LA PROGNOSI DEL MIELOMA MULTIPLO:

LA TERAPIA DI MANTENIMENTO HA UN RUOLO OGGI?

CESENA
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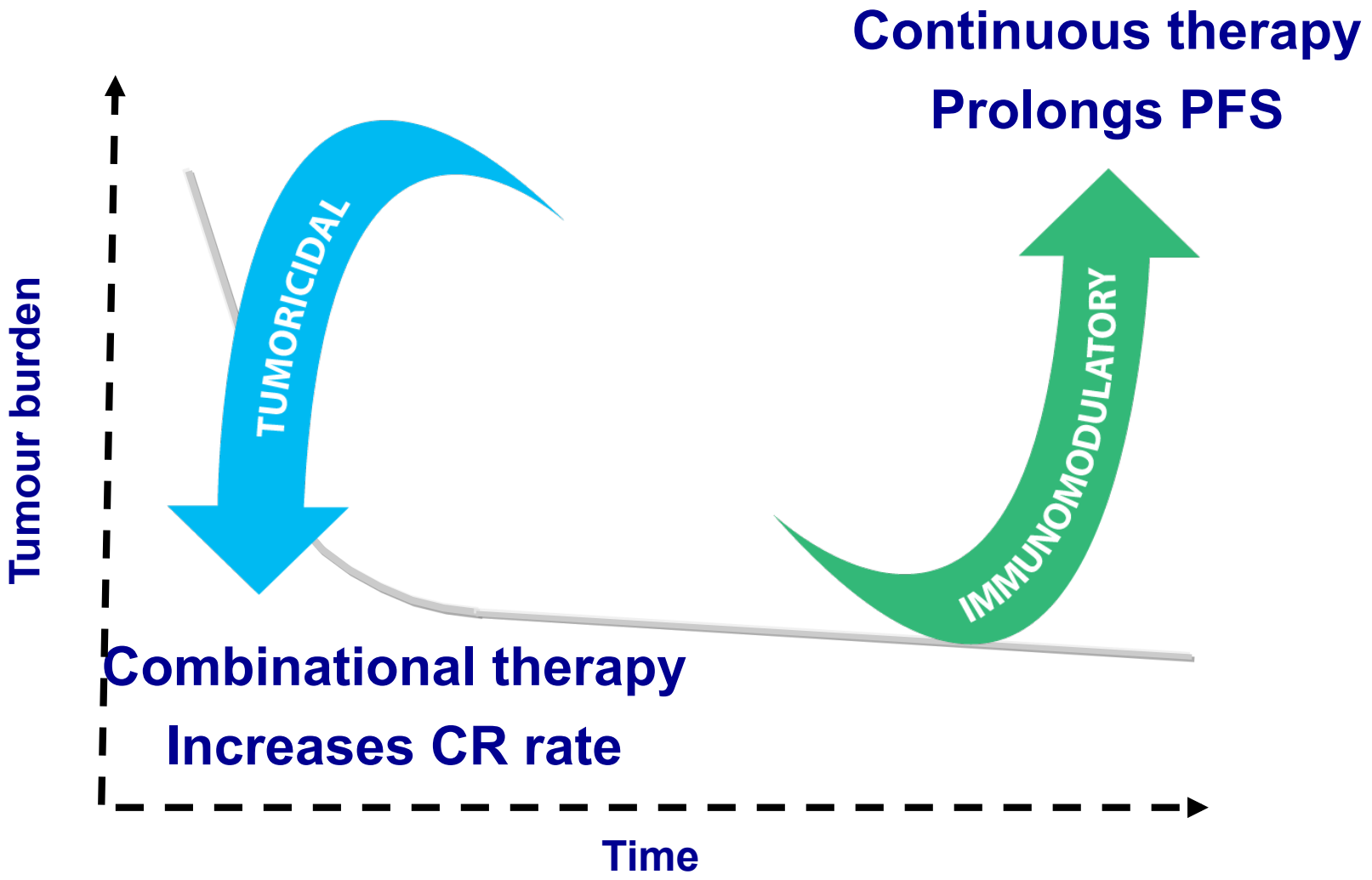
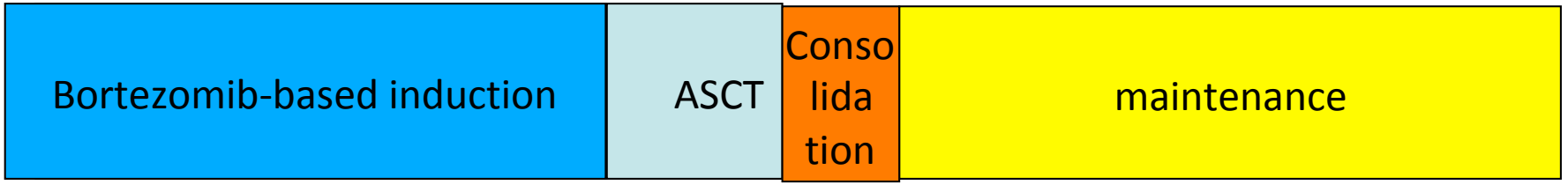
Treatment strategy



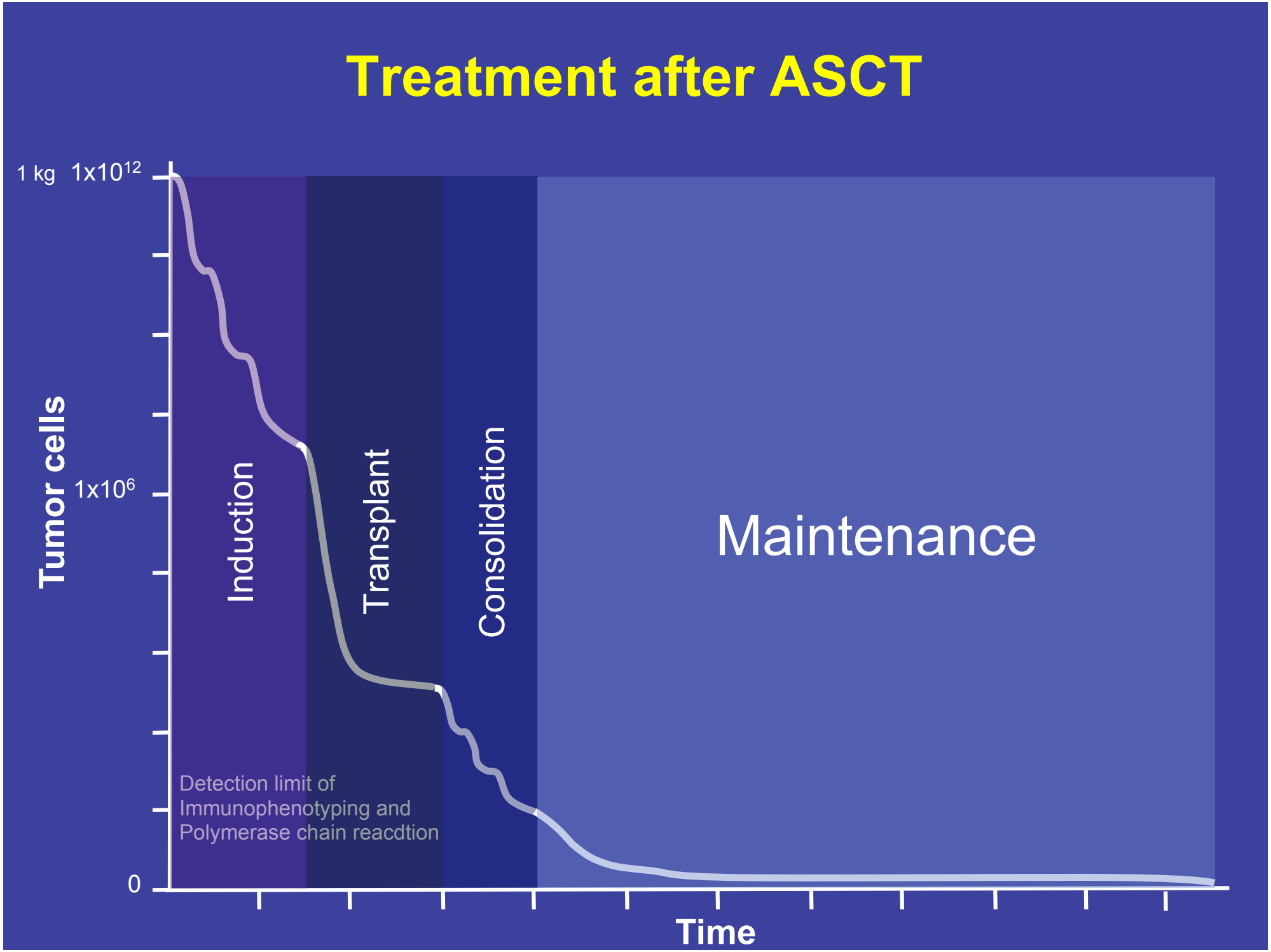
Newly diagnosed fit MM < 70 years



Maintenance options:

- Thalidomide 50-100 mg (648 law)
- Lenalidomide 10 mg (registred indication since 2018)
- Protesoma inhibitors (investigational)

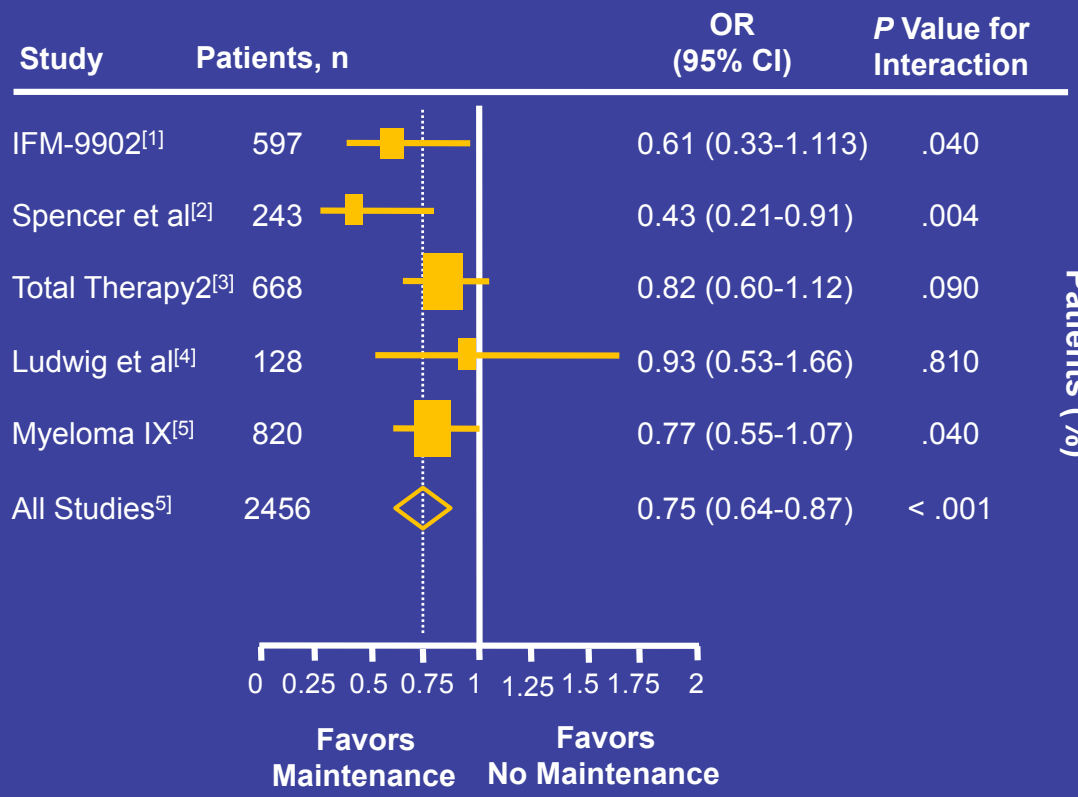
Treatment after ASCT

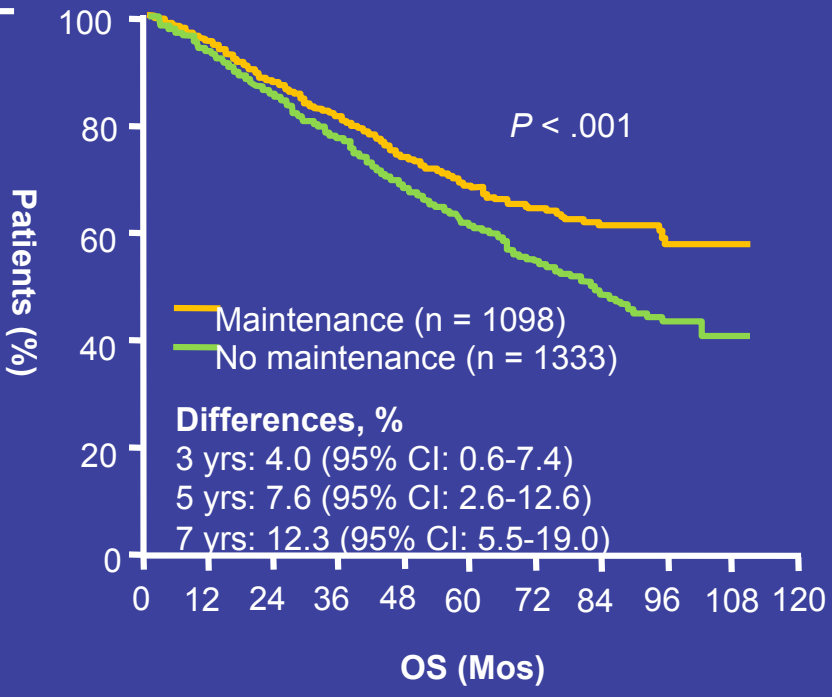


Thalidomide maintenance
Discontinuation and toxicity

study	Discontinuation %	Main toxicity %
TT2[1,2]	30%	Polineuropathy all grade 68%
IFM 99-02[3]	39 %	Polineuropathy grade III-IV 7 %
ALLG MM6[4]	30%	Polineuropathy grade III-IV 10 %
MRC Myeloma IX[5]	52%	VTE 7%
HOVON 50[6]	58%	Polineuropathy all grade 50%

Meta-analysis of Myeloma IX, Other Studies: Late OS Benefit With Thalidomide maintenance

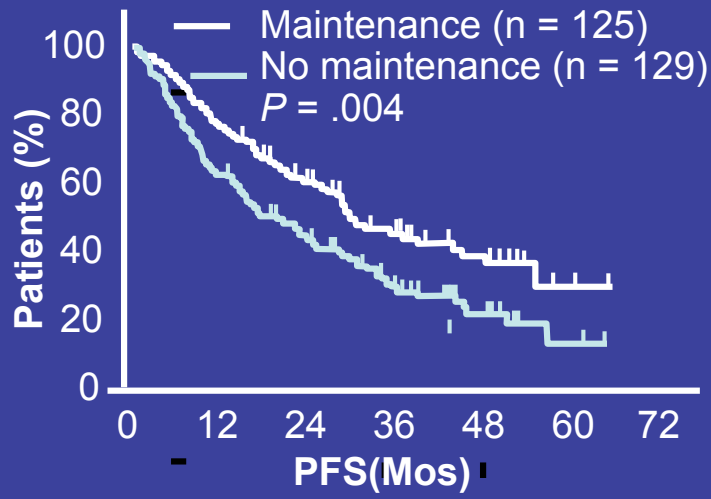


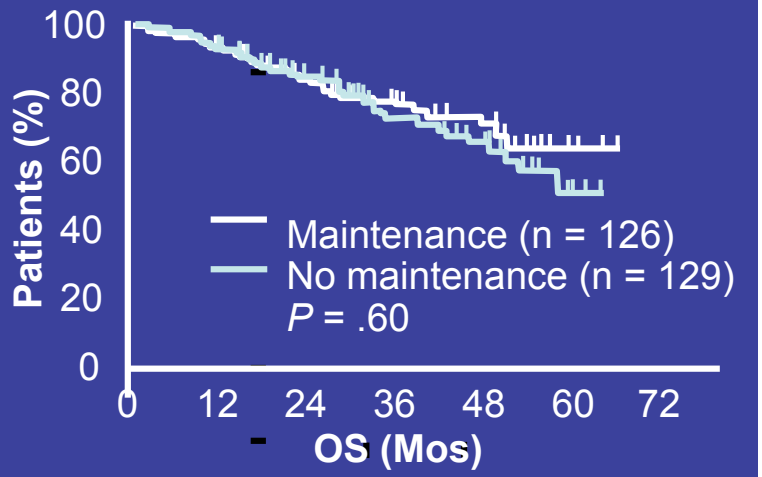


1. Attal M, et al. Blood. 2006;108:3289-3294. 2. Spencer A, et al. J Clin Oncol. 2009;27:1788-1793.
3. Barlogie B, et al. Blood. 2008;112:3115-3121. 4. Ludwig H, et al. Haematologica. 2010;95:1548-1554.
5. **Morgan GJ, et al. Blood. 2012;119:7-15.**

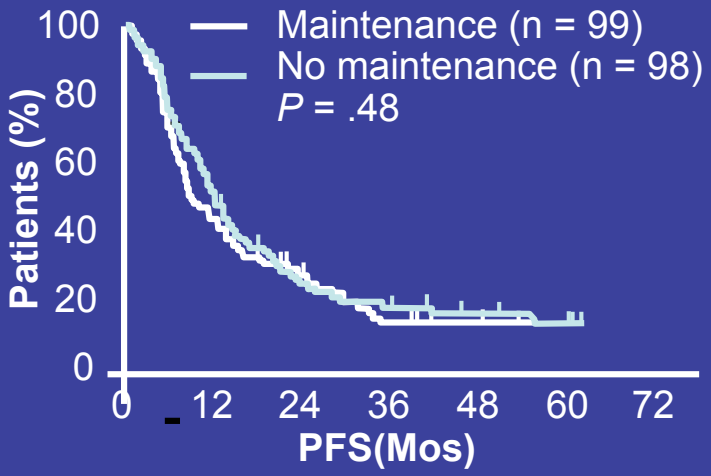
Myeloma IX: Thalidomide Maintenance Effects Differ Based on Cytogenetic Status

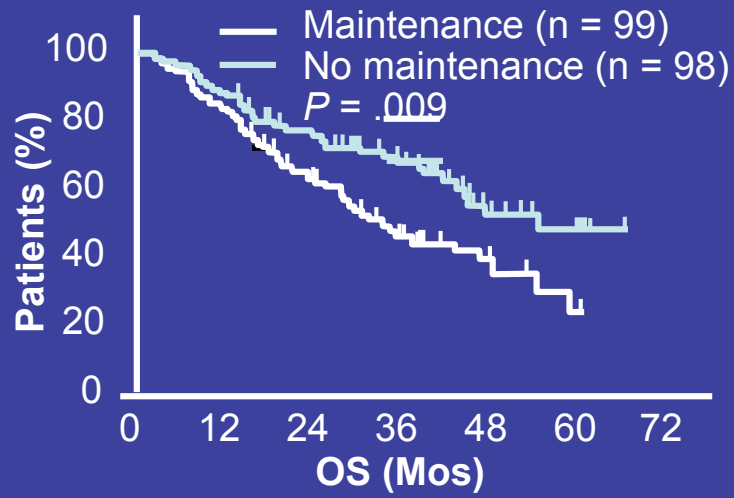
Favorable iFISH





Adverse iFISH



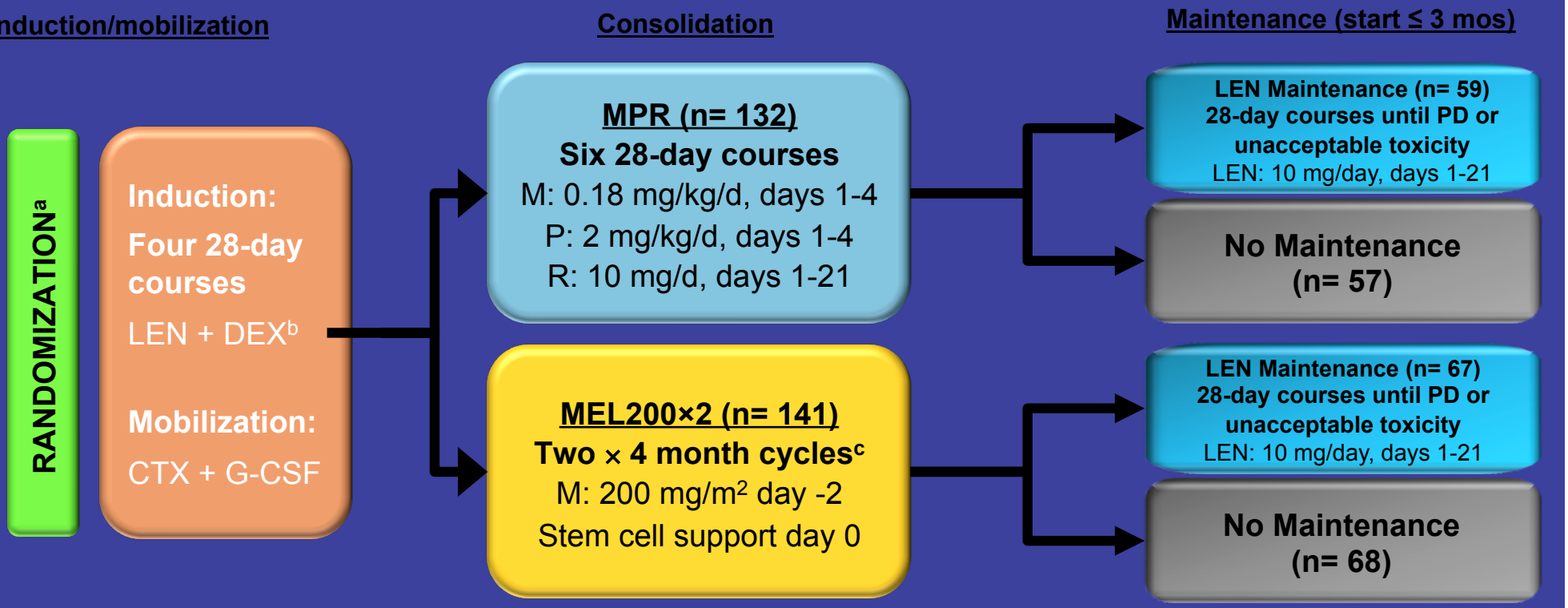


Morgan GJ, et al. Blood. 2012;119:7-15

GIMEMA RV 209 MPR vs. MEL200×2 ± LEN Maintenance

Trial Schema (Randomized, open-label 2-by-2 factorial design)

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, TTR, and safety

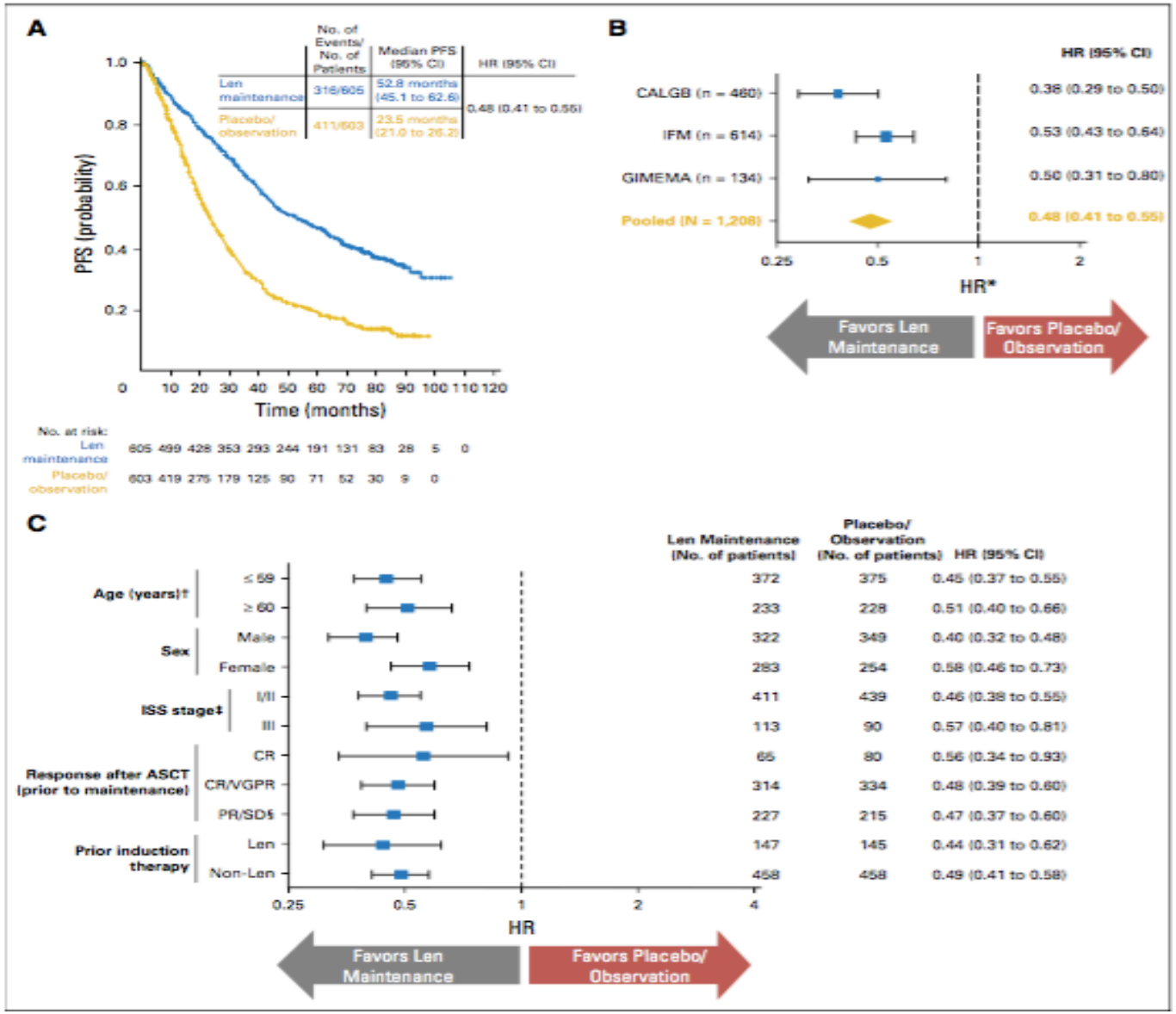


Randomisation: MPR vs. MEL200×2; R maintenance vs. no maintenance; Anti-thrombotic substudy: Aspirin vs. Low molecular weight heparin. [a]Both randomizations were performed at start and concealed until end of induction period for the consolidation treatment and until the end of consolidation treatment for the maintenance treatment. [b]LEN + DEX (LEN: 25mg/d, days 1-21; DEX: 40mg/d, days 1, 8, 15, 22). [c]One course MEL200 if patients achieves VGPR after cycle 1.

CTX: cyclophosphamide; d, day; DEX, dexamethasone; G-CSF, granulocyte colony stimulating factor; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; LEN, lenalidomide; M, melphalan; MEL200×2, melphalan 200mg/m^2 and tandem autologous stem-cell transplant; MPR, melphalan, prednisone, and lenalidomide; ORR, overall response rate; OS, overall survival; P, prednisone; PD, progressive disease; PFS, progression-free survival; R, lenalidomide; TTR, time to response; VGPR, very good partial response.

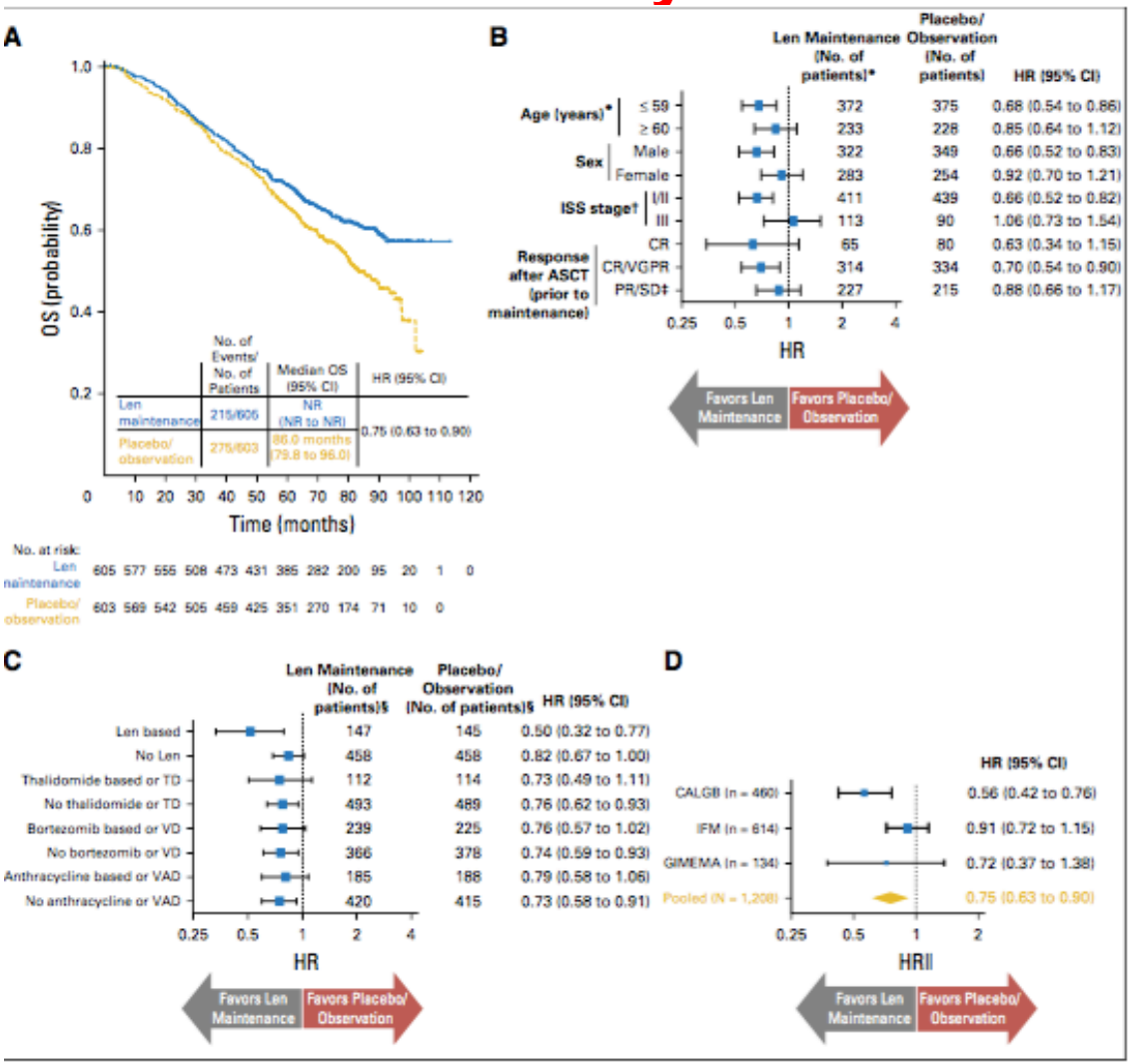
Palumbo A, et al. *N Engl J Med*. 2014;371:895-905.

Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis: PFS



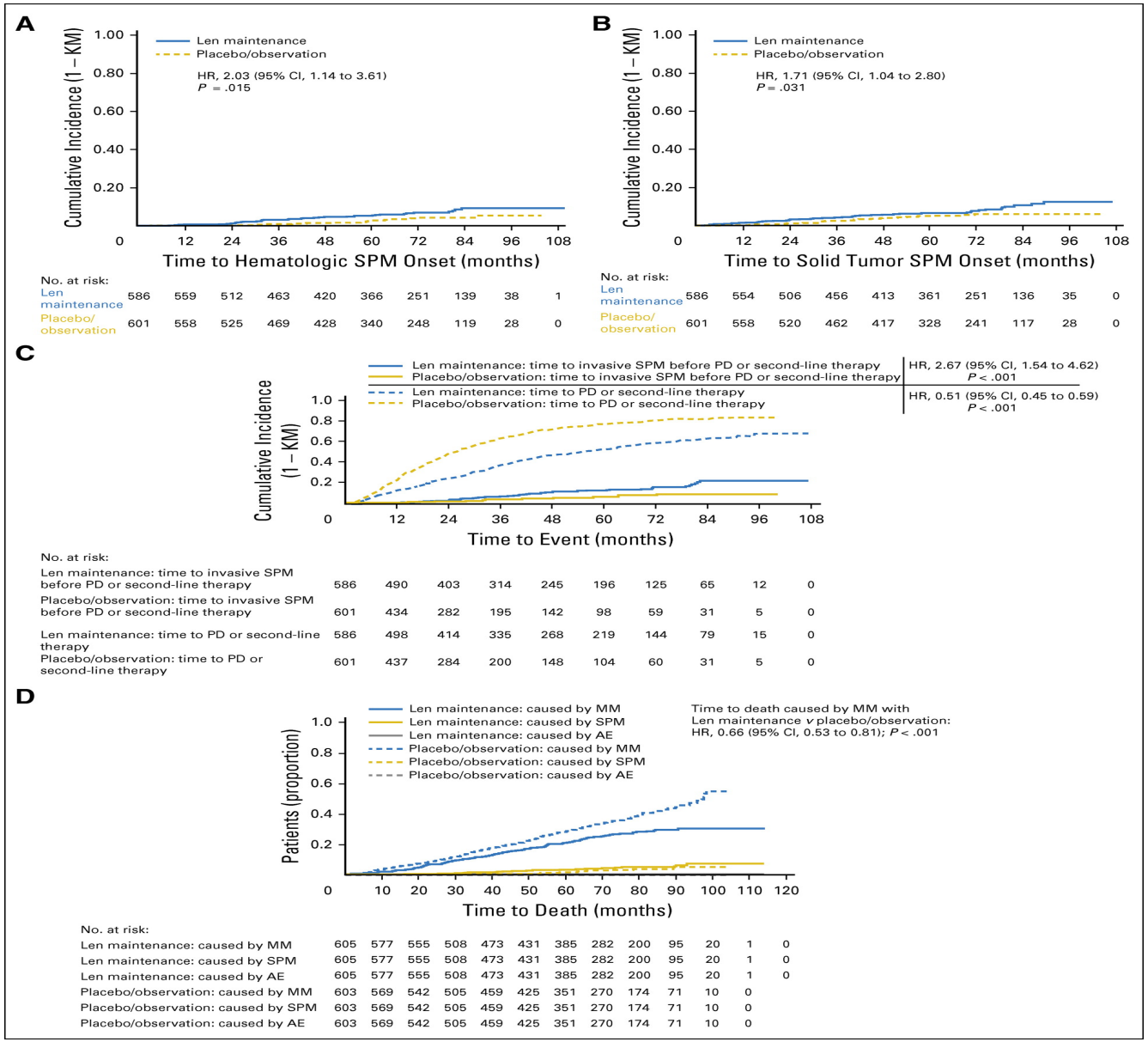
McCharthy et al, JCO 2017

Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis: OS



McCharthy et al, JCO 2017

Second primary malignancies



McCharthy et al, JCO 2017

Lenalidomide maintenance in the Myeloma XI UK Trial

Up-date outcome analysis of the Myeloma XI trial, the largest maintenance study performed to date comparing the impact of lenalidomide to no maintenance.

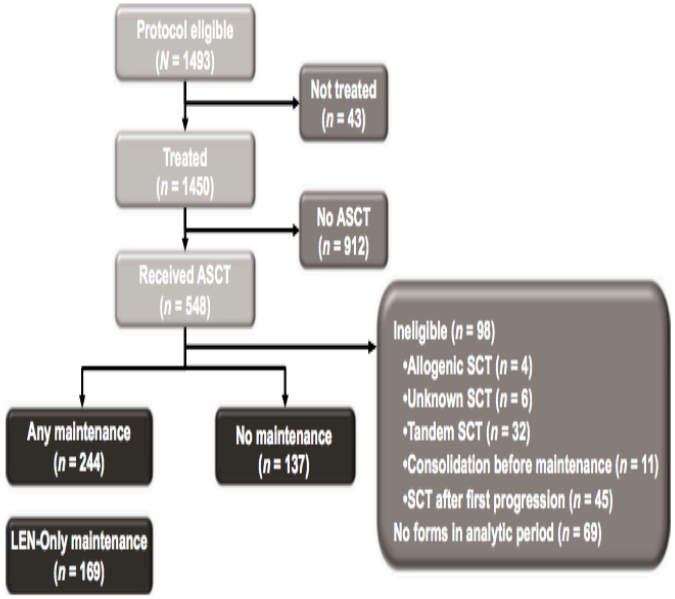
1970 patients , 1247 transplant eligible (TE) and 723 transplant-non-eligible (TNE), median age 61 and 74 years , were randomized between lenalidomide 10 mg day 21/28 (n.1136) and observation (n.834)

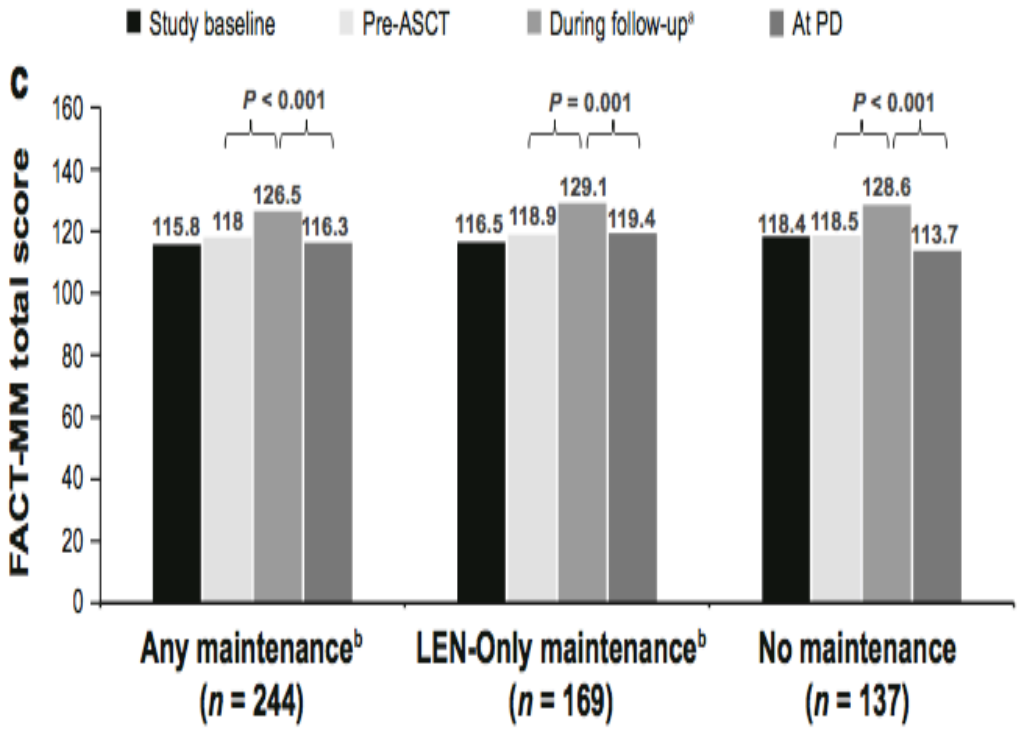
	Lenalidomide	Observation	HR
Median PFS, all	39.1 mo	19.9 mo	0.46
Median PFS, TE	60.3 mo	30.1	0.47
Median PFS, TNE	25.7 mo	11.0	0.44
Median PFS, with del(17p) and or t(4;14)	24.7 mo	10.5	0.31
Median PFS, without del(17p) and or t(4;14)	60.4 mo	30.7	0.35

Lenalidomide maintenance improved outcome irrespective of risk status.

Jackson G et al, ASH 2017, abstract 436

Impact of post-transplantation maintenance therapy on health-related quality of life

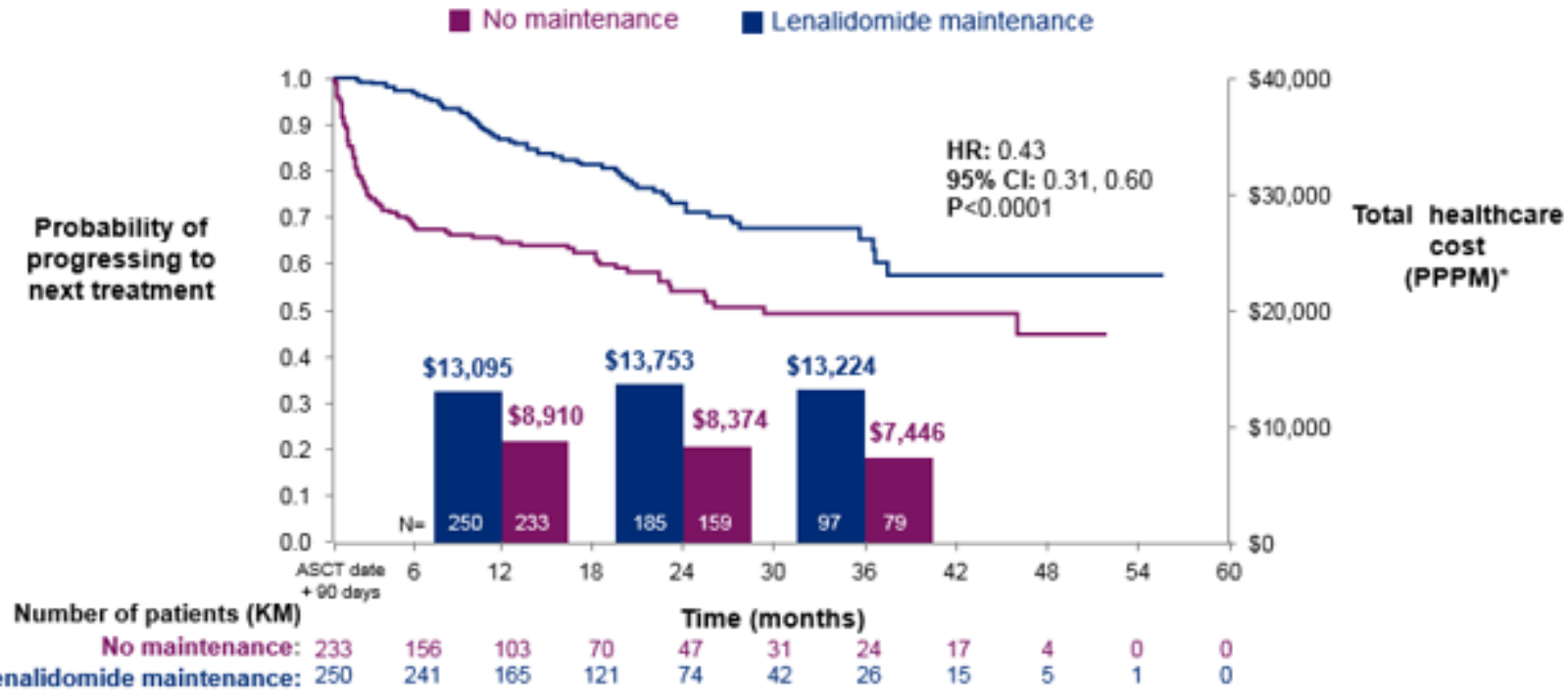




ASH Meeting 2017

Cost-effectiveness of lenalidomide maintenance after ASCT

Figure 1. Time to Next Treatment and Total Healthcare Cost per Patient per Month for Patients Receiving R-MT vs No-MT Post ASCT



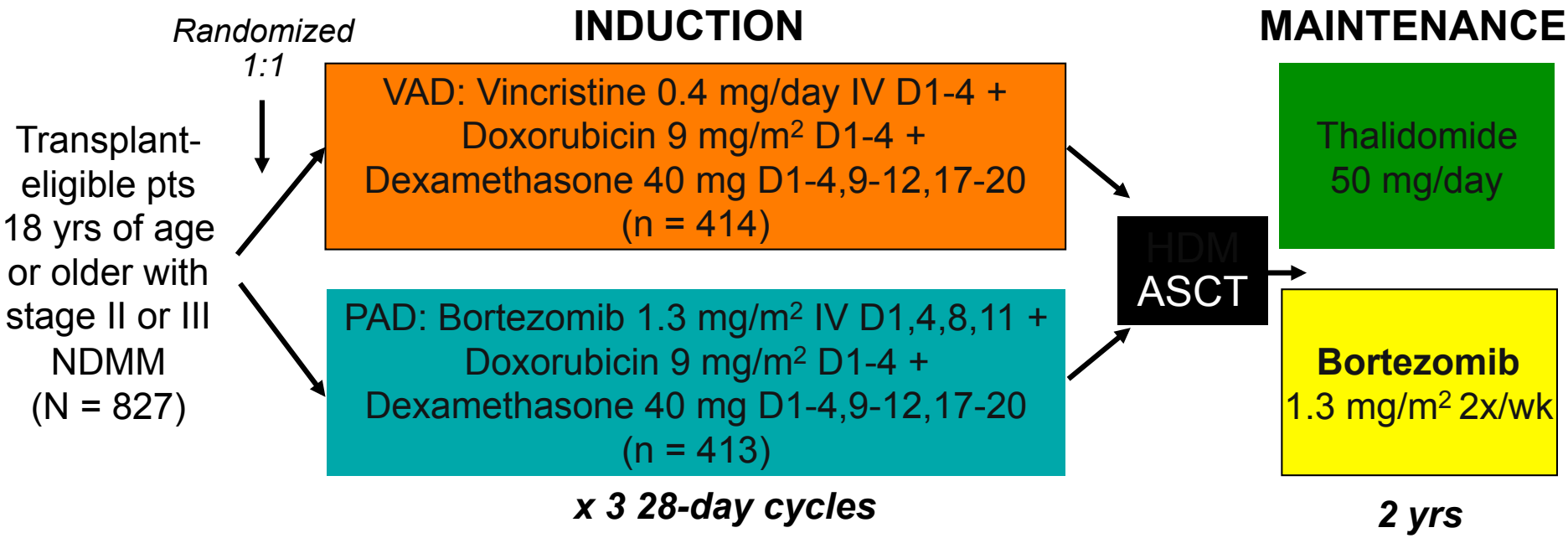
KM=Kaplan-Meier; PPPM=per patient per month
**Total PPPM healthcare costs were measured from 0–12 months, 12–24 months, and 24–36 months*

ASH Meeting 2017

Maintenance with proteosoma inhibitors

HOVON-65/GMMG-HD4 Study

- Randomized, open-label phase III trial



- HDM 200 mg/m^2: 1 cycle for HOVON, 2 cycles for GMMG
- Primary endpoint: PFS adjusted for ISS stage
- Secondary endpoints: Response after induction, HDM and on protocol; OS from randomization; safety; PFS from HDM

Sonneveld P, et al. J Clin Oncol. 2012;30:2946-2955. Sonneveld P, et al. ASH 2015. Abstract 27. Goldsmidth et al, Leukemia 2018

HOVON-65/GMMG-HD4: Efficacy

Outcome	PAD/Bort (n = 413)	VAD/Thal (n = 414)
Best response, %		
▪CR	37	25
▪nCR	13	10
▪VGPR	26	21
▪ORR	91	83
96-mo PFS, %	17	10
HR (95% CI; P value)	0.77 (0.65-0.90; .001)	
96-mo OS, %	48	45
HR (95% CI; P value)	0.87 (0.71-1.04; .22)	

Sonneveld P, et al. ASH 2015. Abstract 27

Goldsmidth et al, Leukemia 2018.

HOVON-65/GMMG-HD4: Double ASCT/HDM Subgroup Analysis II: OS

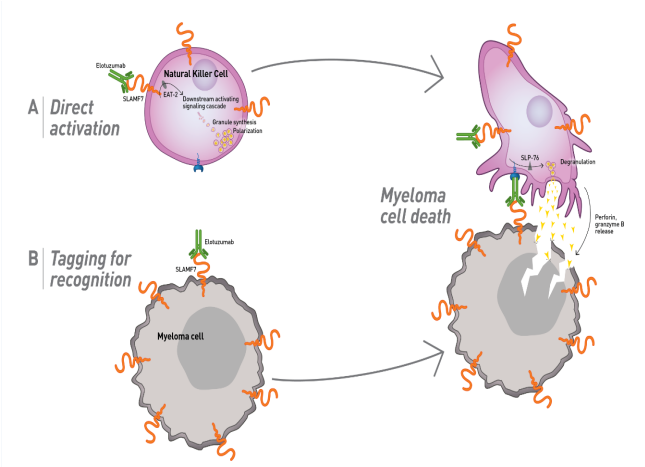
60 m-Survival by Subtype, %	PAD/Bort (n = 413)		VAD/Thal (n = 414)	
	Yes	No	Yes	No
Renal impairment (96 mos)	47	48	12	42
	(P = .6)		(P < .001)	
t(4;14)	33	64	52	75
	(P = .02)		(P = .01)	
amp(1q)	57	79	43	70
	(P < .007)		(P < .001)	
del(17p)	65	72	18	66
	(P = .5)		(P < .001)	

*

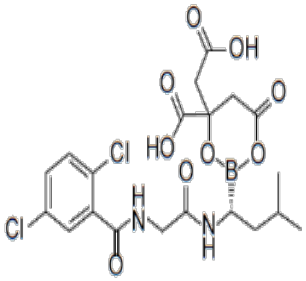
Sonneveld P, et al. ASH 2015. Abstract 27
Goldsmidthet al, Leukemia 2018.

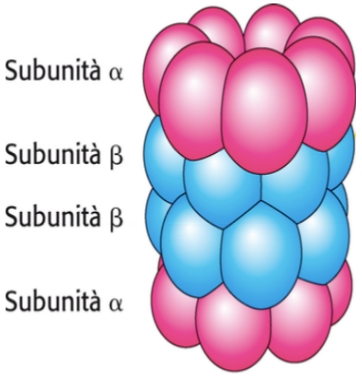
CURRENT AND FUTURE PHASE III TRIALS

Study Eligibility	Induction	AHSCT	Consolidation	Maintenance	Issue being addressed
IFM/DFCI All SCT eligible	VRD x 4	Mel200 Early vs Late	VRD x 2	Lenalidomide until PD in US x 12 months in Europe	Early vs Late SCT Duration of maintenance
ECOG E1A11[2] ENDURANCE Trial Standard Risk Myeloma	VRD vs CRD	At progression		R x 24 cycles versus until PD	Role of carfilzomib in induction Duration of maintenance therapy
ELOQUENT-1[3] Non SCT Eligible	Rd vs Rd Elo			Until PD	Role of elotuzumab in non SCT eligible patients
SWOG 1211 High risk cytogenetics SCT and Non SCT eligible	RVD vs RVD Elo			CR/PR/SD until progression	
BMT CTN 1302	Any	Single Allo Flu/Mel/ V		Ixazomib vs placebo	Allografting for high risk disease
BMT CTN 1401	Any	Single Auto	MM Dendritic Cell fusion vaccine	Len DC Vaccine vs Len	Efficacy of DC vaccine in myeloma
US Intergroup All patients post auto SCT	Any	Single Auto		Len Ixazomib vs Len until PD	Role of ixazomib Maintenance



ELOTUZUMAB





IXAZOMIB

Efficacy and safety of long-term Ixazomib maintenance

Figure: Landmark analysis of PFS from start of maintenance

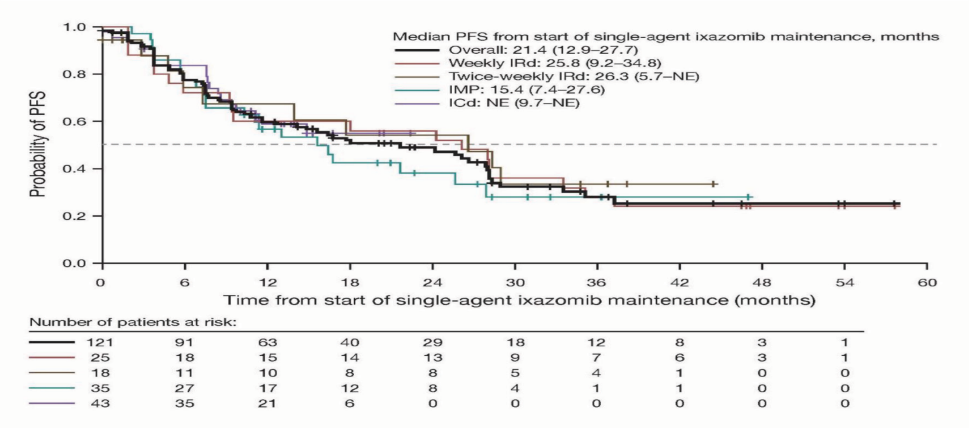


Table: Most common any-grade, all-cause AEs and grade ≥3 drug-related AEs (≥2% of pts) during induction and during maintenance

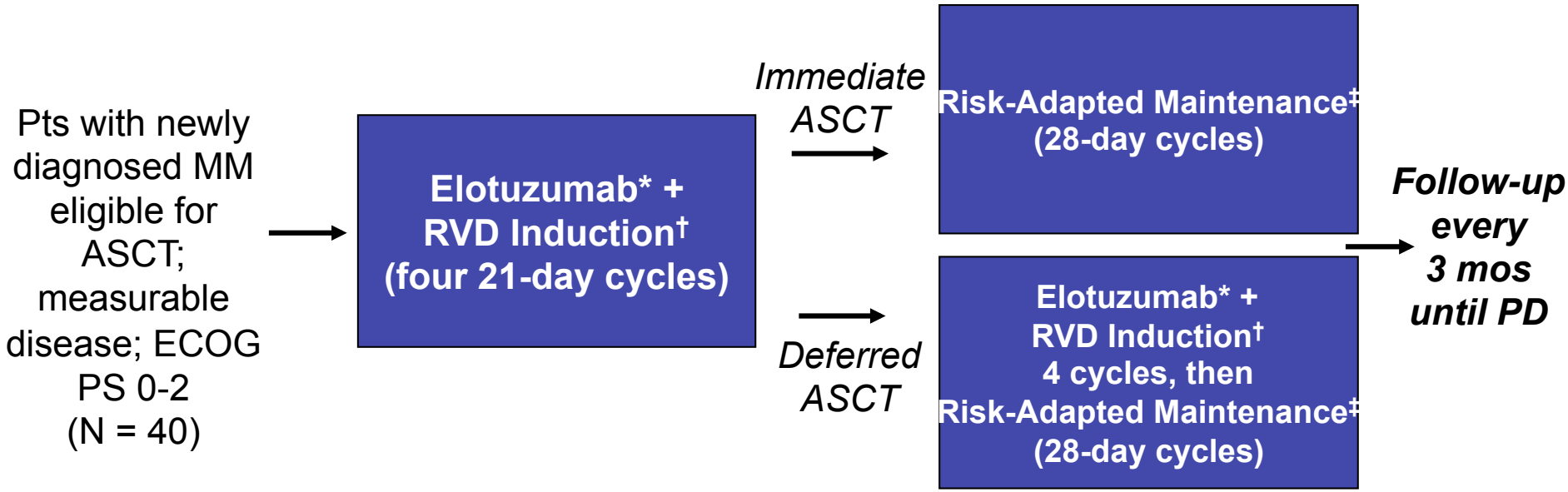
	Incidence during induction (N=121)		Incidence during maintenance (N=121)	
n (%)	Any-grade AEs	Grade ≥3 AEs	Any-grade AEs	Grade ≥3 AEs
Hematologic				
Thrombocytopenia	42 (35)	20 (17)	17 (14)	3 (2)
Neutropenia	41 (34)	27 (22)	11 (9)	3 (2)
Lymphopenia	20 (17)	11 (9)	4 (3)	3 (2)
Anemia	30 (25)	5 (4)	16 (13)	2 (2)
Non-hematologic				
Rashes, eruptions, and exanthems NEC*	57 (47)	8 (7)	24 (20)	2 (2)
Nausea	53 (44)	2 (2)	21 (17)	2 (2)
Peripheral neuropathies NEC*	52 (43)	2 (2)	16 (13)	1 (<1)
Diarrhea	51 (42)	3 (2)	33 (27)	3 (2)
Arthralgia	18 (15)	0	21 (17)	2 (2)
Dizziness	16 (13)	1 (<1)	13 (11)	2 (2)

*NEC, not elsewhere classified, high-level term incorporating multiple preferred terms

Dimopoulos MA et al, ASH 2017, abstract 902

Elotuzumab + RVD in ND MM: Study Design

- Open-label, single-arm phase II a study

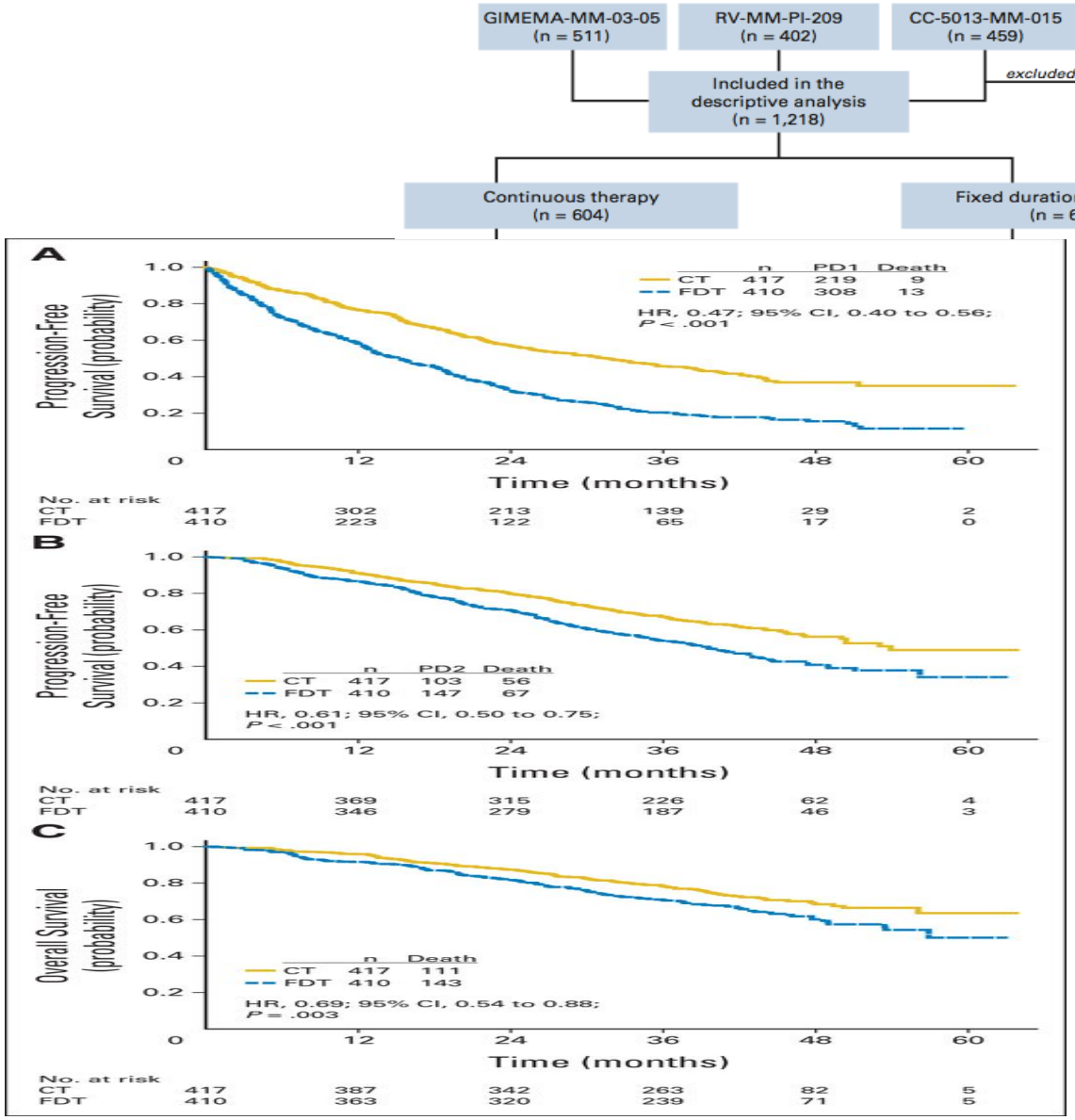


‡High risk (ISS stage III and/or high-risk cytogenetics): ELO + RVD; standard risk (ISS stage I/II w/o high-risk cytogenetics): ELO + Len/Dex.

- Primary objective: response rate after 4 cycles of ELO + RVD
- Secondary objectives: proportion of pts with SC mobilization after 4 cycles ELO + RVD; proportion with dose modification within 4 cycles ELO + RVD; safety; clinical activity

Laubach J, et al. ASCO 2017. Abstract 8002.

continuous therapy versus fixed duration of therapy in newly diagnosed elderly patients

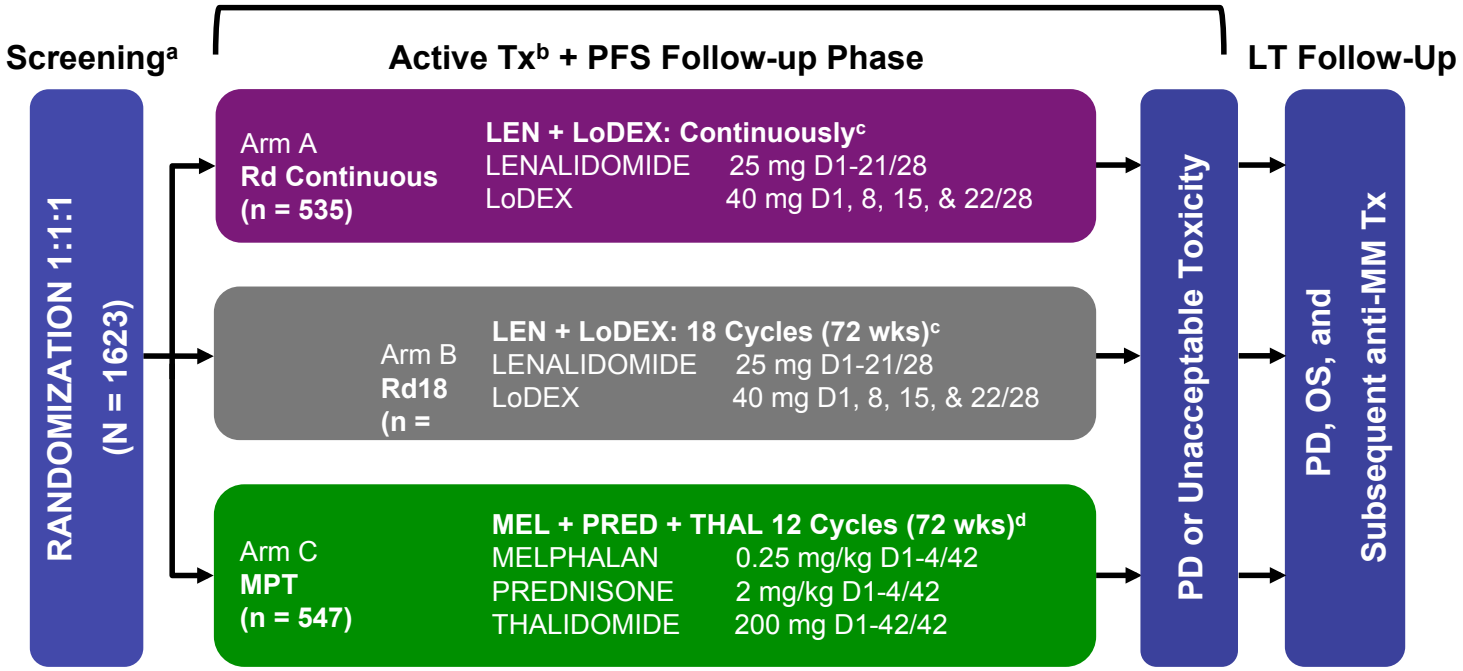


newly diagnosed elderly pts coming from 3 GIMEMA trials comparing continuous therapy (CT) versus fixed therapy (FDT) with novel drugs

comparison of PFS1 (time between random and first relapse), PFS2 (time from random to second disease progression,) and OS

Antonio Palumbo et al. JCO 2015;33:3459-3466

Final analysis of survival outcomes in FIRST study



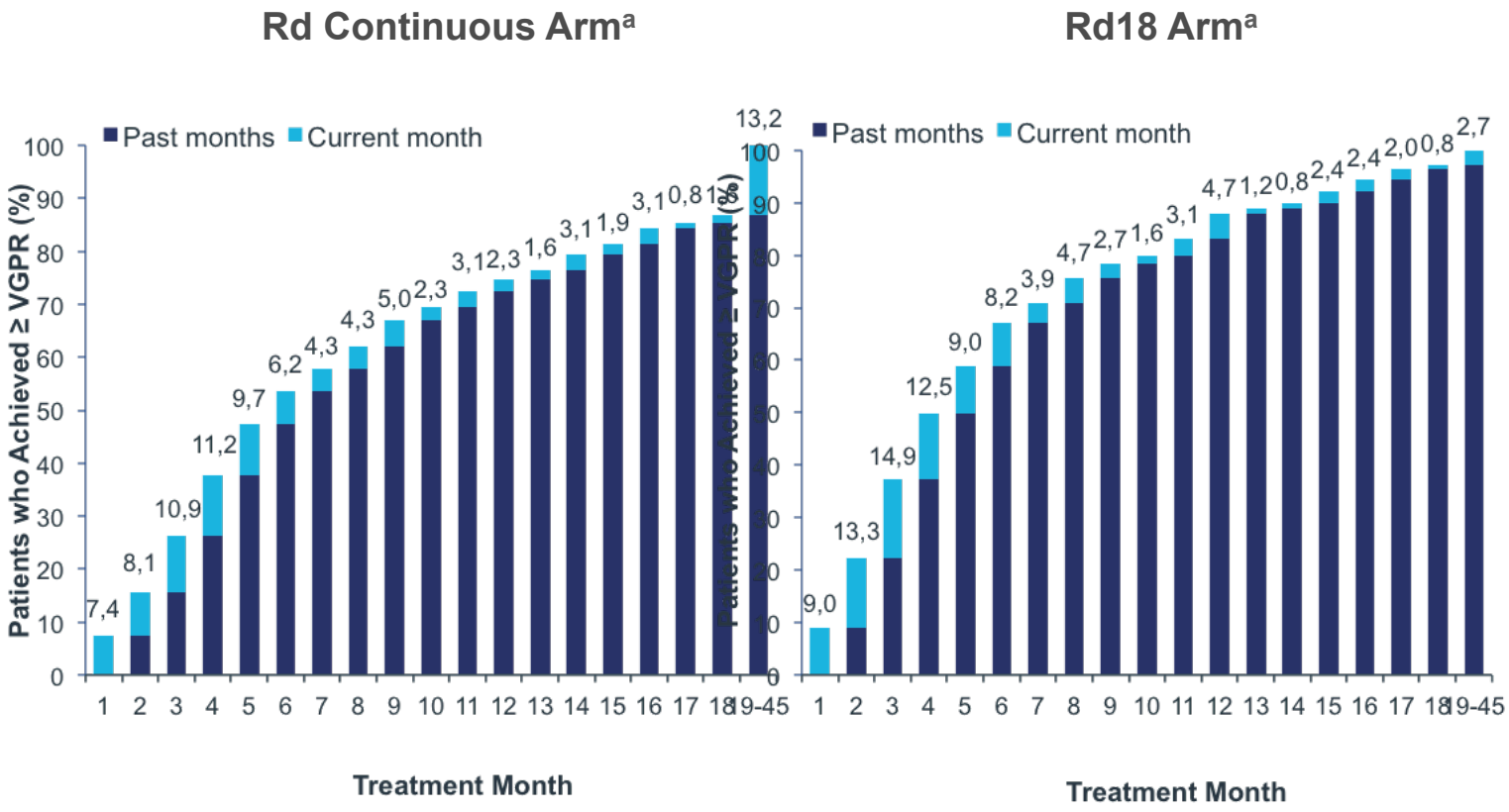
- Pts stratified by age (< 75 vs ≥ 75 yrs), country, and ISS stage (I/II vs III)
- Primary endpoint: PFS
- Secondary endpoints: OS (key secondary endpoint), ORR, TTNT, safety (including SPMs)
- Exploratory endpoints: PFS2 and response to second antimyeloma Tx
- Final data cutoff: January 21, 2016

[A] Facon T, et al. *Blood*. 2017

FIRST Trial: impact of response

Cumulative response rate by Tx month

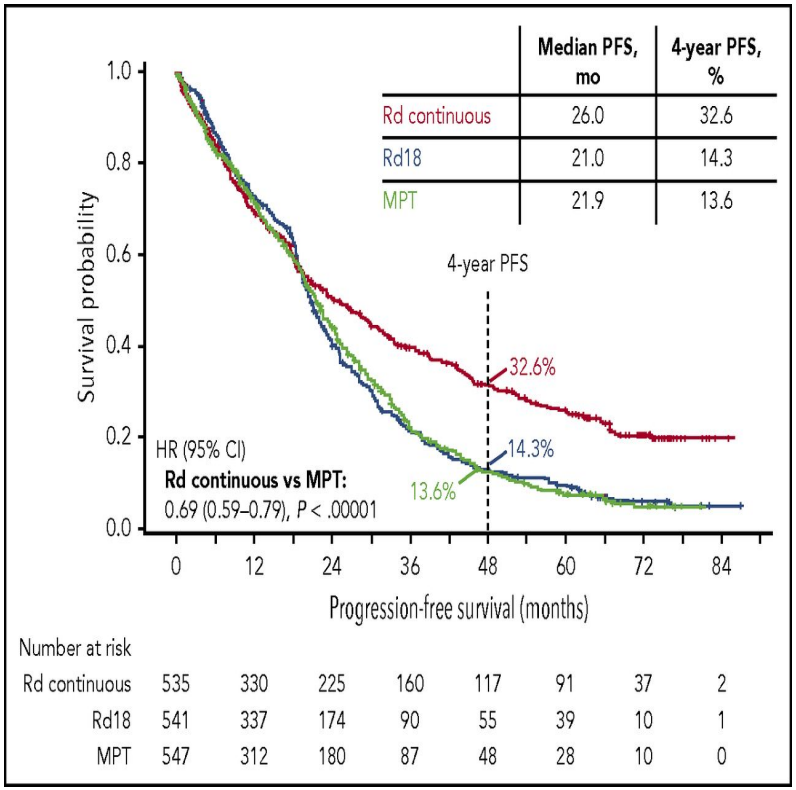
- **Of pts who achieved ≥ VGPR, 13.2% vs 2.7% achieved ≥ VGPR beyond 18 mos of Tx** in the Rd continuous and Rd18 arms, respectively



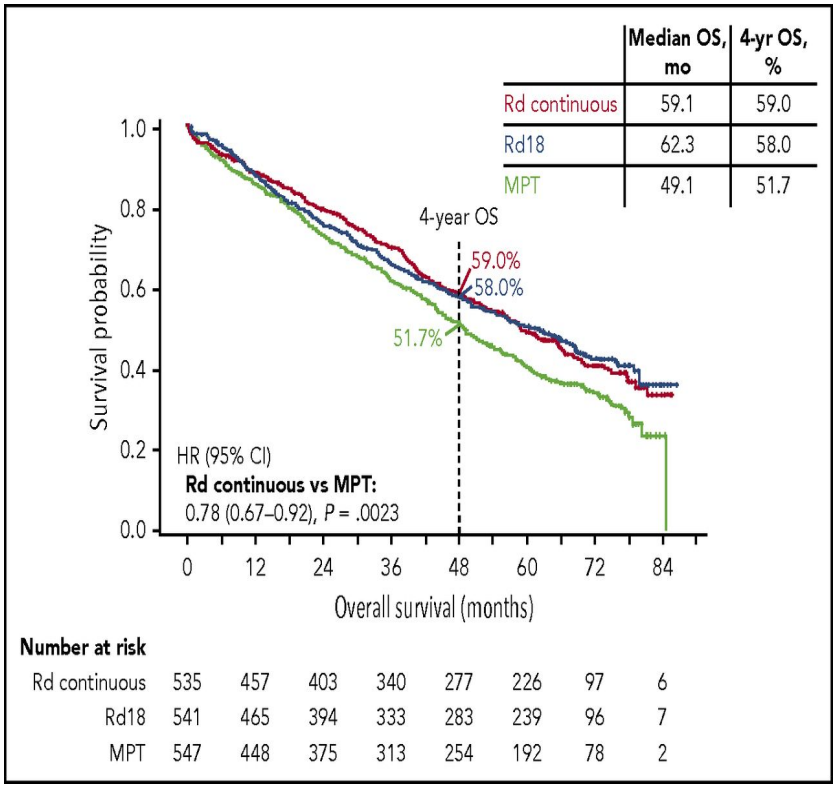
[a] Percentage shown is for pts achieving VGPR or better in the current month

Reprinted from Bahlis NJ, et al. Leukemia. 2017

PFS

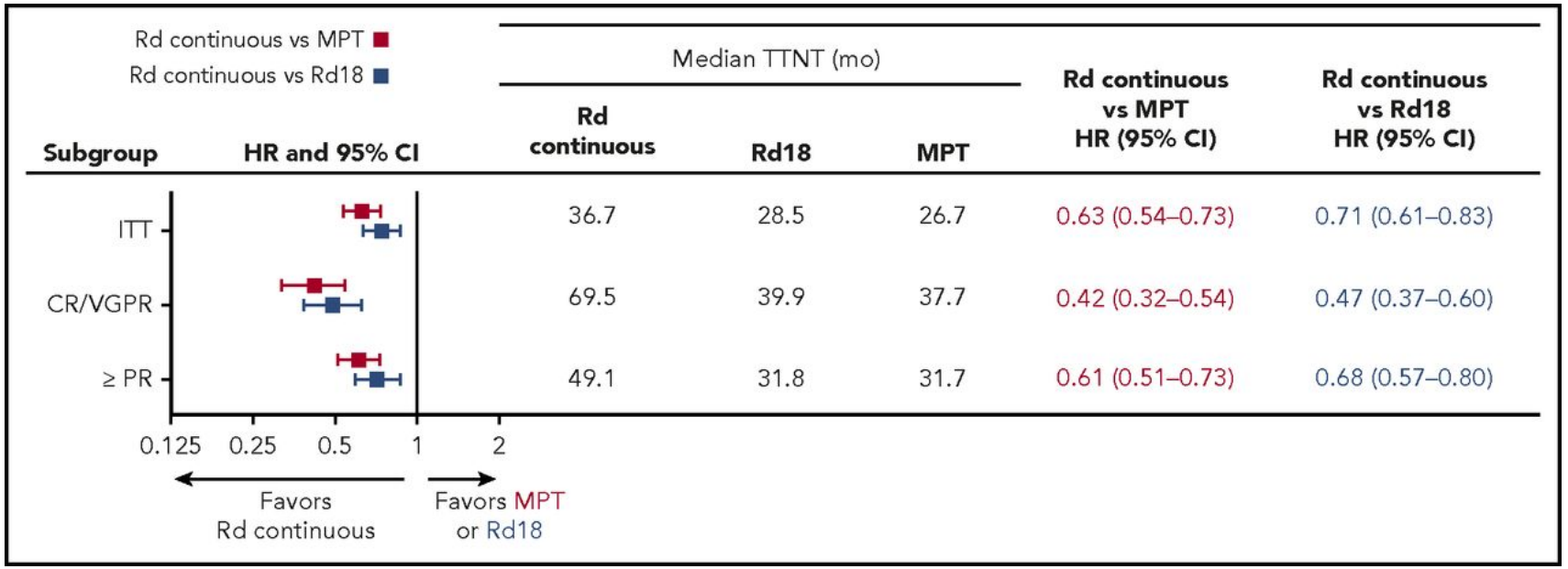


OS



Thierry Facon et al. Blood 2018;131:301-310

Final analysis of survival outcomes in FIRST trial
time to next antimyeloma Treatment



Subgroup	HR and 95% CI	Median TTNT (mo)			Rd continuous vs MPT HR (95% CI)	Rd continuous vs Rd18 HR (95% CI)
		Rd continuous	Rd18	MPT		
ITT		36.7	28.5	26.7	0.63 (0.54–0.73)	0.71 (0.61–0.83)
CR/VGPR		69.5	39.9	37.7	0.42 (0.32–0.54)	0.47 (0.37–0.60)
≥ PR		49.1	31.8	31.7	0.61 (0.51–0.73)	0.68 (0.57–0.80)

Thierry Facon et al. Blood 2018;131:301-310

Final analysis of survival outcomes in FIRST trial
selected grade 3/4 adverse events[1]

Patients With Selected Grade 3/4 AEs	Rd Continuous (n = 532)	Rd18 (n = 540)	MPT (n = 541)
Hematologic, (%)			
Neutropenia	30	26	45
Anemia	19	16	19
Thrombocytopenia	9	8	11
Febrile neutropenia	1	3	3
Non-hematologic, (%)			
Infections	32	22	17
Pneumonia	9	8	6
Cataract	7	3	1
Deep vein thrombosis	5	4	3
Diarrhea	5	3	1
Pulmonary embolism	4	3	4
Constipation	2	2	5
Peripheral sensory neuropathy	1	< 1	9

There were **no new safety concerns compared with earlier analyses**[2,3]

1. Facon T, et al. *Blood*. 2017 Nov 17 [Epub ahead of print]. 2. Benboubker L, et al. *N Engl J Med.* 2014;371:906-917. 3. Hulin C, et al. *J Clin Oncol*. 2016;34:3609-3617.

Final analysis of survival outcomes in FIRST trial
second primary tumours

SPM	Rd Continuous (n = 532)	Rd18 (n = 540)	MPT (n = 541)
Invasive, n (%)	36 (7)	38 (7)	46 (9)
Hematologic	4 (1)	2 (< 1)	14 (3)
AML	1 (< 1)	1 (< 1)	5 (1)
MDS	2 (< 1)	1 (< 1)	5 (1)
MDS to AML	0	0	4 (1)
B-cell leukemia	1 (< 1)	0	0
Solid Tumor	32 (6)	37 (7)	32 (6)

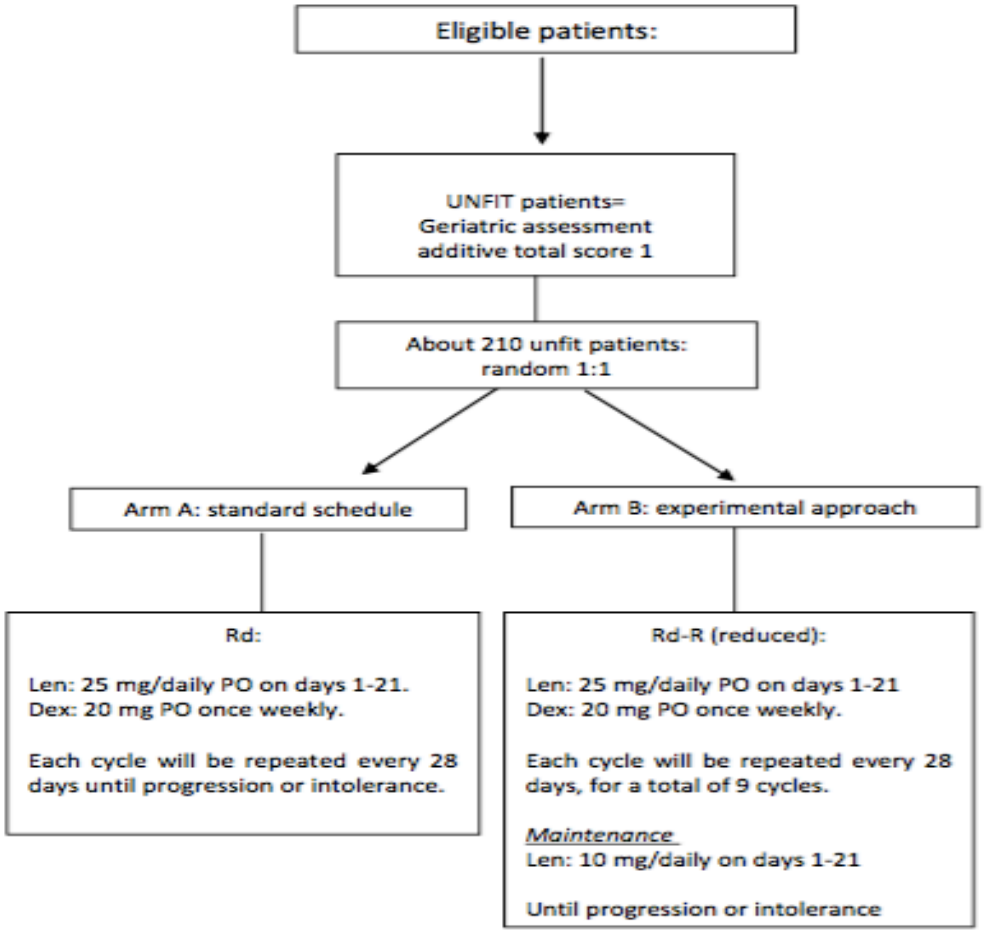
- **Hematologic SPMs were more frequent with MPT** (3%) than with Rd continuous (1%) or Rd18 (< 1%)
- **Incidence of solid tumor SPMs was similar across all treatment arms** (6%, 6%, and 7% with Rd continuous, MPT, and Rd18, respectively)

Facon T, et al. *Blood*. 2017 Nov 17 [Epub ahead of print].

Protocol Title:

A PHASE III, MULTICENTRE, RANDOMIZED, CONTROLLED STUDY TO DETERMINE THE EFFICACY AND SAFETY OF STANDARD SCHEDULE VERSUS A NEW ALGORITHM OF DOSE REDUCTIONS IN ELDERLY AND UNFIT NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS RECEIVING LENALIDOMIDE PLUS STEROIDS

SCHEMA OF THE STUDY



CONCLUSIONS

- In newly diagnosed, both transplant eligible and ineligible MM, maintenance has demonstrated to be effective in prolonging PFS, TNT and (at least for some subgroups of patients) OS and to have acceptable tolerability in the short to medium term.

- Therefore, maintenance is the standard of care in newly diagnosed MM.

- Maintenance has to offered to all patients, particularly to those with high quality responses after induction treatment.

- Maintenance does not comprimise response to salvage treatments in case of progression, therefore it does not select resistant MM clones.

- Up to now lenalidomide is the only registered drug for maintenance.

OPEN QUESTIONS

- Duration of maintenance (until progression? For 2-3 years? on the basis of minimal residual disease?)
- Maintenance in high risk MM?
- New drugs: oral proteosoma inhibitors, monoclonal antibodies