Highlights from IMW 2019

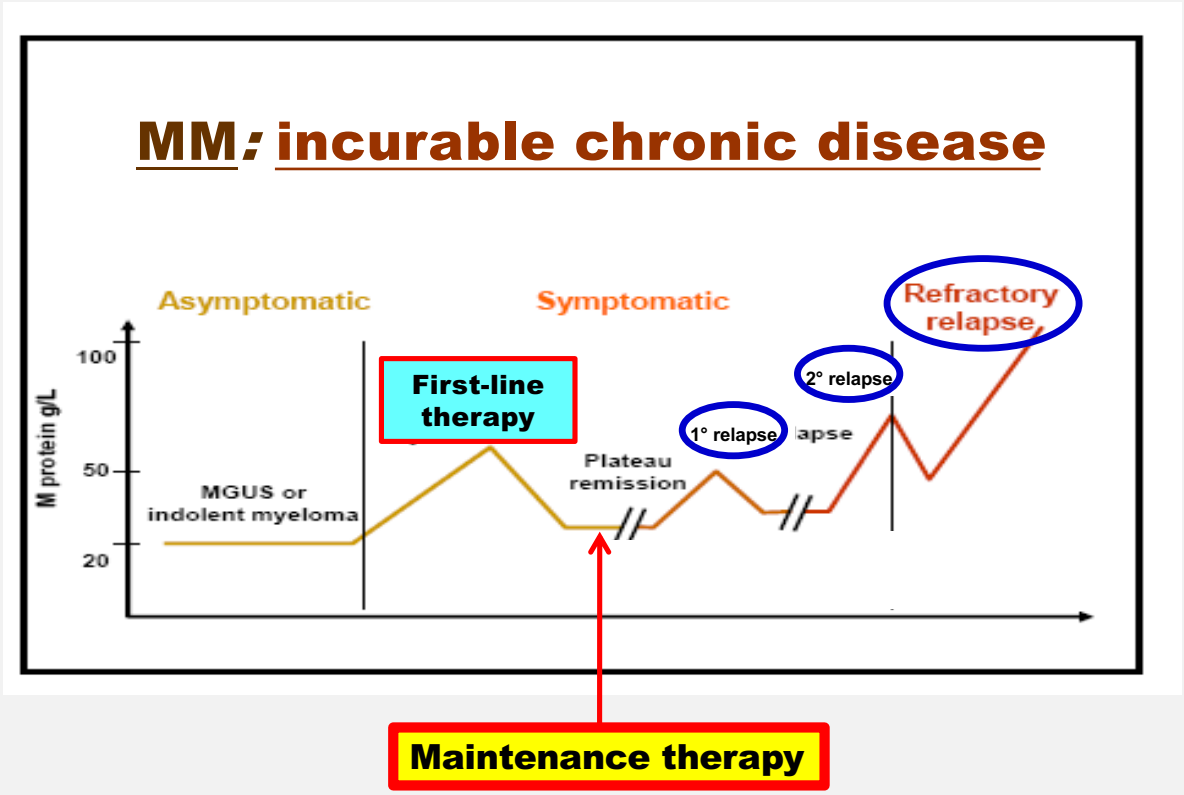
19-20 novembre 2019
Bologna
Royal Hotel Carlton

Stelvio Ballanti
Istituto di Ematologia e Immunologia Clinica
Ospedale S. Maria della Misericordia
PERUGIA

La terapia di maintenimento: di durata fissa o indefinita ?

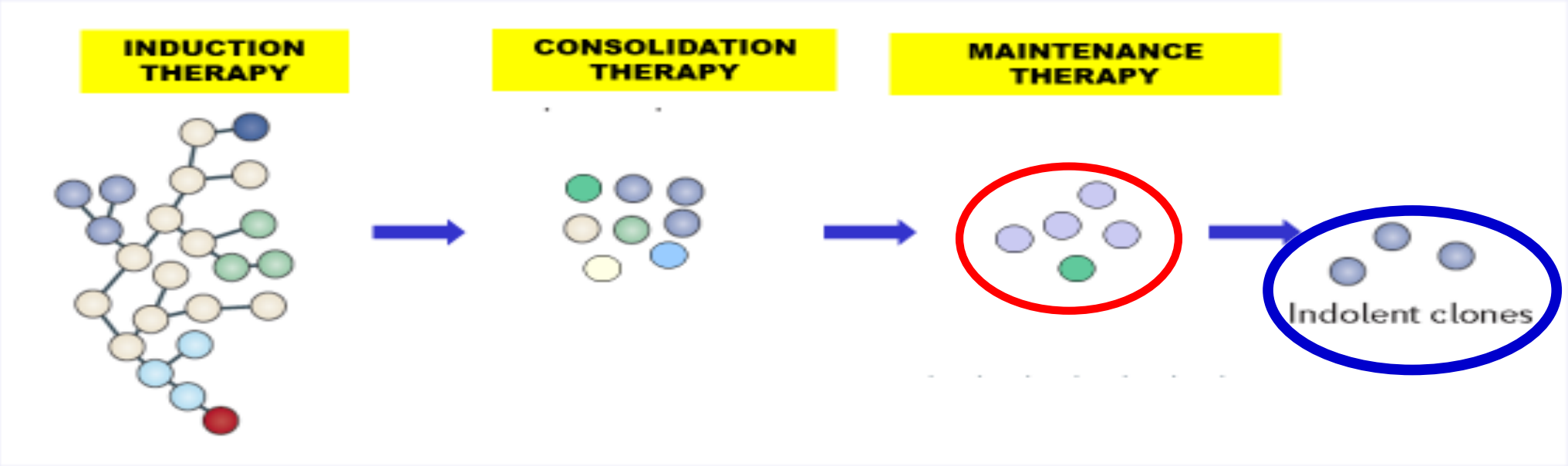
Maintenance Therapy

Rational



Sequential therapy

Adjust pressure to select for indolent clones



Maintenance Therapy

Long-term objectives

1) longer PFS-EFS
2) longer OS (desirable target)

Badros … NEJM 2012
Palumbo .. CCR 2011

Maintenance Therapy

after ASCT

Standard of cure

Post-ASCT maintenance therapy with **Lenalidomide**, administered alone and until progression, is the standard of care and has been approved by EMA and FDA .

The mechanism of action of Lenalidomide make it an ideal backbone of future maintenance studies incorporating other agents such proteasome inhibitors, monoclonal antibodies and HDAC inhibitors

Richardson .. Exp Rev Anticancer Ther 2018

Maintenance Therapy

Lenalidomide

	Induction prior-ASCT	Maintenance	Dose Lenalid	Follow up	PFS / TTP Lena Plac	OS Lena Plac
Attal 12 **IFM 2005-02** 614 ptz	VAD VD	R → Lena R → Placebo	10-15 mg gg 1-28 **until progression**	67 mo	46 mo 24 mo *p < 0.001*	82 mo 81 mo *p = 0.8*
McCarthy 12 **CALGB 100104** 568 ptz	TAL 45% LEN 35% BOR 41%	R → Lena R → Placebo	10-15 mg gg 1-28 **until progression**	91 mo	57 mo 29 mo *p < 0.0001*	114 mo 84 mo *p = 0.0004*
Palumbo 14 **GIMEMA** **RV-MM-PI-209** 402 →202→116 pt	RD	R → Lena R → Obs	10-15 mg gg 1-21 **until progression**	51 mo	*from time diagnosis* (ITT) 55 mo 37 mo *p = S*	*from time diagnosis* (ITT) 5yr-OS 78% 67% *p = NS*
Morgan **MIELOMA XI** 1551 (828 TE) pts	CTD CRD VCD	R → Lena R → Obs	10 mg gg 1-21 **until progression**	31 mo	57 mo 30 mo *p < 0.0001*	3yr-OS 87.5% 80% *p = 0.014*

Metaanalysis

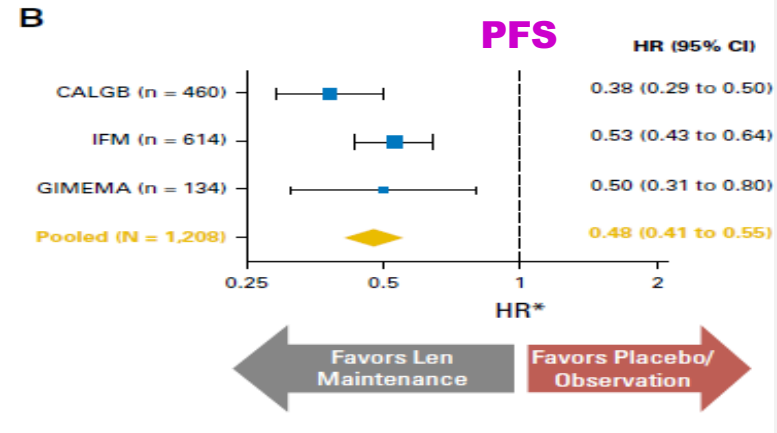
IFM 2005-02, CALGB 100104, GIMEMA RV-MM-PI-209D

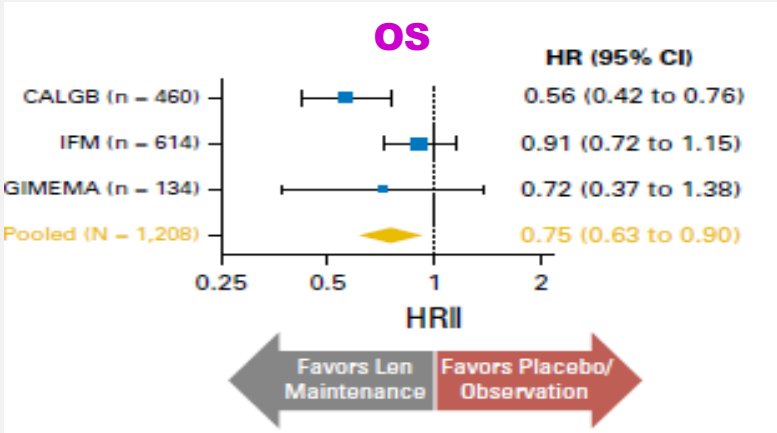
Median follow up of 79,5 → 88.8 months

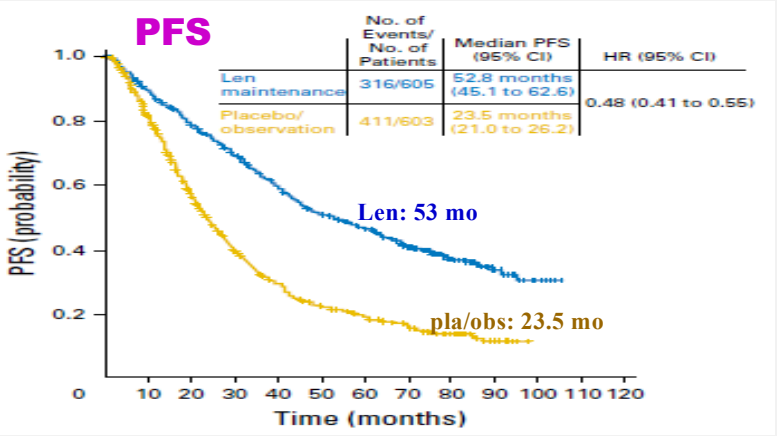
Progression Free Survival

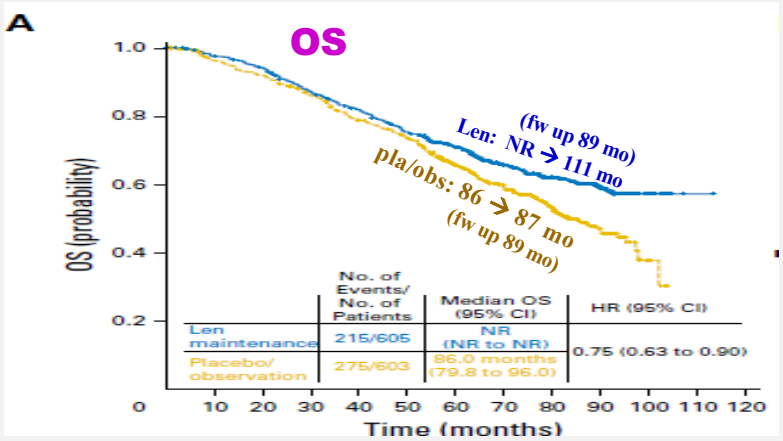
1208 patients

Overall Survival









McCarthy .. JCO 2017

Richardson .. Exp Opin Pharm 2017

Maintenance Therapy

Optimal duration

Until progression ?

Three concerns

1) Risk of selecting resistant clones
2) Risk of Secondary Primary Malignancies
3) High costs

Richardson .. Exp Opin Pharm 2017
Richardson .. Exp Rev Anticancer Ther 2018

Maintenance Therapy

Until progression: ?

First concern

Risk of selecting resistant clones

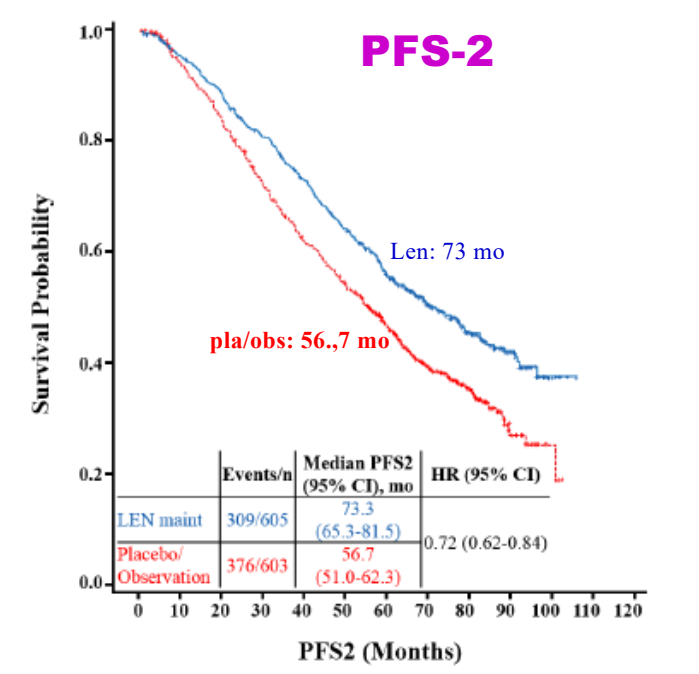
Richardson .. Exp Opin Pharm 2017
Richardson .. Exp Rev Anticancer Ther 2018

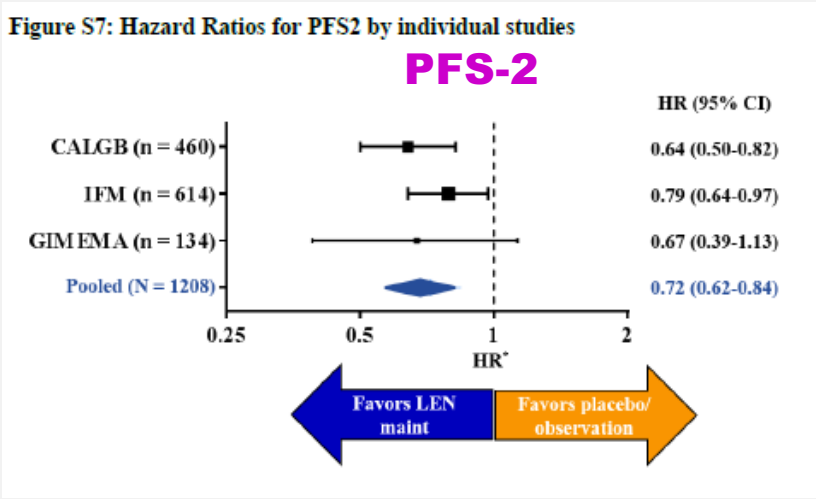
Risk of selecting resistant clones

Metaanalysis

IFM 2005-02, CALGB 100104, GIMEMA RV-MM-PI-209D

PFS-2

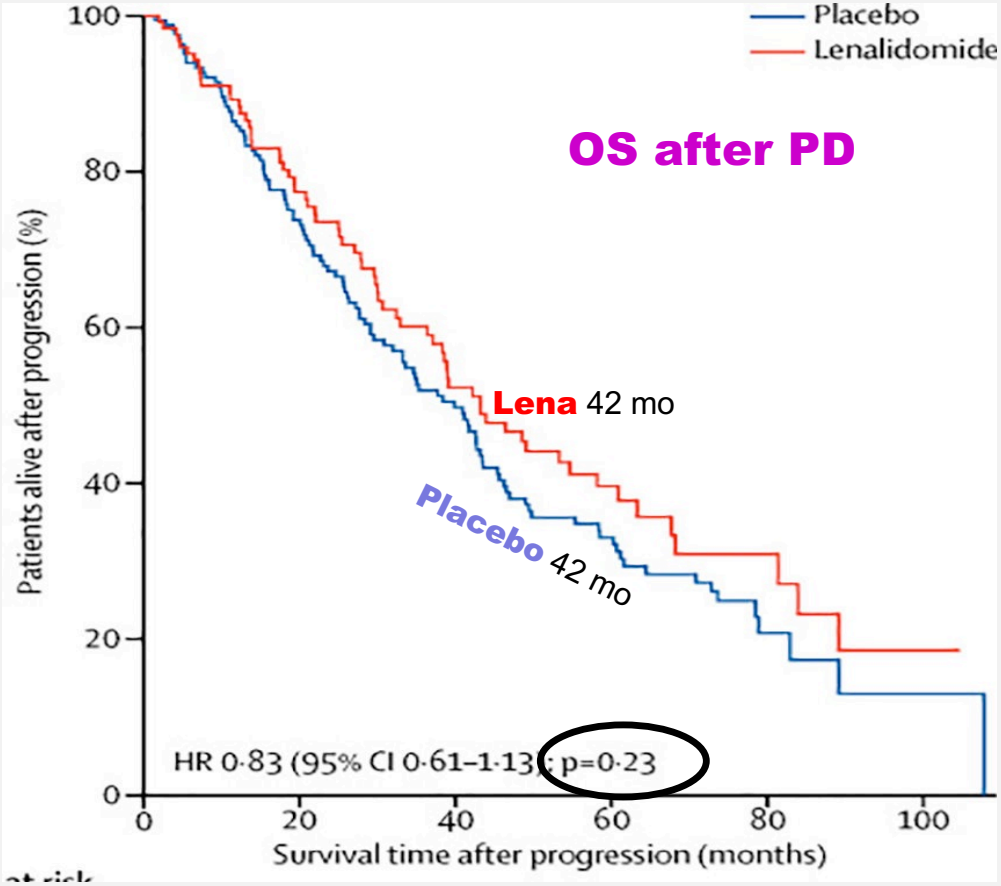




McCarthy … JCO 2017

Risk of selecting resistant clones

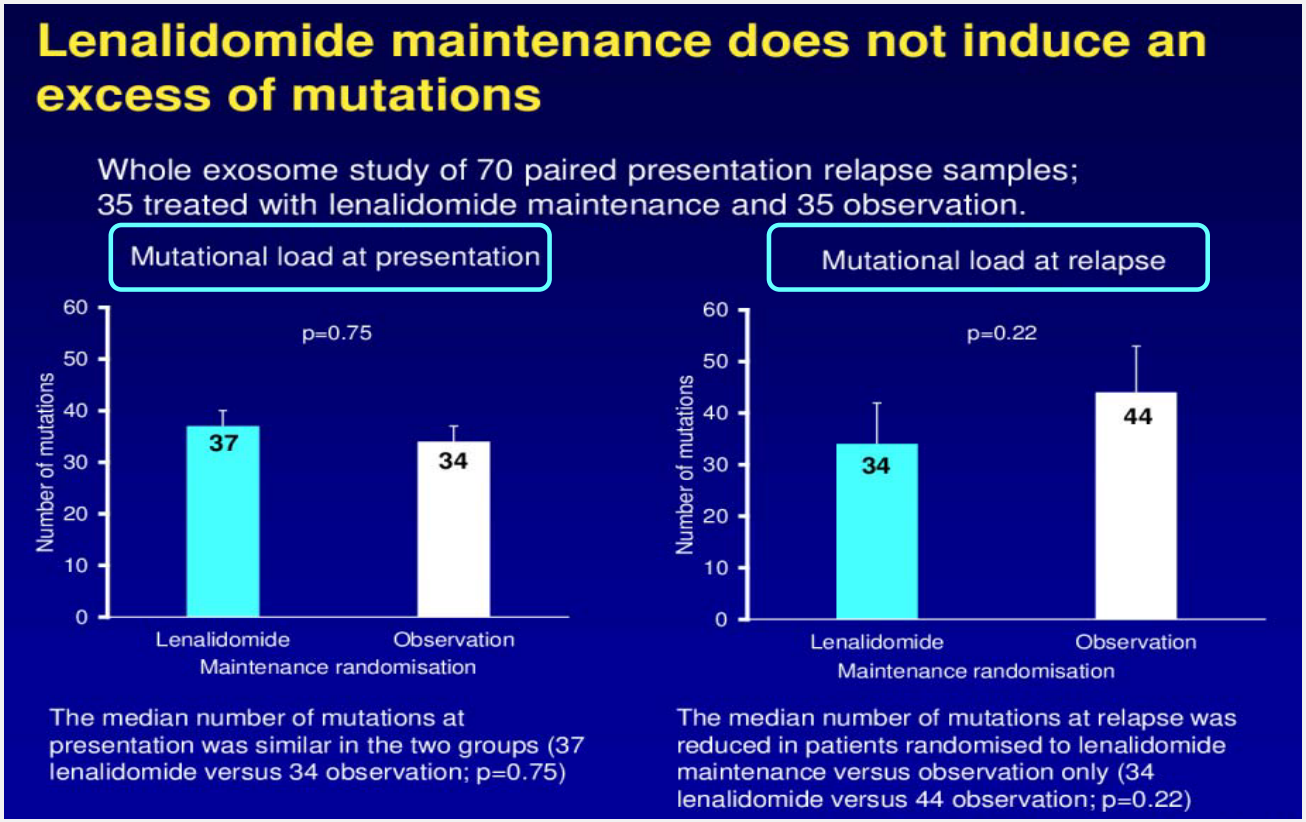
Update analisys of CALGB 100104



Holstein and McCarthy … Lancet Hemat 2017

Risk of selecting resistant clones

Myeloma XI trial



Jackson .. ASH 2016 abs 1143

Risk of selecting resistant clones

Conclusion

⇓

Continous lenalidomide maintenance
does not induce resistant clones

Maintenance Therapy

Until progression: ?

Second concern

Risk of Second Primary Malignancies (SPMs)

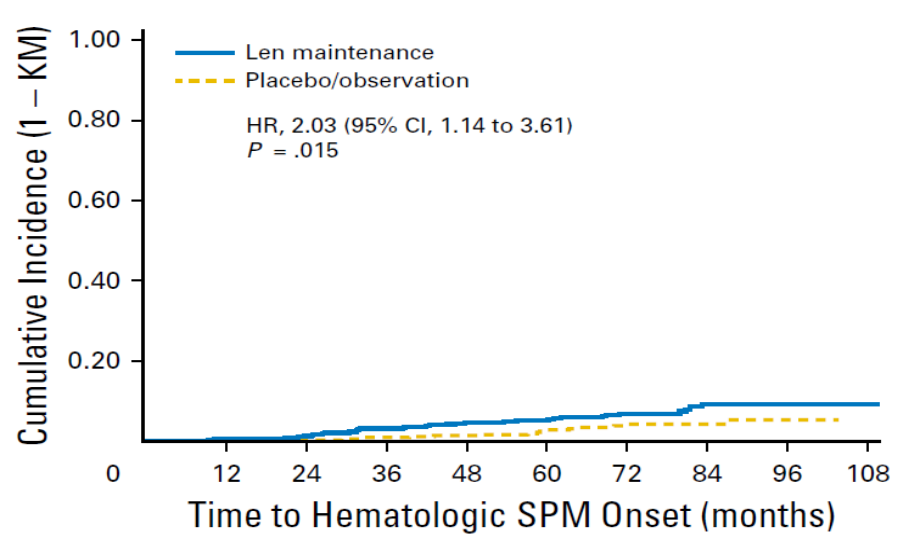
Richardson .. Exp Opin Pharm 2017

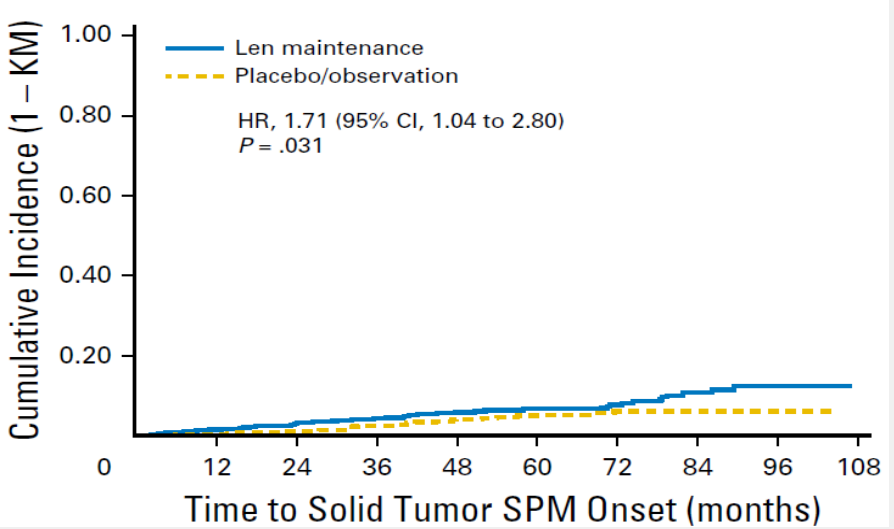
Risk of Second Primary Malignancies

Frequency of SPMs

	Lenalidomide	Placebo / Obs
Hematologic SPMs	Before PD **5.3%** Before and after PD 6.1%	Before PD **0.8%** Before and after PD 2.8%

	Lenalidomide	Placebo / Obs
Solid tumor SPMs	Before PD **5.8%** Before and after PD 7.3%	Before PD **2%** Before and after PD 4.2%





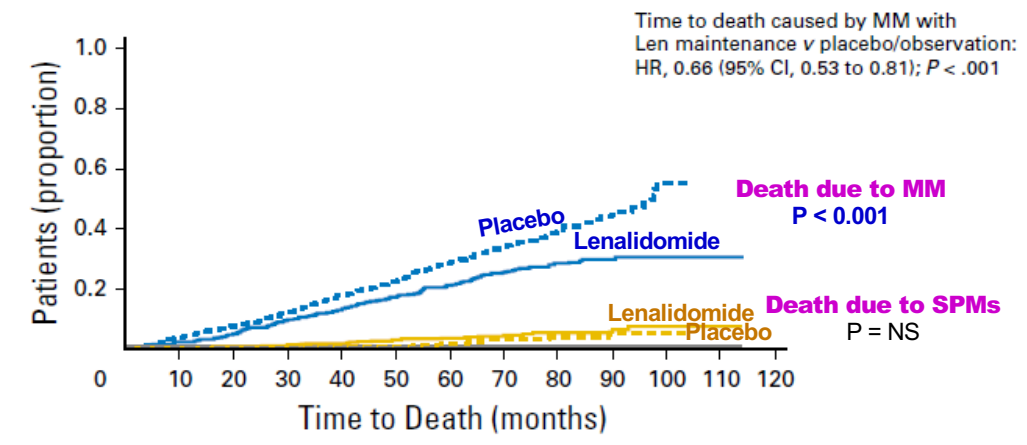
The median time to haematological tumor: **50 months**

The median time to solid tumor: **22 months**

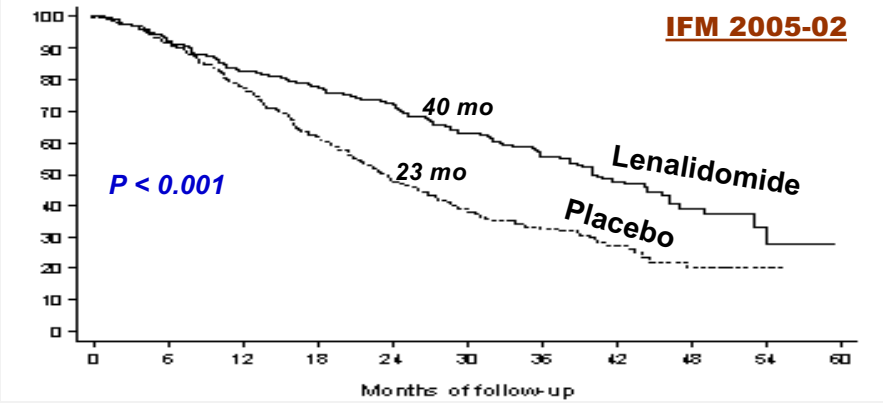
McCarthy … JCO 2017

Risk of Second Primary Malignancies

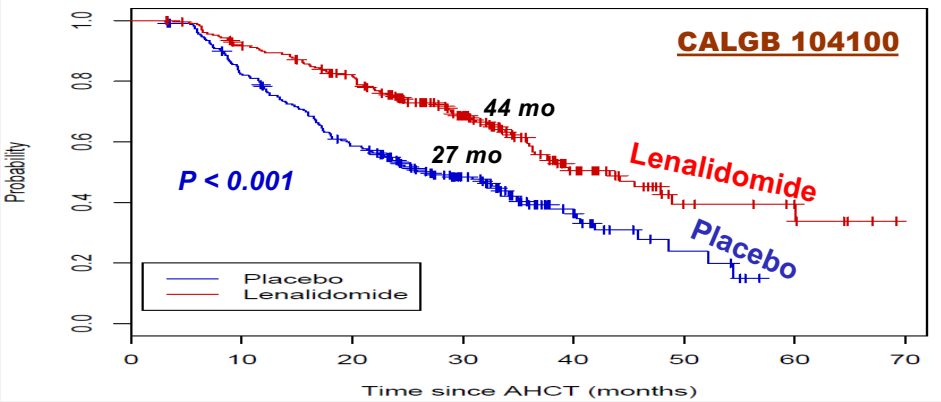
Time to Death



EFS



EFS



McCarthy … JCO 2017

Risk of Second Primary Malignancies

Conclusion

The incidence rate of SPMs with Lenalidomide maintenance is higher respect Placebo/Observation …

…. but the longest time to progression disease and the survival benefit of Lenalidomide Maintenance outweigh the risk of developing an SPM

Maintenance Therapy

Until progression: ?

Third concern

High costs

Cost-effectiveness of lenalidomide maintenance in patients with multiple myeloma who have undergone autologous transplant of hematopoietic progenitor cells

Antonio Olry de Labry Lima[1,2,3] · Vicente Gimeno-Ballester[4] · Rafael Ríos Tamayo[2,5] · David Epstein[6] · Antonio Matas Hoces[7] · Esmeralda Ríos Sánchez[8] · Leticia García Mochón[1,2,3] · Emilio Jesús Alegre-del Rey[8]

Cost effectiveness

Analysis based on costs extrapolated from CALGB 100104 and IFM 2009-02 trials, according to the perspective of the Spain National Health System

Cost-utility analysis by partitioned survival model with 4 mutually exclusive health states:

- progressione free
- progression
- progression after following line
- death

The results in health were measured as:

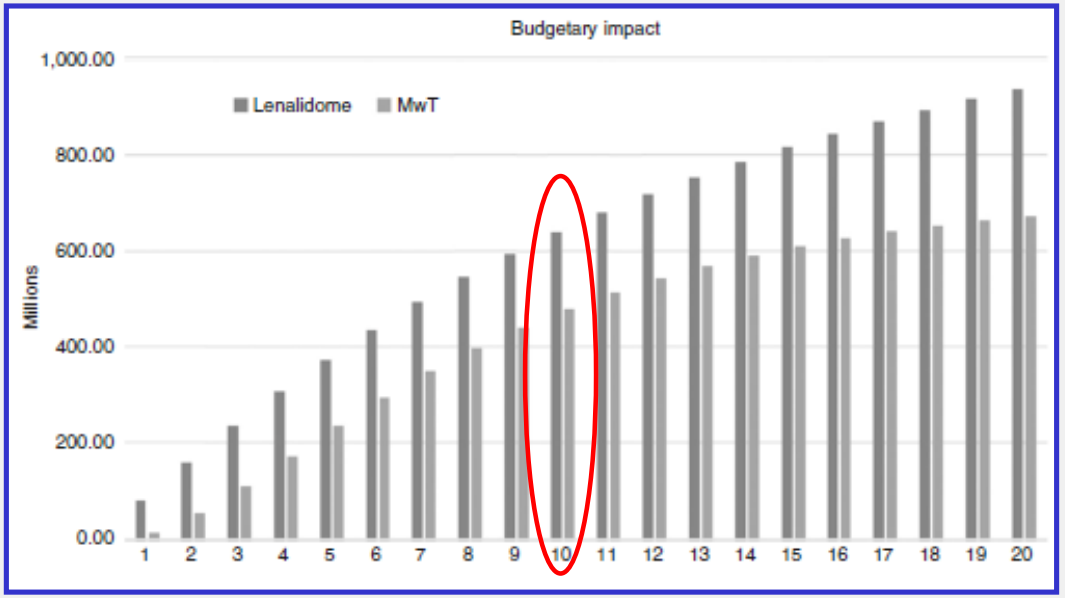
- years of life gained (**YGs**)
- quality-adjusted life years (**QALYs**).

Outcome misures used:

- Incremental cost-efficacy ratio (**ICER**)
- Incremental cost-utility ratio (**ICUR**)

SPAIN according to WHO

- Incidence MM 2420 cases/year
- Candidates for ASCT: 33%
- Consequently ~ 799 pts/yr go to the ASCT



CALGB 104100: Costs per single patient at 10 years		
	Lenalidomide mainten	Osservazione
Efficacy	7.59 YGs (5.72 QALY)	6.58 YGs (4.61 QALY)
Costs	789.578 €	528.963 €
ICUR	235.107 € / QALY	
ICER	256.913 € / YGs	

Olry de Labry Lima … BMT 2019

Cost effectiveness

Lenalidomide maintenance is an important therapeutic advance that should be made available to patients, but its price is high and this adds incertainty about the optimal duration of the treatment

Maintenance Therapy

Optimal duration

On one side

OS benefit

From the other

Concern about SPMs
Concern about Costs

Fixed or Continuous therapy ?

We wait results of **phase III studies ongoing** comparing
fixed versus continous maintenance ……

Maintenance Therapy

Optimal duration

Premature discontinuation of Lenalidomide Maintenance in IFM 2005-02 may have prevented the survival benefit

	Induction prior-ASCT	Maintenance	Dose Lenalid	Follow up	PFS / TTP Lena Plac	OS Lena Plac
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Optimal duration

Median Duration of Maintenance

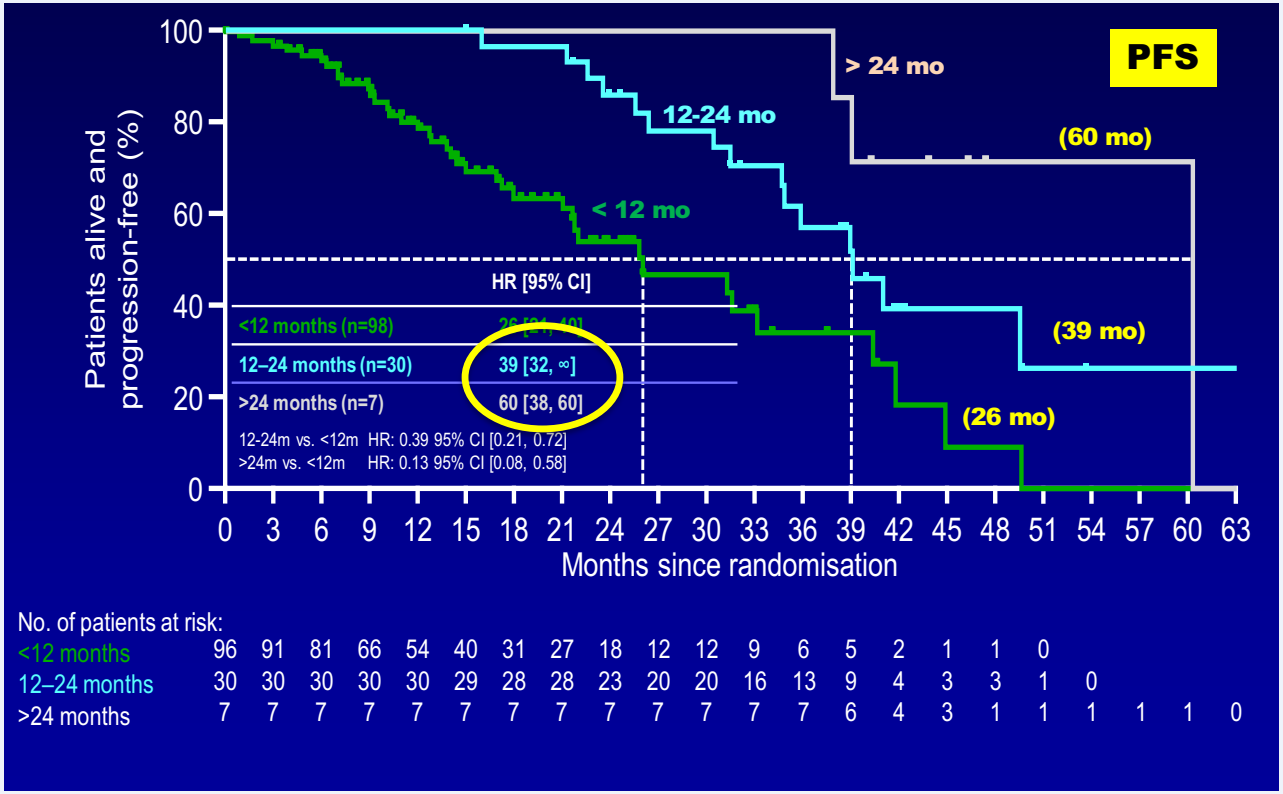
	CALGB			IFM*			GIMEMA		Pooled	
		Placebo (n = 221)		Len Maintenance (n = 306)						
Treatment Duration	Len Maintenance (n = 224)	Placebo Up to Crossover (n = 221)	Len After Crossover (n = 76)†	All Patients (n = 306)	Cohort Treatment Stopped Jan 2011 (n = 119)‡	Placebo (n = 302)	Len Maintenance (n = 56)	Observation (n = 67)	Len Maintenance (n = 586)	Placebo or Observation (n = 590)
Mean, months (range)§	30 (0-108)	13 (0-51)	25 (0-61)	25 (0-55)	39 (27-55)	20 (0-49)	35 (2-71)	29 (0-75)	28 (0-108)	22 (0-86)
Duration category, No. (%)										
≥ 1 year	150 (67.0)	95 (43.0)	46 (60.5)	217 (70.9)	119 (100)	211 (69.9)	44 (78.6)	51 (76.1)	411 (70.1)	391 (66.3)
≥ 2 years	116 (51.8)	32 (14.5)	33 (43.4)	170 (55.6)	119 (100)	121 (40.1)	33 (58.9)	36 (53.7)	319 (54.4)	230 (39.0)
≥ 3 years	82 (36.6)	6 (2.7)	24 (31.6)	88 (28.8)	74 (62.2)	32 (10.6)	29 (51.8)	23 (34.3)	199 (34.0)	95 (16.1)
≥ 4 years	54 (24.1)	1 (0.5)	18 (23.7)	11 (3.6)	11 (9.2)	2 (0.7)	24 (42.9)	17 (25.4)	89 (15.2)	44 (7.5)

McCarthy … JCO 2017

Optimal duration

Mieloma XI

Comparison <12 months, 12–24 months and >24 months



Longer time on LEN maintenance tharapy reduced risk of progression

Jackson .. ASH 2016 abs 1143

Optimal duration

Prolonged Survival With a Longer Duration of Maintenance Lenalidomide After Autologous Hematopoietic Stem Cell Transplantation for Multiple Myeloma

Idrees Mian, MD[1]; Denái R. Milton, MS[2]; Nina Shah, MD[3]; Yago Nieto, MD, PhD[3]; Uday R. Popat, MD[3]; Partow Kebriaei, MD[3]; Simrit Parmar, MD[3]; Betul Oran, MD[3]; Jatin J. Shah, MD[4]; Elisabet E. Manasanch, MD[4]; Robert Z. Orlowski, MD, PhD[4]; Elizabeth J. Shpall, MD[3]; Richard E. Champlin, MD[3]; Muzaffar H. Qazilbash, MD[3]; and Qaiser Bashir, MD[3]

Retrospectively analysis: **464 patients** placed on maintenance lenalidomide after auto-HCT between 2007 and 2013.(USA)
Discontinuation rate 20% (due to adverse events)
Effect of duration of maintenance therapy was assessed in multivariate analysis (not specified if patients in PD have been removed from the analysis)

Multivariable Analysis for Progression-Free and Overall Survival

	Progression Free Survival		Overall Survival	
Subgroups	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
High-risk cytogenetics (yes vs no)	1.81 (1.18, 2.78)	0.006	3.79 (2.01, 7.14)	<0.001
Initiation of maintenance therapy (early vs late)	0.92 (0.64, 1.32)	0.64	0.90 (0.49, 1.66)	0.73
CR after auto-HCT (yes vs no)	1.17 (0.80, 1.71)	0.41	1.28 (0.69, 2.38)	0.43
CR with maintenance therapy (yes vs no)	0.85 (0.44, 1.64)	0.63	0.38 (0.10, 1.49)	0.17
Duration of maintenance therapy				
(> 2 years vs ≤ 2 years)	0.13 (0.04, 0.38)	<0.001	0.09 (0.03, 0.26)	<0.001
(> 3 years vs ≤ 3 years)	0.02 (0.00, 0.44)	0.012	0.05 (0.00, 0.83)	0.037

No association between duration of maintenance and development of **SPMs**

Mian .. Cancer 2016

Optimal duration

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2018.1473577

Taylor & Francis
Taylor & Francis Group

Check for updates

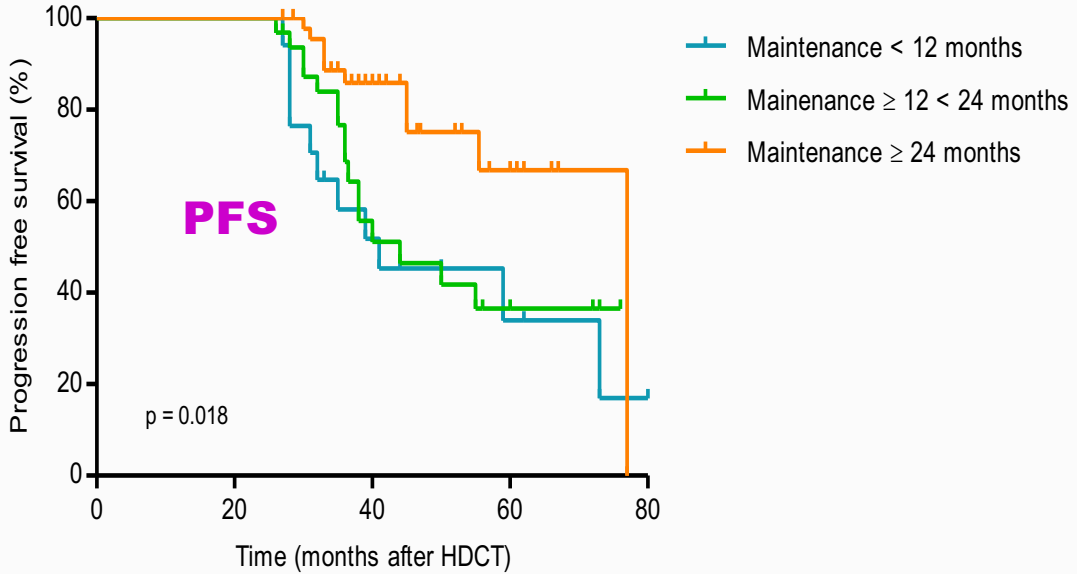
LETTER TO THE EDITOR

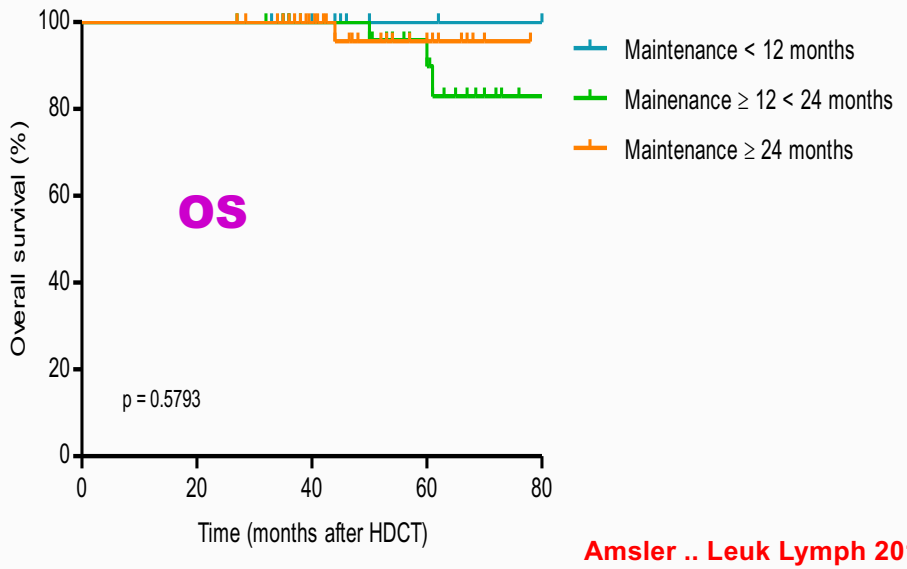
Prolonged survival with increasing duration of lenalidomide maintenance after autologous transplant for multiple myeloma

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]

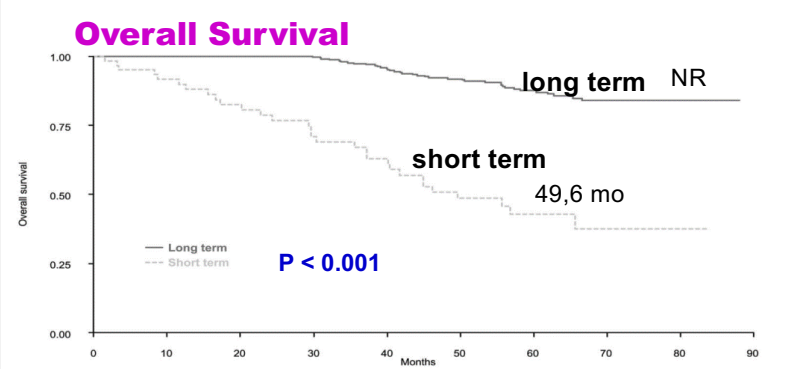
Retrospective analisis: **149 patients** from single-center (Bern, Switzerland) between 2010 and 2014
Median duration maintenance lenalidomide was 14 months (range 1-64 mo)
Excluded from analysis pts who stopped maintenance before 2 years due to PD

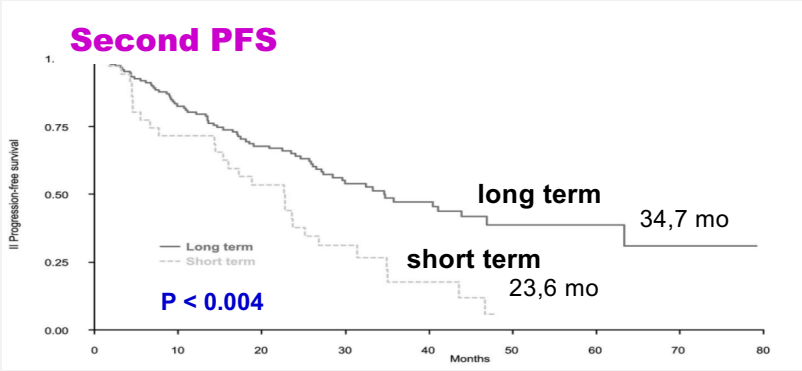
3 groups on the basis of the duration of lenalidomide treatment
- Maintenance **≥ 24 months** (group 1)
- Maintenance **12-24 months** (group 2)
- Maintenance **< 12 months** (group 3)

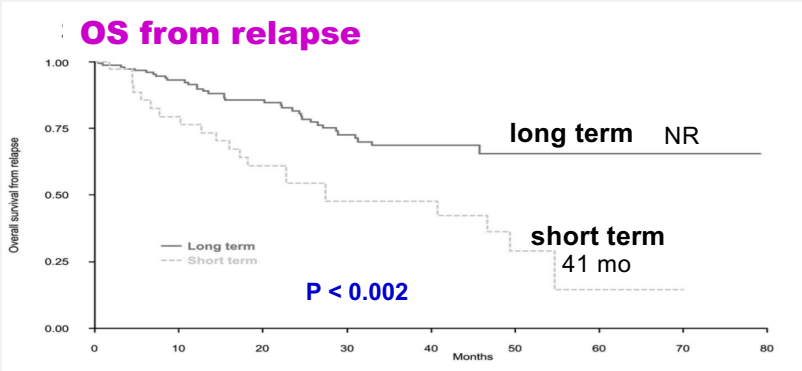




Amsler .. Leuk Lymph 2018







Pooled analysis two phase III trials (RV-MM-EMN-441 + EMN01)

RV-MM-EMN-441: induction 4 Rd → 2 ASCT → maint R vs RP
induction 4 Rd → 6 CRD → maint R vs RP

EMN01: induction 9 Rd → maint R vs RP
induction 9 MPR → maint R vs RP
induction 9 CPR → maint R vs RP

Median follow-up 58 months

2 groups on the basis of the duration of lena therapy
- Maintenance > 24 months (group 2)
- Maintenance < 24 months (group 3)

Excluded from analysis patients who stopped maintenance before 2 years due to PD

Secondary endpoint:
impact of duration of lenalidomide on long-term outcome
- **OS from start of maintenance**
- **Second PFS**
- **OS from relapse**

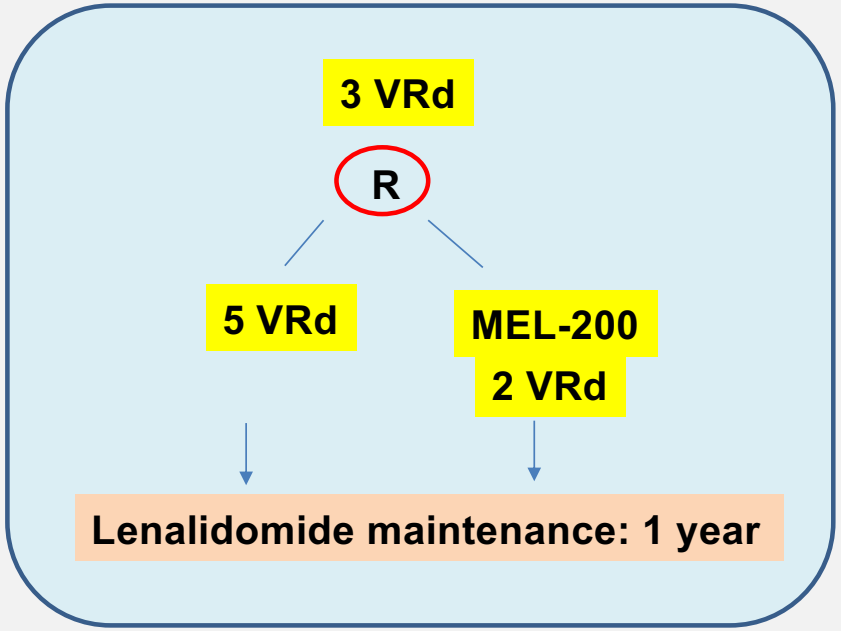
Improvement of approximatively 10 months from PFS to TTNT in the overall population (biochemical relapses require more time to become symptomatic: * progressive decrease tumor burden and *absence of significant induced resistance)

Gay et al… 2019

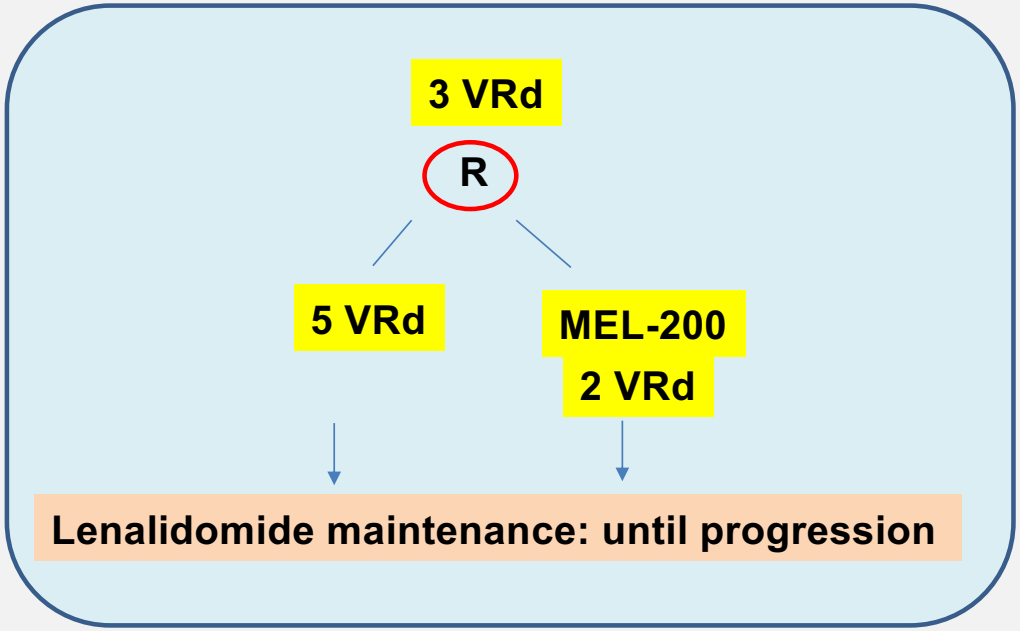
Cross trial comparison

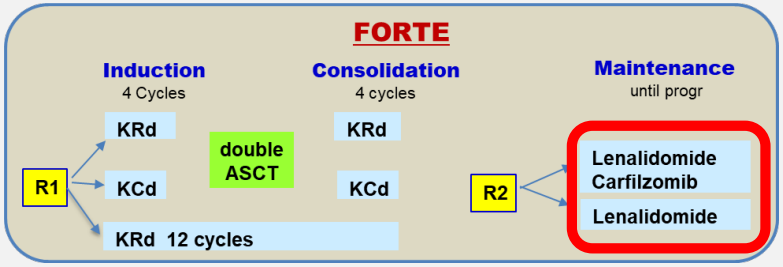
between these two studies will be interesting

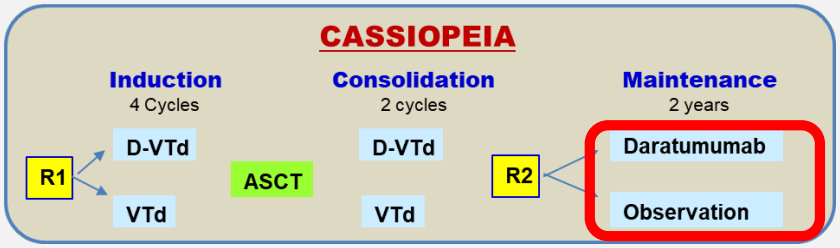
IFM 2009 trial : 700 pts NDMM

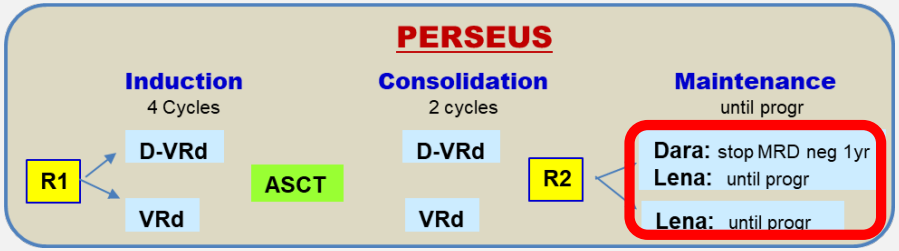


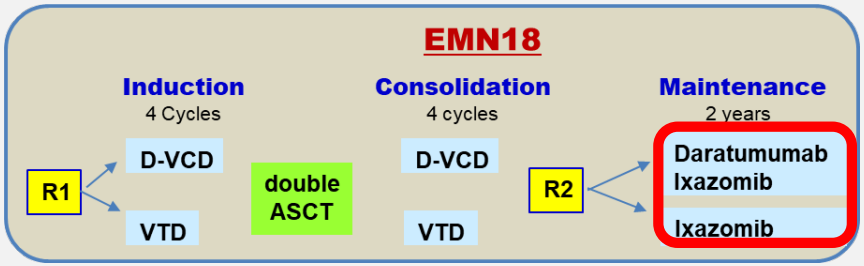
DFCI 2009 trial: 660 pts NDMM











Maintenance

3° generation studies

These studies do not consider duration of maintenance: " fixed vs continuous "

SUMMARY

Lenalidomide maintenance until progression represents the standard of care for TE patients and was approved on the basis of four phase III studies e a meta-analysis (EMA and FDA)

Lenalidomide maintenance until progression **extends PFS** and **OS** and increases the **rate of neg-MRD responses** (recent data from EMN02 study showed that 50% of patients who are MRD positive before maintenance became MRD negative after ≥ 1 year and within the first 2 years of lenalidomide maintenance)

The **optimal duration** of lenalidomide maintenance therapy (continous until progression vs prolonged but fixed duration) still remains an **open issue**

Long term duration of lenalidomide maintenance in retrospective post hoc analyses is **superior** to short maintenance

Ongoing randomized, prospective phase 3 trial, MRD based compared fixed versus continous maintenance. **Monitoring of MRD status** during the treatment may be informative about maintenance cessation: how deep the MRD negativity ? at what time points ? with negative imaging ?

CONCLUSION

At the moment
Lenalidomide maintenance after-ASCT should be applied
until disease progression

Recommended at least 2 years
(effective median duration of therapy in most trials)

THE END