Continuous Therapy as a Standard of Care CON

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In France and in the IFM all debates

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Start like this

In France and in the IFM all debates

Start like this

But finish like that

Sometimes we can learn from the past

Continuous or maintenance therapy has always prolonged PFS in responding patients:

Is it that surprising ?

- **Chemotherapy**

Br J Cancer. 1988 Jan;57(1):94-9.

A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients.

Belch A[1], Shelley W, Bergsagel D, Wilson K, Klimo P, White D, Willan A.

- **Interferon**

N Engl J Med. 1990 May 17;322(20):1430-4.

Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy.

Mandelli F[1], Avvisati G, Amadori S, Boccadoro M, Gernone A, Lauta VM, Marmont F, Petrucci MT, Tribalto M, Vegna ML, et al.

- **Thalidomide**

Blood. 2006 Nov 15;108(10):3289-94. Epub 2006 Jul 27.

Maintenance therapy with thalidomide improves survival in patients with multiple myeloma.

Attal M[1], Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, Yakoub Agha I, Bourhis JH, Garderet L, Pegourie B, Dumontet C, Renaud M, Voillat L, Berthou C, Marit G, Monconduit M, Caillot D, Grobois B, Avet-Loiseau H, Moreau P, Facon T; Inter-Groupe Francophone du Myélome (IFM).

But the key question is OS BENEFIT

Adverse events and extra-cost of continuous therapy are justified only if there is an OS benefit

- **Chemotherapy**: no OS benefit [1]
- **Interferon:** 4 to 8 m benefit [2,3]
- **Thalidomide :** no OS benefit (6 RCT [4] , one meta-analysis [5])

In the thalidomide arms survival could be shorter after relapse since in the no thalidomide arm patients received thalidomide at relapse

And new agents were not always available

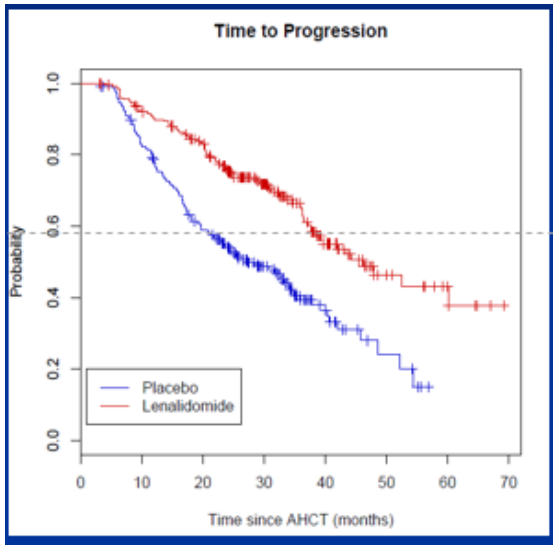
EARLY versus LATE Thalidomide

1 Belch Br J Cancer 1988;57:94 2 Ludwig H Acto Oncol 2000;39:815 Myeloma trialists Br J Haematol 2001;113:1020
4 Ludwig H Blood 2012;119:3003 5 Wang Y J Natl Cancer Instit 2016;108;dlv 342

Lenalidomide maintenance therapy after autologous transplantation

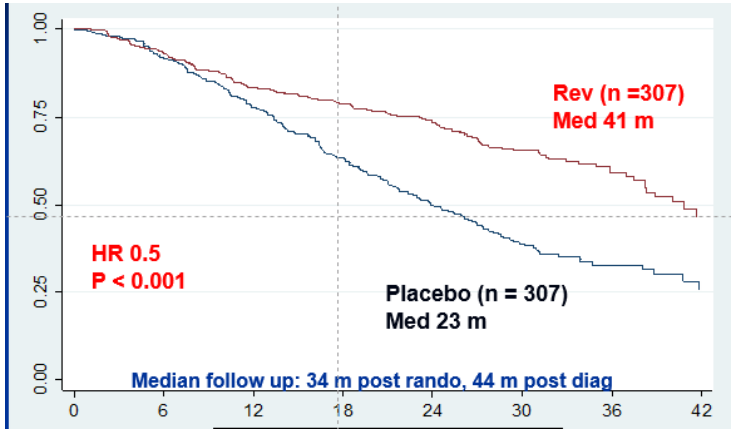
Four randomized trials versus placebo or observation

Four randomized trials show a dramatic improvement of PFS



HR 0.37

McCarthy P (CALGB) NEJM 2012; 366:1770



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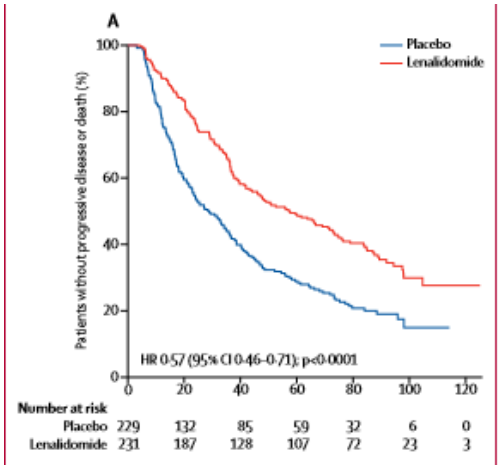
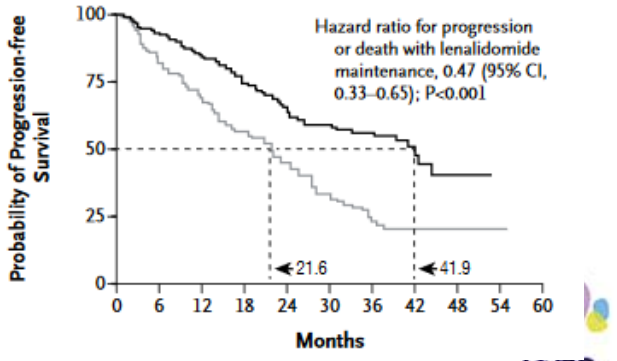
Attal M (IFM) NEJM 2012;366:1778



HR 0.57

Jackson G ASH 2017



HR 0.47

Palumbo A NEJM 2014;371:895

Lenalidomide Maintenance Safety

	CALGB	IFM [1]	GIMEMA	Pooled
N	231	307	87	605
Mean duration	30 m	25 m	35 m	28 m
≥ 3 years	37 %	29 %	52 %	34 %
Interruption due to SAE(%)	28 vs 9	30 vs 15	---	29 vs 12

1 In the IFM study maintenance was stopped in 119 patients in the len arm after imbalance of SPM observation (mean duration 39 months)

Mc Carthy P JCO 2017;35:3279

Number and Frequency of Patients with ≥ 1 SPM

(As of Dec 2014)

SPM Category, n (%)	IFM 2005-02 Lenalidomide (N = 306)	IFM 2005-02 Placebo (N = 302)	CALGB 100104 Lenalidomide (N = 222)	CALGB 100104 Placebo (N = 216)
All SPMs	46 (15.0%)	27 (8.9%)	37 (16.7%)	24 (11.1%)
Invasive	38 (12.4%)	22 (7.3%)	31 (14.0%)	17 (7.9%)
Hematological	20 (6.5%)	9 (3.3%)	15 (6.8%)	7 (3.2%)
AML	6(2.0%)	3(1.0%)	7(3.2%)	0
MDS	4 (1.3%)	3 (1.0%)	4 (1.8%)	4 (1.9%)
B-cell	11 (3.6%)	2 (0.7%)	4 (1.8%)	3 (1.4%)
T-cell	0	1 (0.3%)	0	0
Solid tumor	19 (6.2%)	13 (4.3%)	16 (7.2%)	11 (5.1%)
Non-melanoma skin cancers	10 (3.3%)	7 (2.3%)	8 (3.6%)	9 (4.2%)

ifm

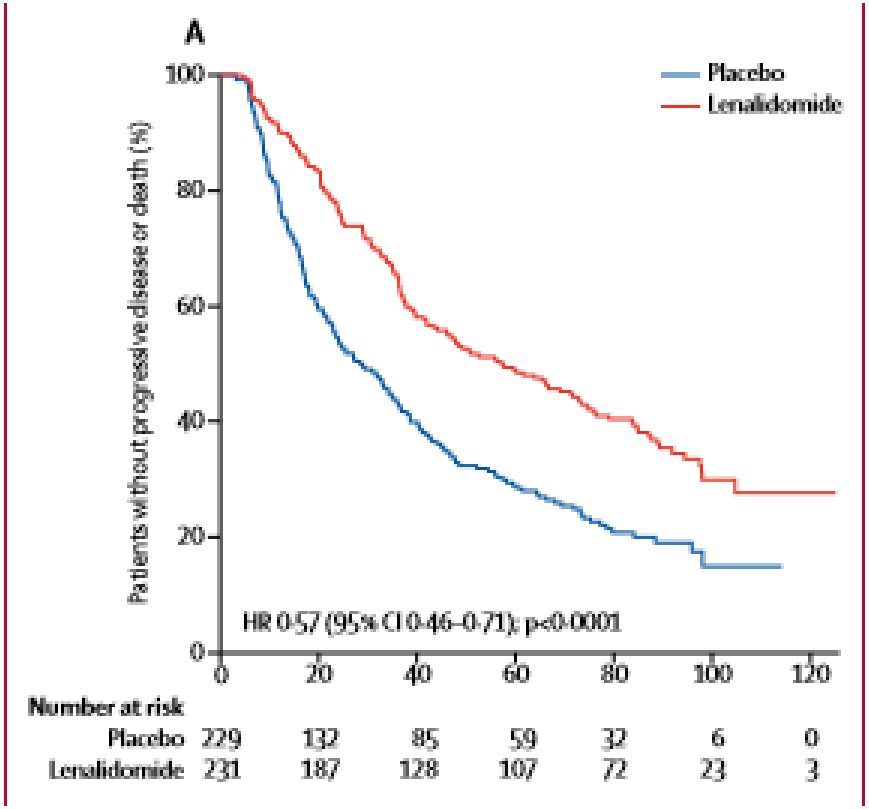
COSTS

- The price of Lenalidomide varies across countries
- But is X thousands Euros/month
- For a median of 30 months
- Currently not affordable in many countries

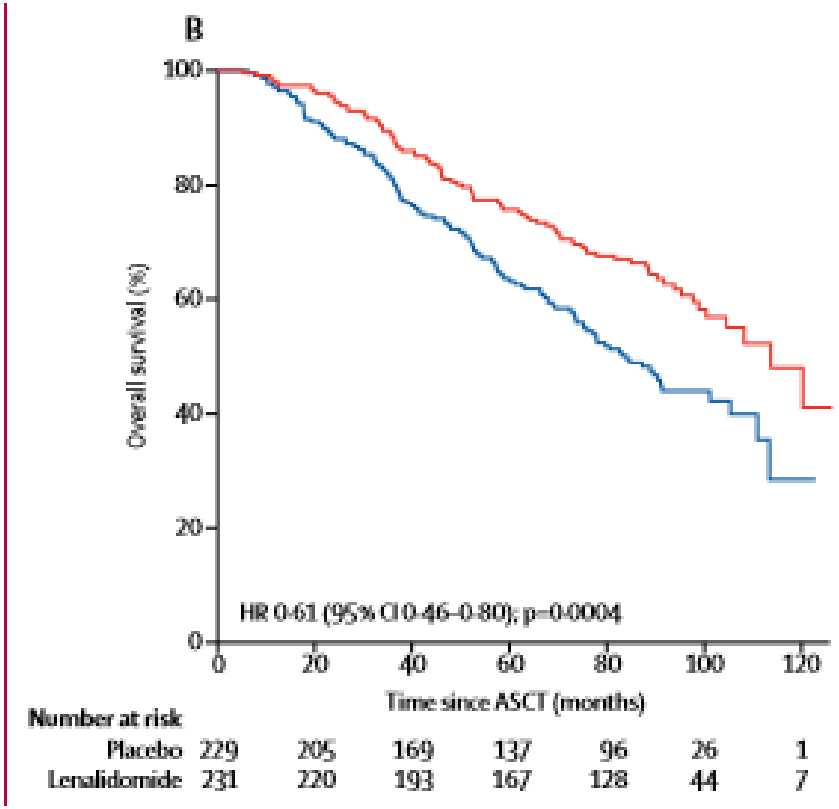
Len maintenance improved OS in the CALGB trial

Updated analysis(460 pts 91 months median f-up)

Progression-Free Survival



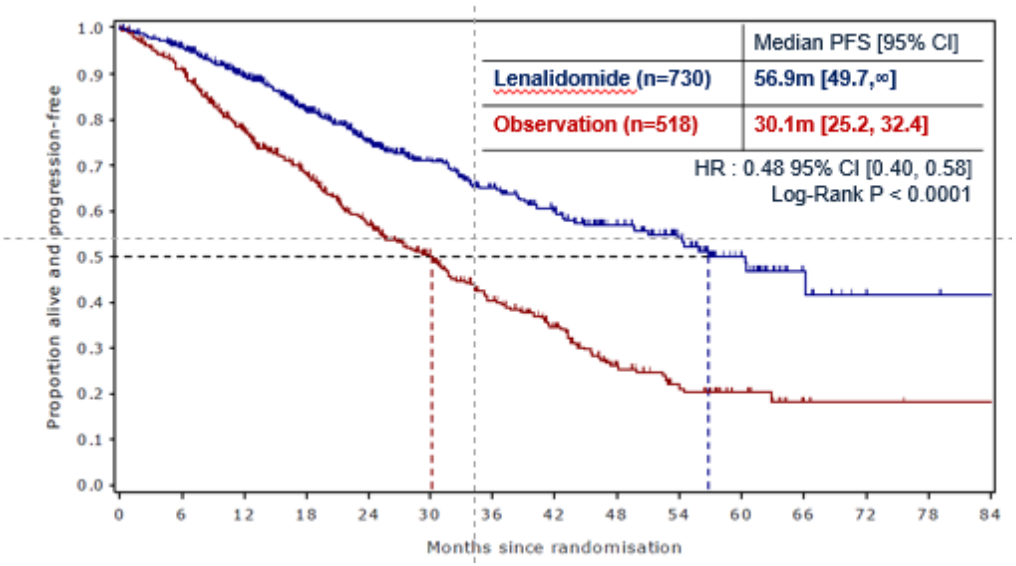
Overall Survival



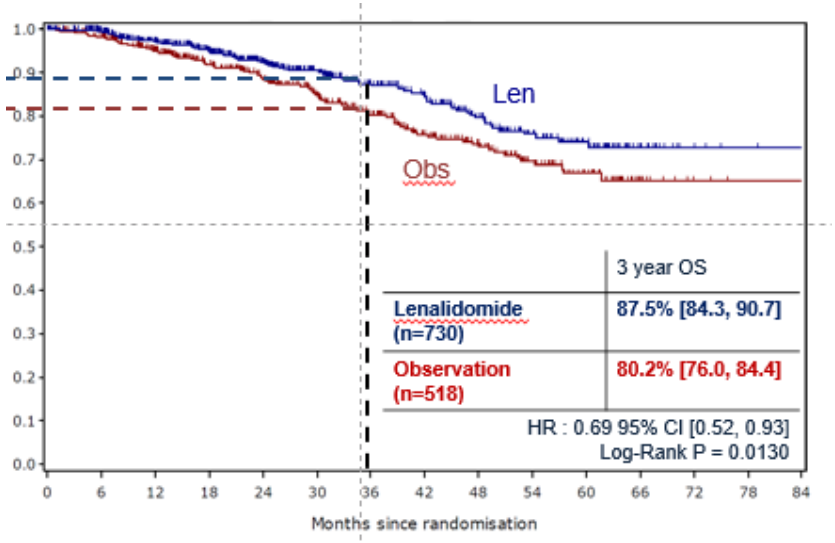
Holstein SA et al Lancet Haematology 2017;4:e431-42

LENALIDOMIDE MAINTENANCE
THE MRC XI trial

PFS



OS

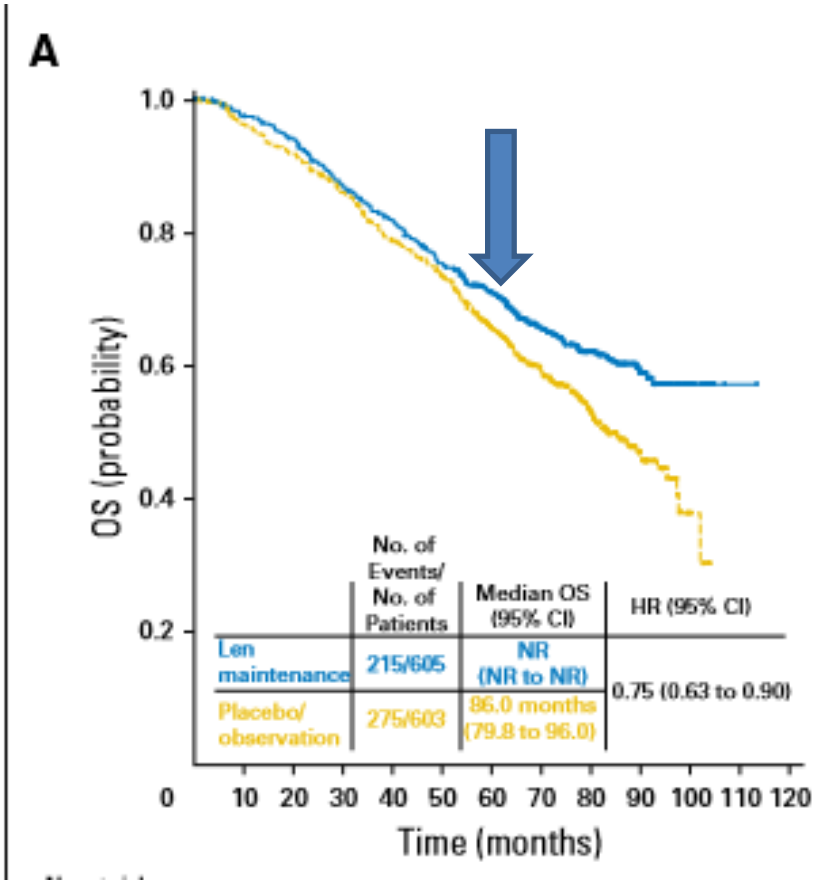


1248 PTS MEDIAN F-UP 30.6 MONTHS

G.JACKSON ASH 2017

The OS benefit may be delayed due to better salvage treatments

- Meta-analysis of the 3 trials (1208 pts, 79.5 mo median f-up)
- The benefit of a longer duration of first response translates into a longer OS only after 5 years

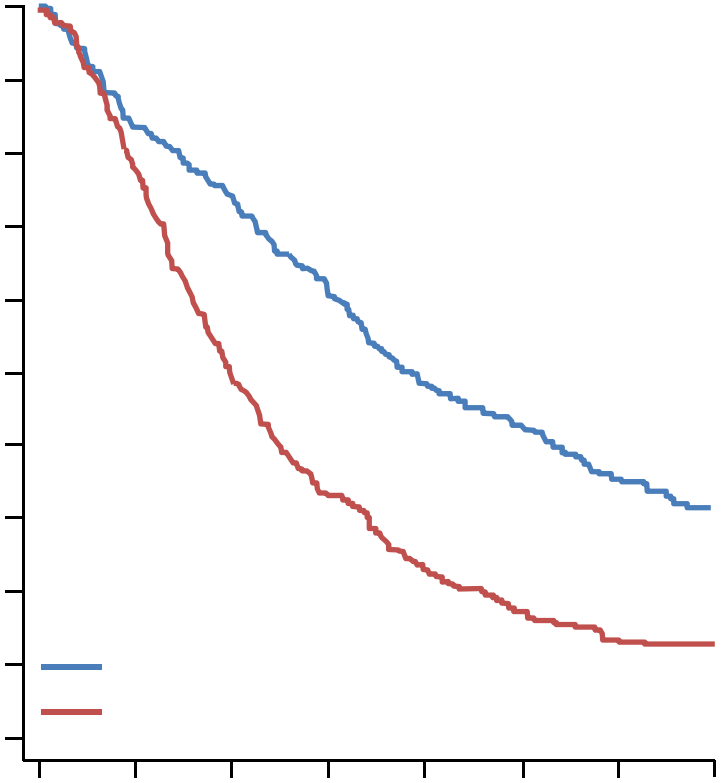


Mc Carthy P (JCO 2017 online)

But OS is not improved in all studies

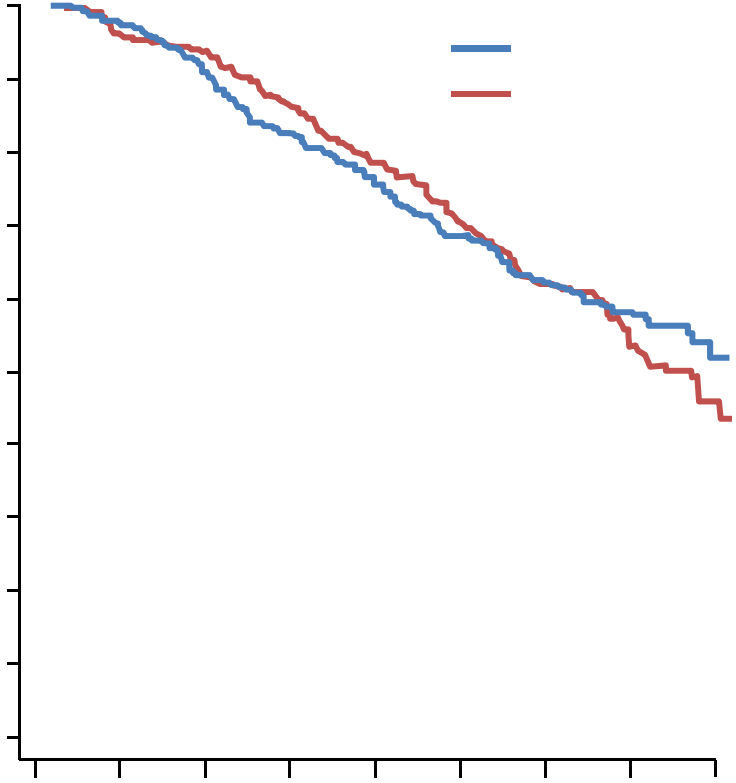
IFM 2005-02 : updated PFS and OS (As of Feb 2015)

PFS
(Median follow-up: 82 months)



No at risk								
LEN	307	244	209	158	122	104	81	39
Placebo	307	225	141	92	63	47	34	13

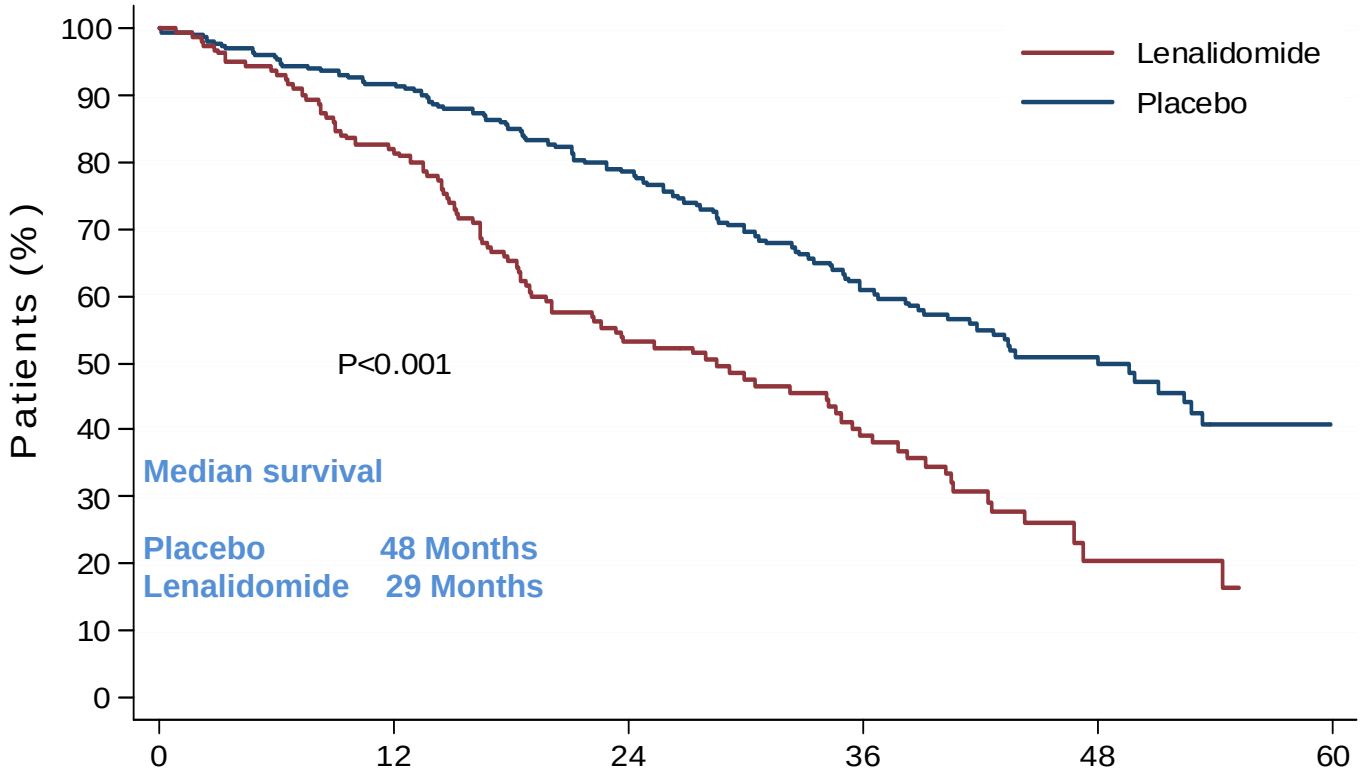
OS
(Median follow-up: 84 months)



No at risk									
LEN	307	294	264	237	216	195	173	90	12
Placebo	307	287	276	250	227	199	174	75	8

Survival after 1st progression was shorter in the IFM 05-02 with lenalidomide

Patients in the lenalidomide arm responded less well to HD Len-Dex at relapse



N at risk						
Lenalidomide	165	122	67	36	7	3
Placebo	241	209	161	101	44	7

LENALIDOMIDE MAINTENANCE AFTER ASCT :

- Lenalidomide maintenance after ASCT is now approved by FDA and EMA since PFS and OS (in some studies) are improved

What is the optimal duration ?

- In all 4 randomized trials low-dose lenalidomide was prescribed until progression

- No randomized trial addressed the question of the duration

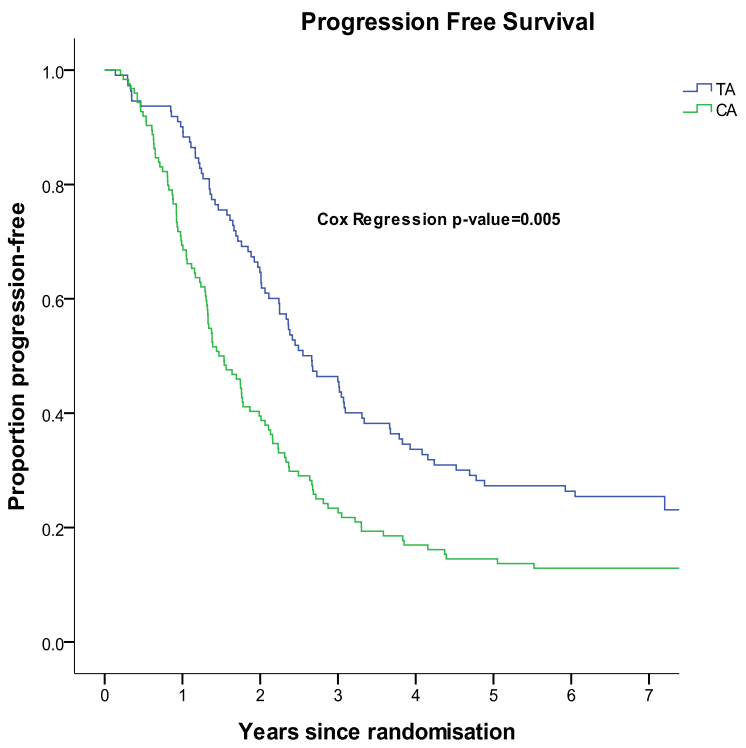
Sometimes we can learn from the past

Survival benefit of a short maintenance treatment

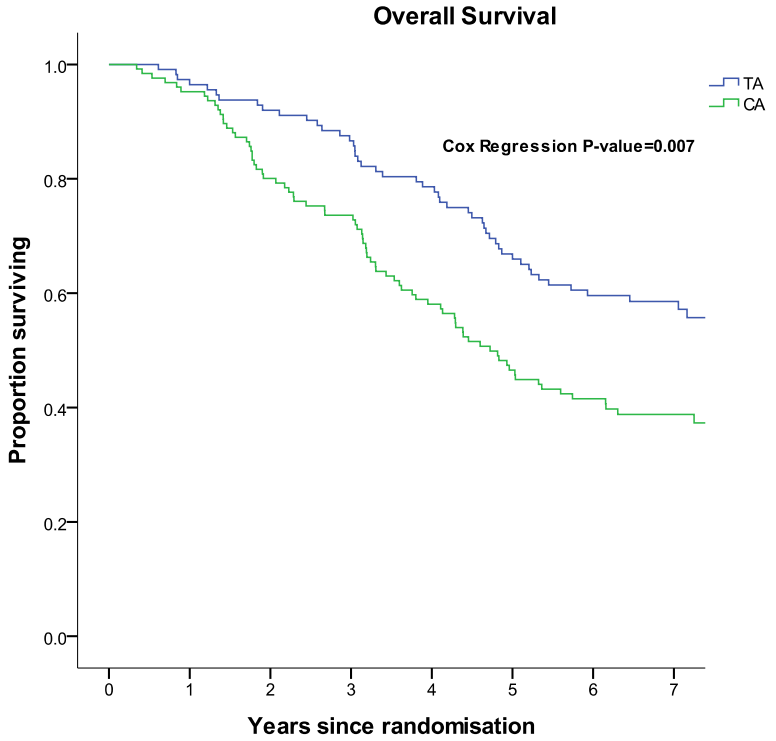
Updated results of the Australian Study

269 patients median f-up 5.4y

Thalidomide (average daily dose 155mg) plus PDN for 1 year



5yr PFS: 27% vs 15%
HR 0.16; 95% CI 0.044 to 0.582
P=0.0054



5yr OS: 66% vs 47%
HR 0.12; 95% CI 0.028 to 0.558
P=0.0072

Kalff A et al Lancet Oncol 2014;

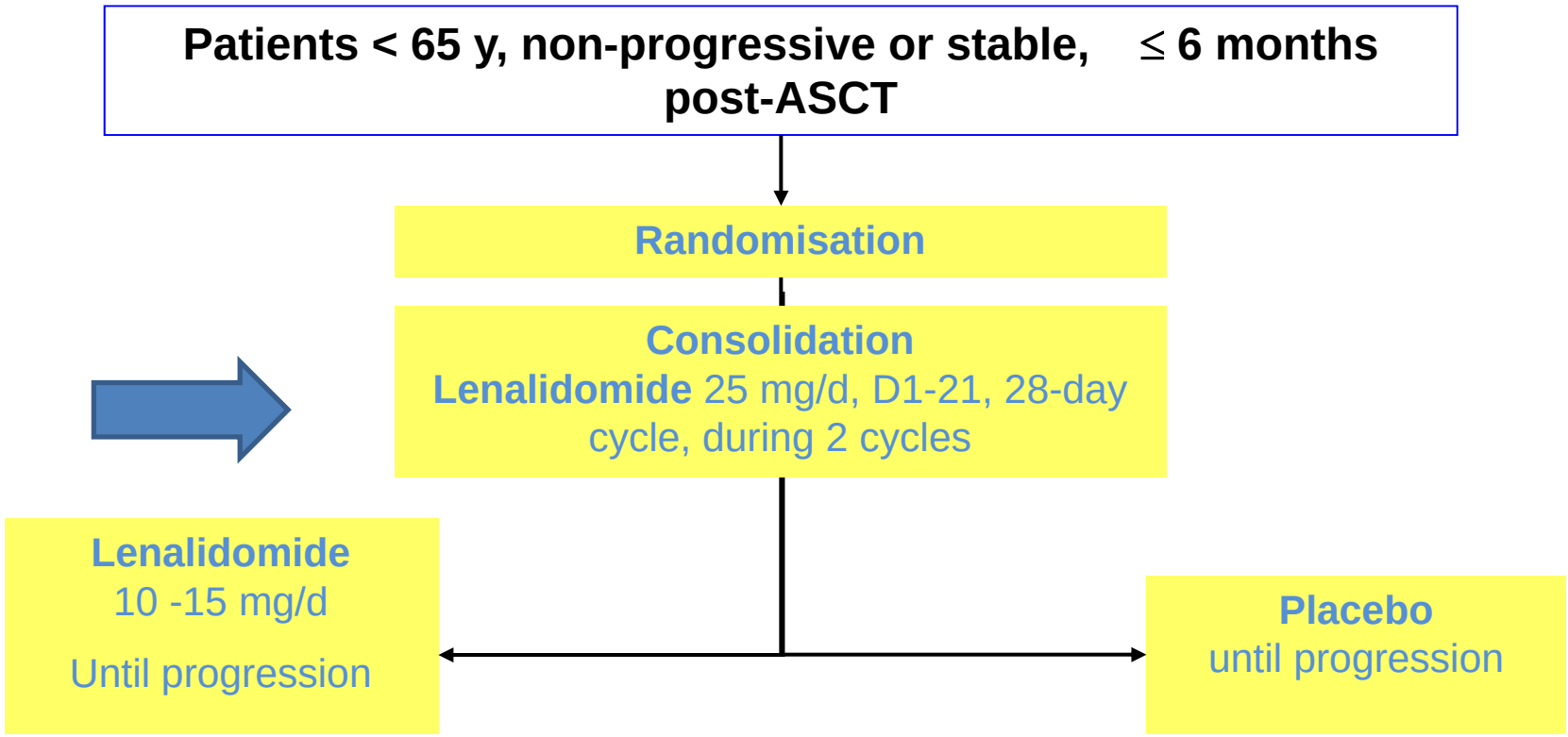
IFM/DFCI 2009 Study
Impact of the duration of lenalidomide maintenance ?

Second question : what is the benefit maintenance after consolidation ?

- In only one of the 4 randomized studies, patients received a consolidation before maintenance

IFM 2005-02: lenalidomide maintenance after ASCT

Phase III prospective randomised, versus placebo



Primary end-point : TTP
Secondary end-points: CR, PFS, OS, feasibility-toxicity

Attal et al , NEJM 2012; 366:1782-91

Second question : what is the benefit of maintenance after consolidation ?

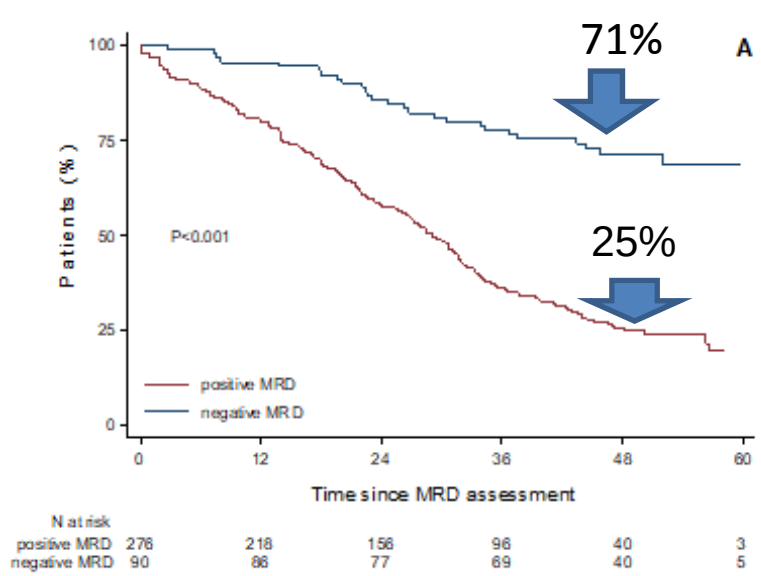
- In only one of the 4 randomized studies, patients received a consolidation before maintenance

- This question should be addressed after modern triple consolidation or with anti-CD38 antibodies

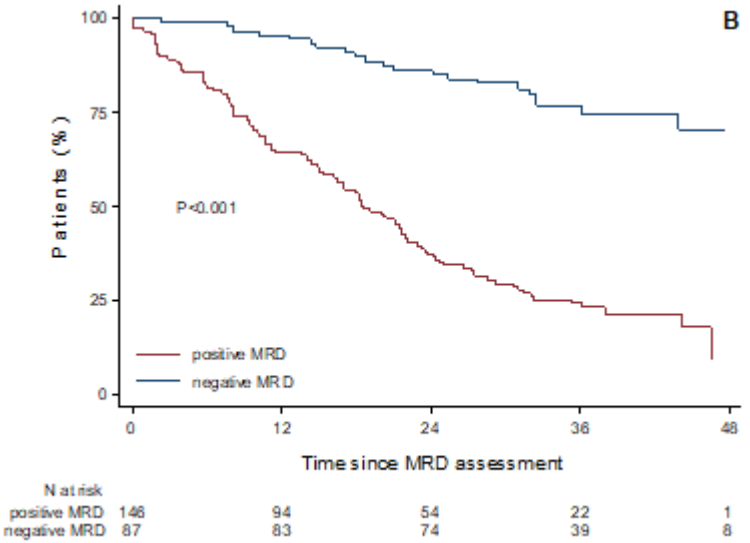
- In particular in patients achieving < 0 MRD after consolidation

Patients with <0 MRD before maintenance have the same PFS than patients with <0 MRD after maintenance (NGS 10-6 level)

PFS 0 <MRD pre-maintenance



PFS <0 MRD post-maintenance



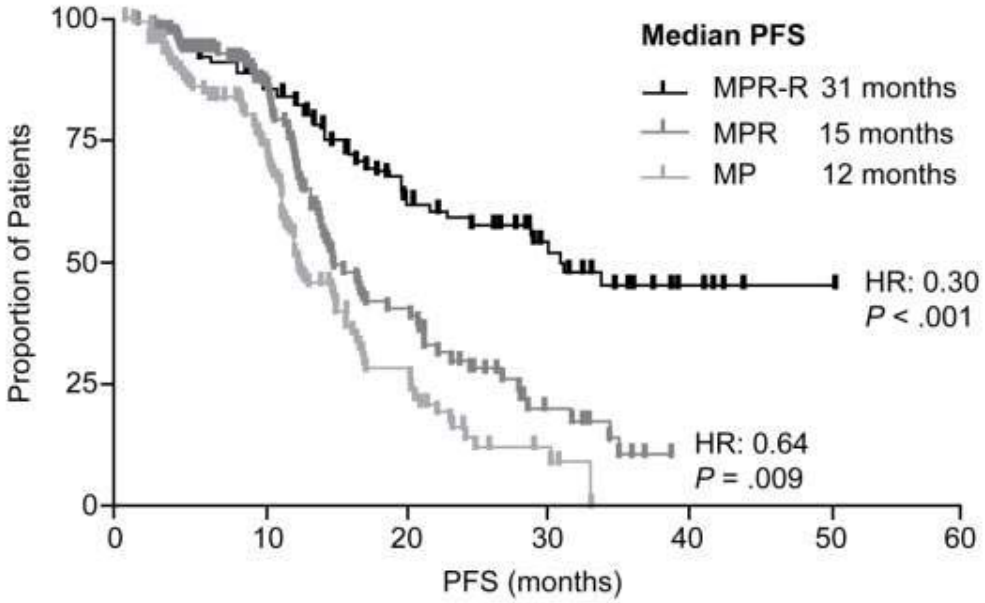
Avet Loiseau Results of the IFM 2009 trial submitted

Maintenance or continuous therapy in elderly patients

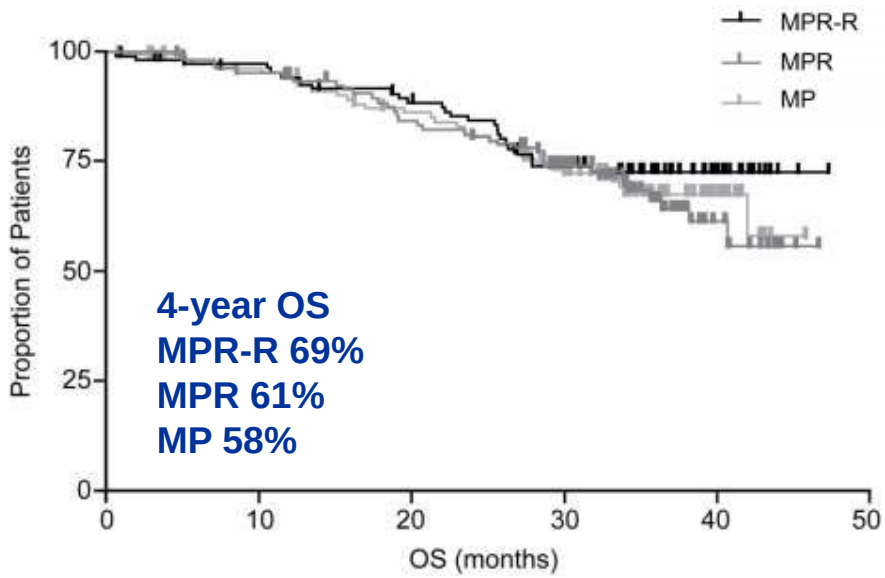
MM-015: MP 9 cycles vs MPR 9 cycles +/- R

PFS and OS (459 pts)

PFS



OS



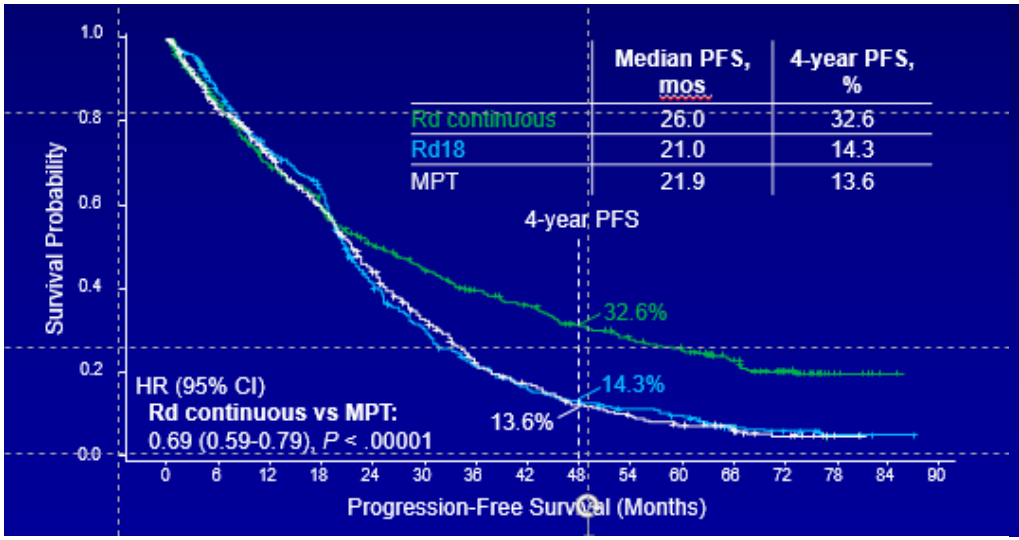
- **Trend for extended OS with MPR-R vs MP (estimated 3-yr OS: 73% vs 65%; p=0.254)**

Palumbo et al. NEJM 2012;366:1759-69

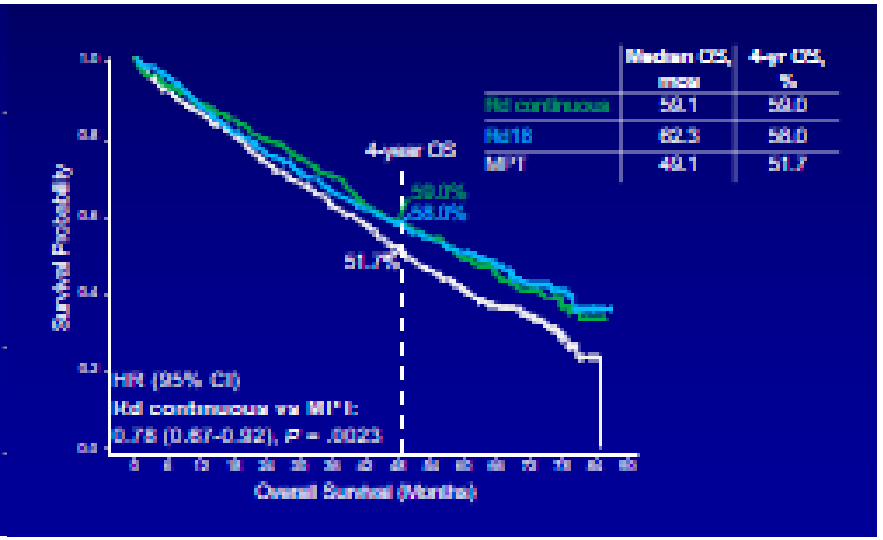
FIRST trial (1623 pts)

MPT 12 cycles vs Rd 12 cycles vs Rd continuous

PFS



OS



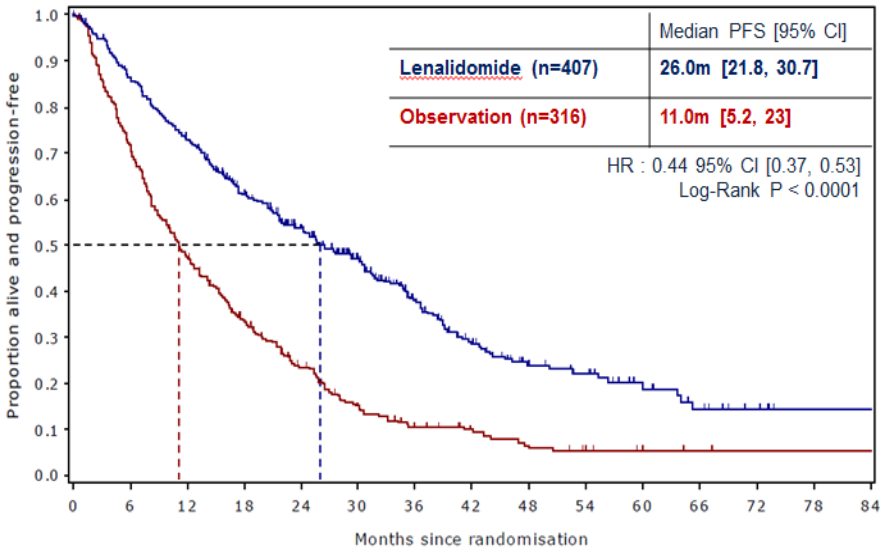
Rd>MPT (PFS and OS)
Rd continuous not >Rd 18m for OS

Benboubker L NEJM 2014;371:906 T Facon Blood 2018;131:301

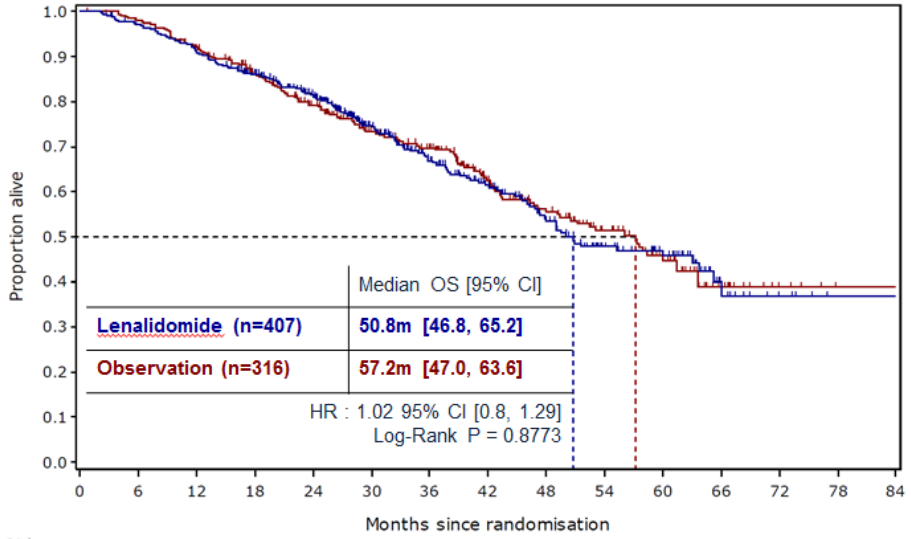
MRC XI TRIAL

Lenalidomide maintenance in the TNE Pathway

PFS med 26 m vs 11 m



OS med 51 m vs 58 m



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Maintenance or continuous therapy in elderly patients

- In the absence of OS benefit(until now)
- Prolonged risk of adverse events and extra cost do not justify prolonged treatment with lenalidomide

  (beyond 18 months)

Prolonged treatment in first relapse

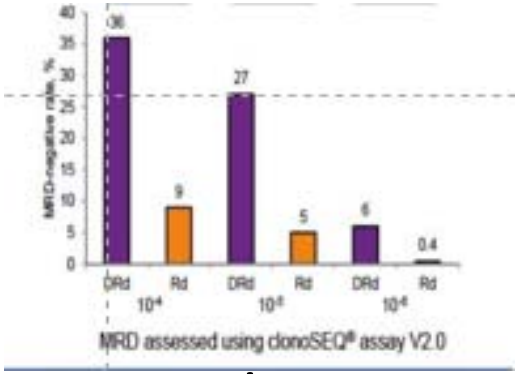
CAN WE SHORTEN THE DURATION OF EXPENSIVE RELAPSE TREATMENT ?

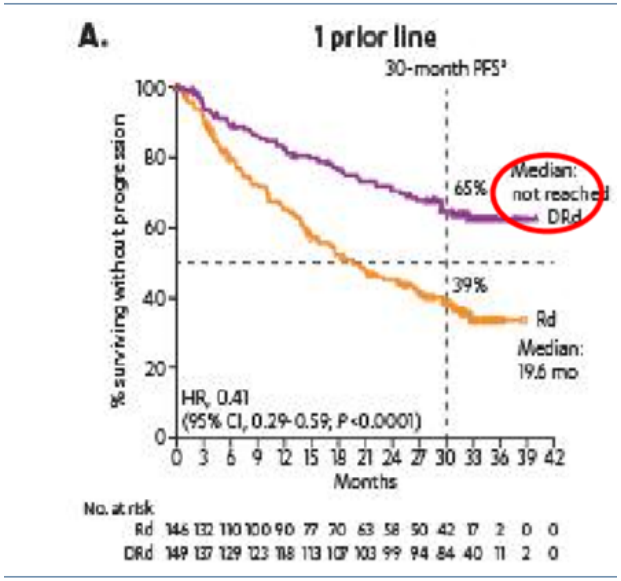
- Currently relapse treatment is precribed until next progression or SAE
- However in some cases in responding patients treatment is stopped earlier following patient's request
- Until now it was difficult to adress the question of relapse treatment duration because results were not good enough

Cost optimization Trial

Dara-Rd in First Relapse

- Future IFM trial supported by the French ministry of Health (PI: M Mohty)
- Based on the updated results of the Pollux trial (Moreau P ASH2017)





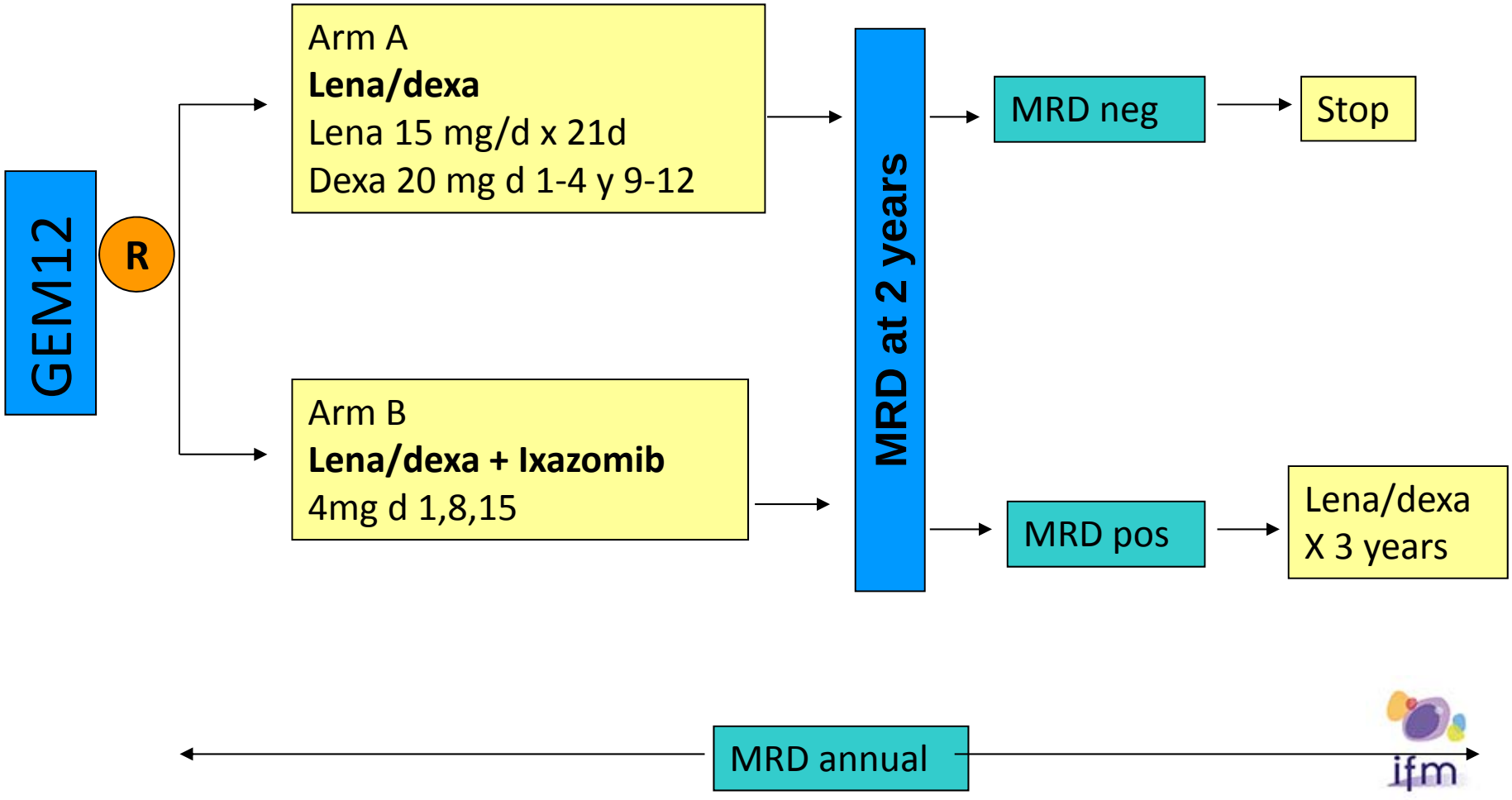
- Dara-Rd until progression vs 2 years of treatment
- Hypothesis: equal OS (longer PFS 2?)

Is it possible to guide treatment duration with MRD assessment to determine

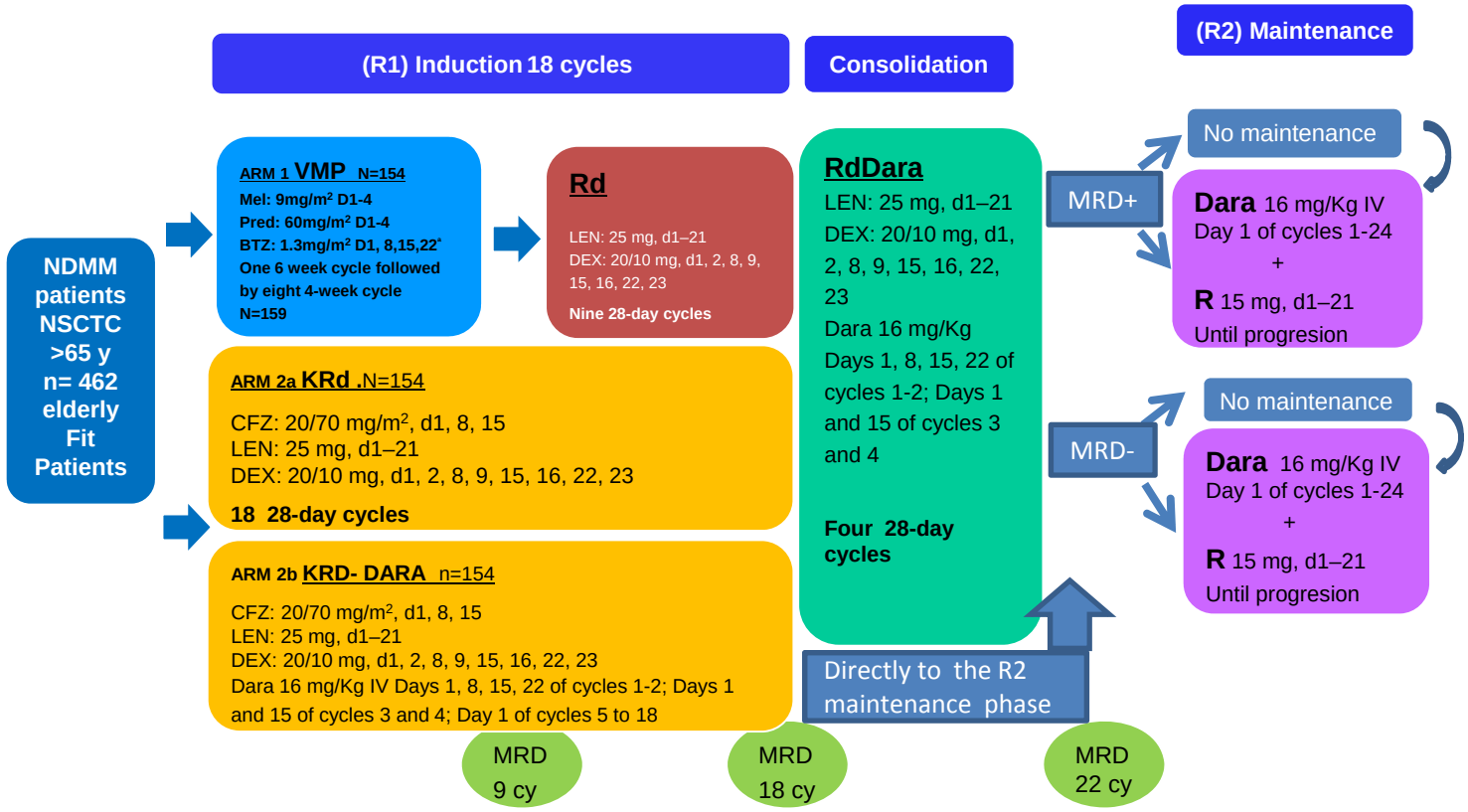
- in which patients the treatment should be continued
- and in which patients it could be stopped

GEM14

In patients ≤ 65 y after ASCT



A spanish study for fit elderly NDMM patients; GEMFIT2016



Primary endpoint immonuphenotypic complete response
Secondary exploratory outcome: PFS

CONCLUSIONS

- After ASCT lenalidomide maintenance is validated but we **need randomized studies to address the question of optimal duration**

– in the context of better induction and consolidation therapies

- In TNE patients currently **no indication of continuous therapy**
- The question should be addressed with new effective but expensive treatments in first relapse
- MRD assessment could be used for adapting the duration of maintenance