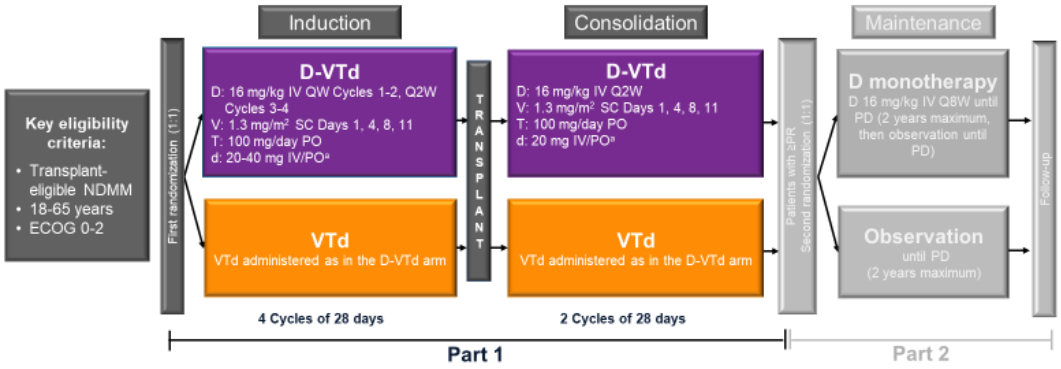
Recommendations for Treatment: TE

- **IMID/PI induction - No preference on PI, len preferred over thal**
- **Depth and speed of response is important**
- **Short duration therapy (4-6 cycles) before consolidation**
- **Avoid low dose alkylators except in the setting of PCL**
- **Role of transplant**
  - Single vs tandem: may be related to access to drugs.
    Tandem not routinely recommended where VRD is an option
- **Post transplant consolidation**
- **Maintenance**
  - Not rev/thal alone
  - PI
  - PI/IMID
  - Emerging role for MOABs

Lonial S et al. IMW 2017

CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017

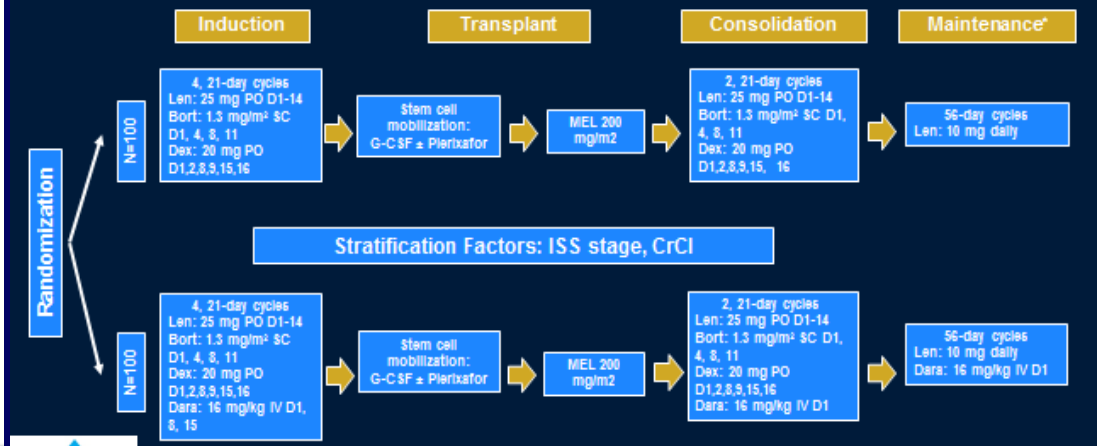


D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Philippe Moreau, MD

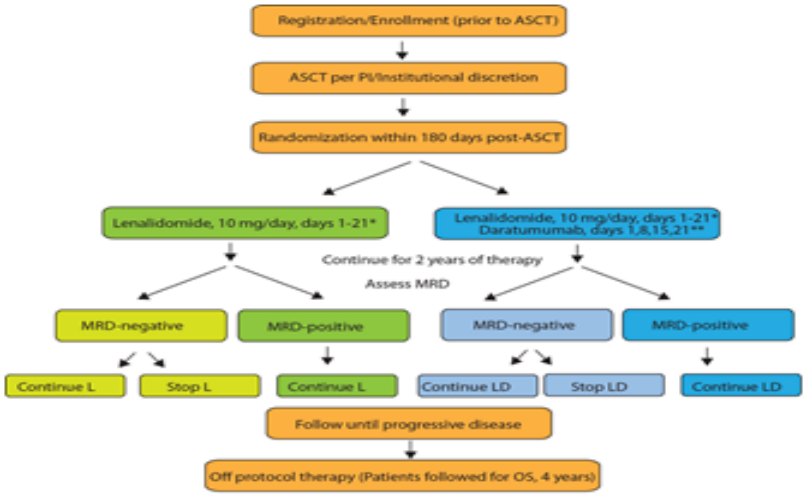
Moreau P et al Lancet 2019[4]

AFT-29 / MMY2004. A randomized, phase II study of lenalidomide, bortezomib and dexamethasone +/- daratumumab with Safety Run-in: P.I. Peter Voorhees



*Maintenance on protocol therapy lasts 2 years but patients are encouraged to remain on lenalidomide monotherapy until disease progression thereafter

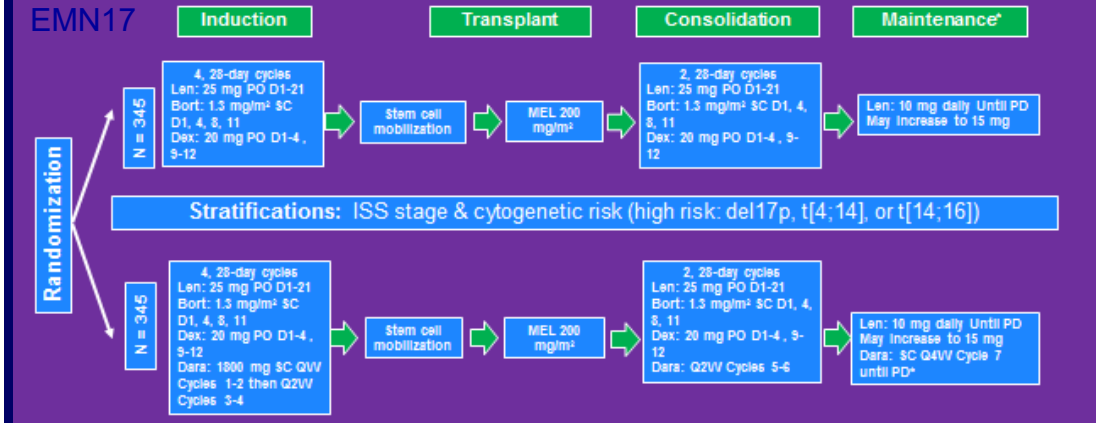
Treatment/Schema



*After 3 months, may be raised to 15 mg/day if ANC and platelet counts acceptable; non heme tox to Gr 0-1
**Dosing will be changed to monthly dosing after month 2

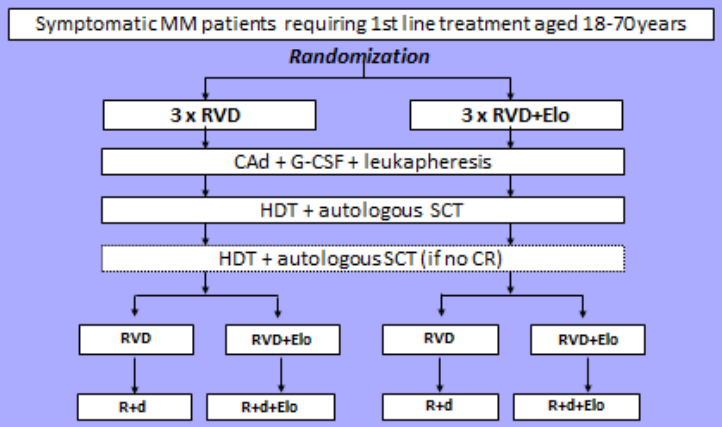
Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DARA) in pts with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): A multicenter, randomized, phase III study (PERSEUS).

EMN17



N=690, Primary Outcome: PFS, ~ up to 9 yrs on protocol therapy. *All pts receive Len until PD. MRD-negative (10^{-5}) NGS, pts in DARA arm will stop DARA after MRD negativity for 12 mo & ≥24 mo of maintenance. Pts continue len maintenance until PD or unacceptable toxicity. For DARA arm pts, Upon loss of CR or MRD-negative status, restart DARA treatment. https://clinicaltrials.gov/ct2/show/NCT03710603

GMMG HD6: NDMM transplant-eligible



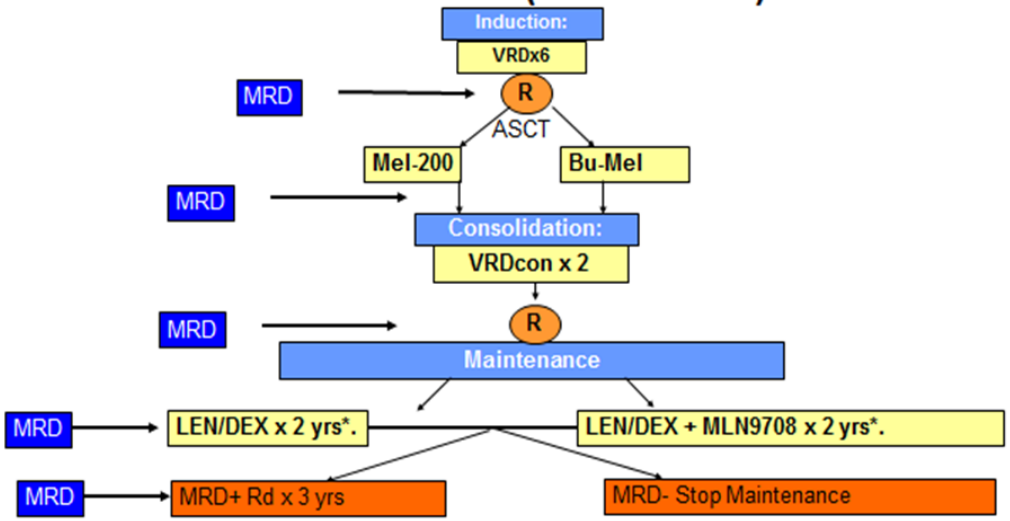
Phase III
Enrollment: n=516, ongoing
FPI Q42014, LPI planned Q4 2017

Primary endpoint: PFS
Maintenance for 26 cycles

EudraCT: 2014-003079-40
ClinicalTrials.Gov NCT02495922

A, Adriamycin; C, Cyclophosphamide; D, Dexamethasone; Elo, Elotuzumab; HDT, High Dos Therapy (melphalan); R, lenalidomide; SCT, Stem Cell Tranplant; V, Bortezomib.

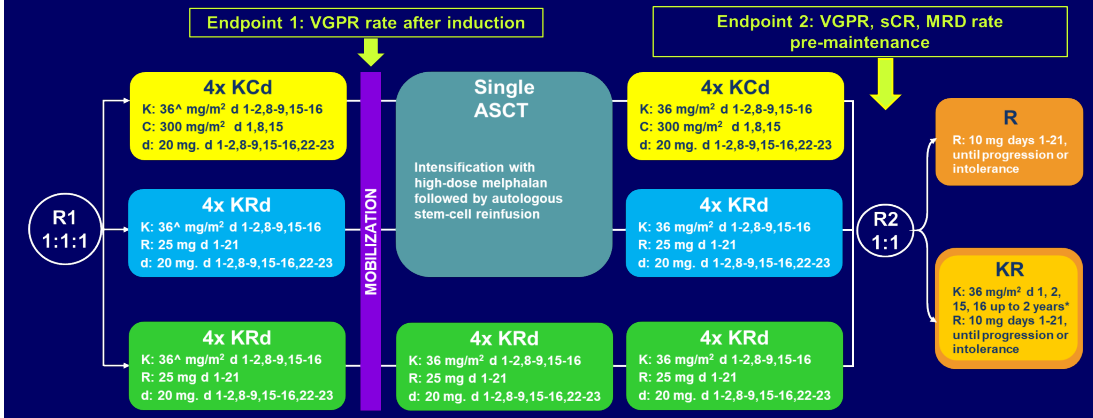
Maintenance (GEM14 MAIN)



* Patients with positive MRD will continue with LEN/DEX for 3 more years

FORTE Trial design

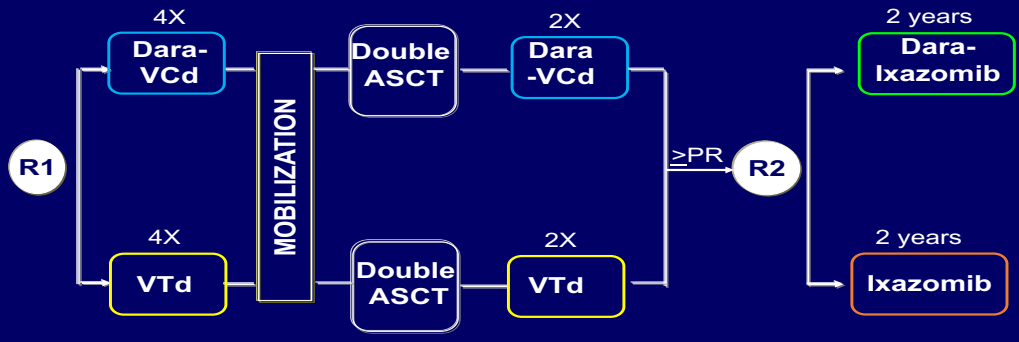
NDMM patients, transplant-eligible and younger than 65 years



^20 mg/m² on days 1-2, cycle 1 only. *Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.
R1, randomization 1; R2, Randomization 2; IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation; R, lenalidomide; KR, carfilzomib, lenalidomide. NDMM, newly diagnosed multiple myeloma; VGPR, very good partial response.

EMN18 Treatment schema

N=400



R: randomization; Dara-VCd: Daratumumab, Bortezomib, Cyclophosphamide, Dexamethasone; VTd:Bortezomib, Thalidomide, Dexamethasone; ASCT: autologous stem cell Transplant: Dex: Dexamethasone

Summary

- Lenalidomide maintenance after ASCT is the current approved standard
- Optimal duration/MRD driven strategy to be adressed
- Unclear benefit in high-risk (definition/sensitivity to lenalidomide)
- Novel combination approach may be better in high-risk patients→ PI/Pis + IMIDs ? MoAbs?
- Prospective trials with random stratified for risk are needed

We are grateful to all patients, nurses and physicians of the participating centers

1.	**ALESSANDRIA**	Ladetto, Baraldi
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3.	**ASCOLI PICENO**	Galieni
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6.	**AVIANO**	Micheli, Rupolo
7.	**BARI**	Silvestris, Ria
8.	**BARI**	Specchia
9.	**BENEVENTO**	Vallone
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37.	**MANTOVA**	Franchini, Zamagni
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39.	**MESSINA**	Mannina
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42.	**MILANO**	Cairoli, Cafro
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86.	**TORINO**	Vitolo, Pregno, Benevolo
87.	**TORINO**	Saglio
88.	**TREVISO**	Gherlinzoni
89.	**TRICASE**	Pavone
90.	**TRIESTE**	Festini, De Sabbata
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