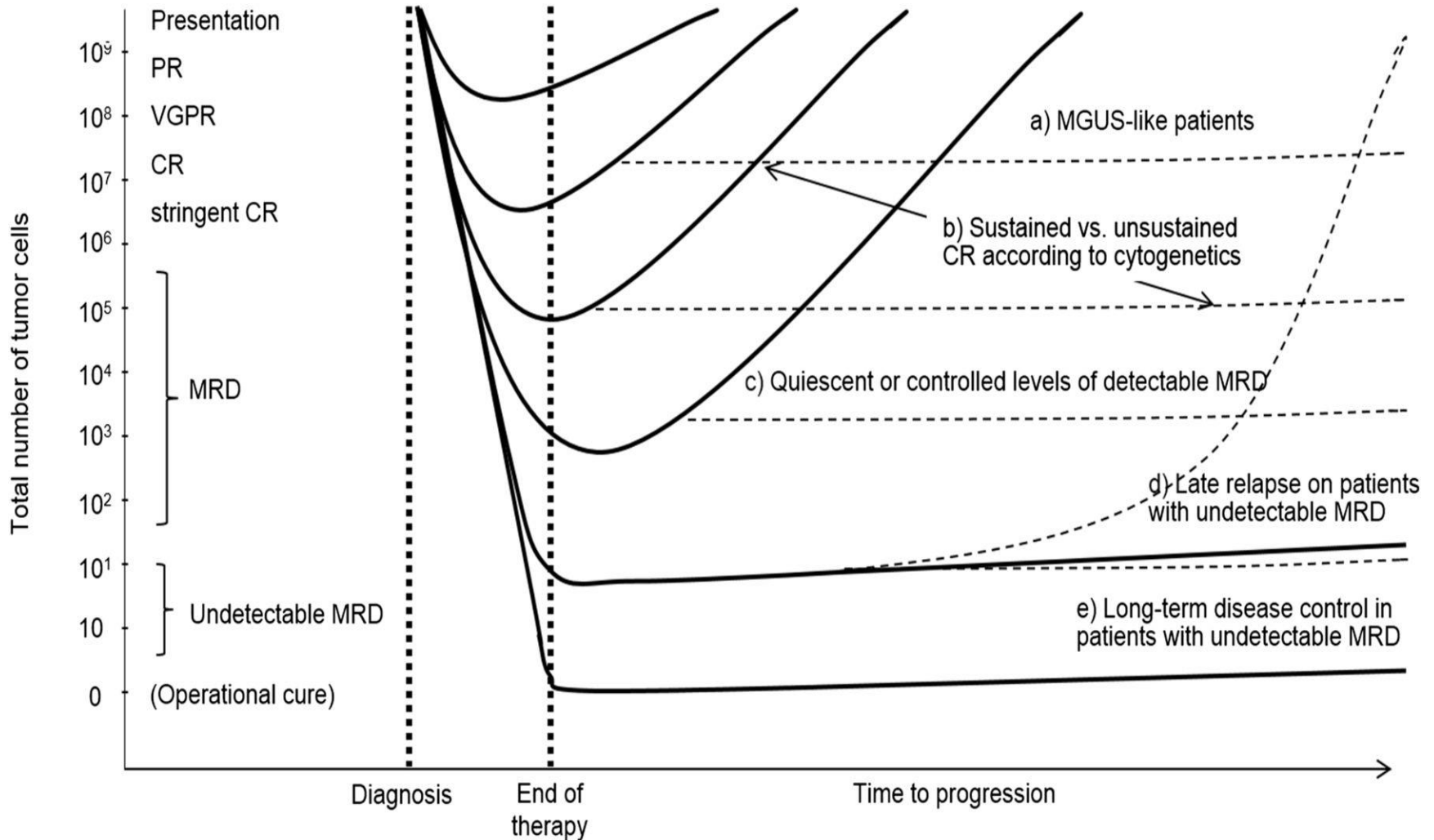


# MULTİPL MİYELOMDA İDAME

*Dr. Sevgi Kalayoğlu Beşışık*  
İstanbul Tıp Fakültesi

# MM'da yanıt derinliği kliniği etkiler



# Myelom tedavisindeki akım 2016



# MM'da idame tedavisi ilişkili son durum

- İdame tedavisinin MM'da PFS ve OS'a etkisi nedir?
- İdame tedavisinde ilaç seçimi hangi durumlara dayandırılmalıdır?
- İdame ilaç(lar)ı hangi dozda verilmelidir?
- İdame tedavisinin süresi ne olmalıdır?
- İdame tedavisinin sakıncaları var mıdır?

# Miyelomda interferon idamesi sağ kalımı etkiler

*Annals of Oncology* 11: 1427–1436, 2000.

## **Interferon- $\alpha$ treatment in multiple myeloma: Meta-analysis of 30 randomised trials among 3948 patients**

E. Fritz & H. Ludwig

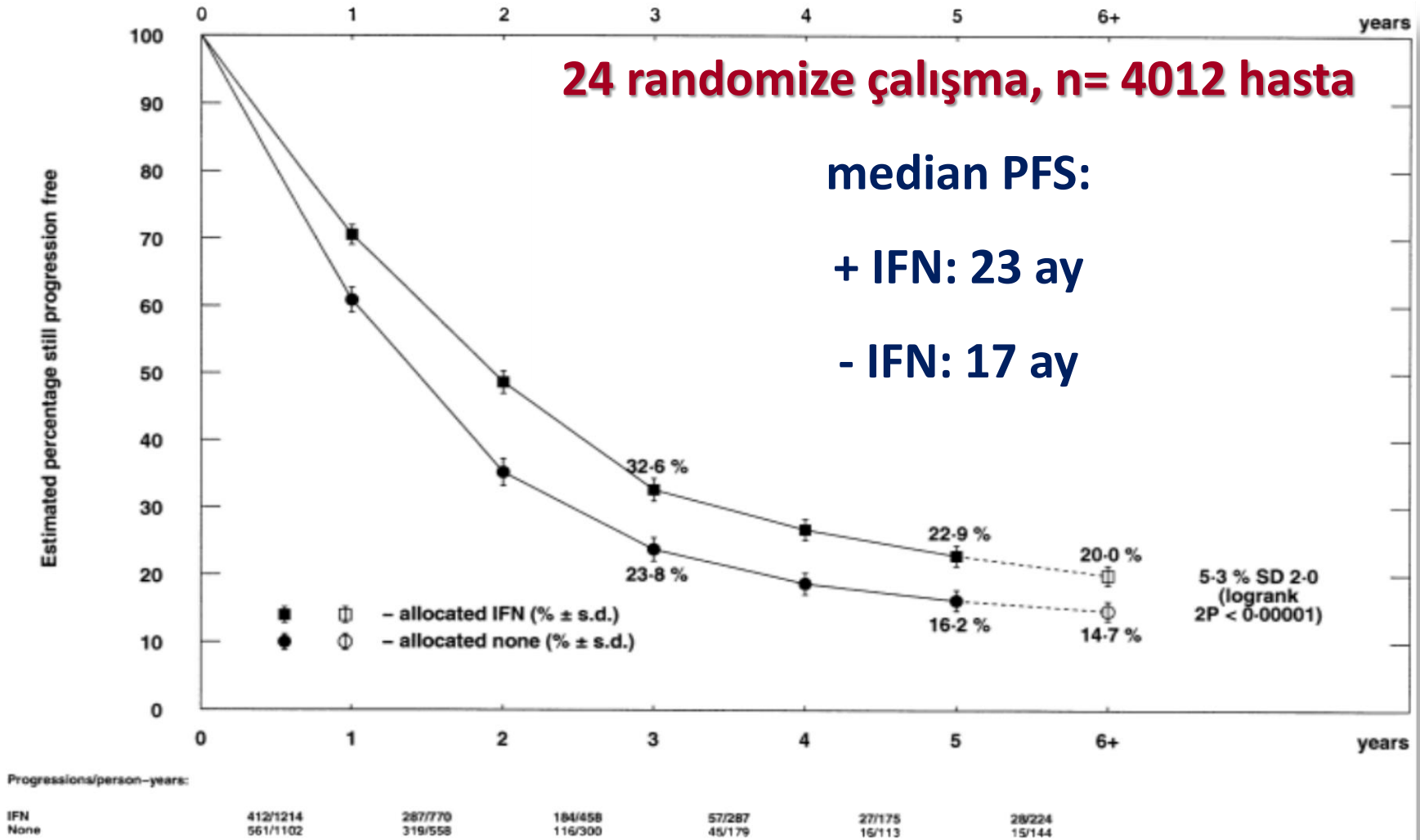
*British Journal of Haematology*, 2001, 113, 1020–1034

## **Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients**

THE MYELOMA TRIALISTS' COLLABORATIVE GROUP Secretariat based at Imperial Cancer Research Fund/Medical Research Council Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK

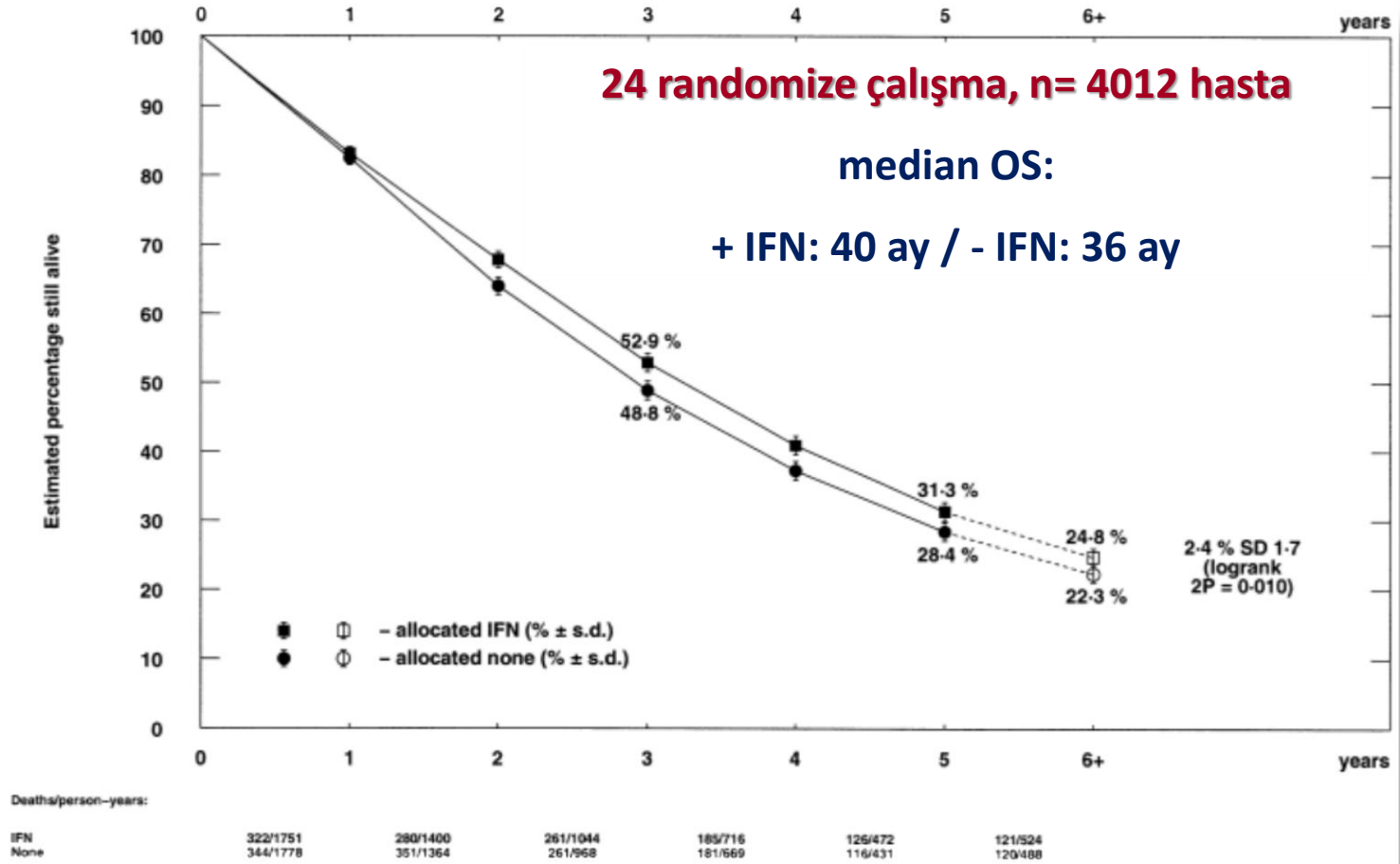
# Miyelomda interferon idamesi

PFS'i uzatmaktadır



# Miyelomda interferon idamesi

OS'ı uzatmaktadır



British Journal of Haematology, 2002, 115 1020-1034,



# Miyelomda interferon idamesi sonrası nüks dekzametazona duyarlıdır

Am J Hematol. 2000 Nov;65(3):204-9.

## **Randomized trial of alpha-interferon or dexamethasone as maintenance treatment for multiple myeloma.**

Alexanian R<sup>1</sup>, Weber D, Dimopoulos M, Delasalle K, Smith TL.

### **Abstract**

In order to assess the role of alpha-interferon or dexamethasone as maintenance therapy for multiple myeloma, 172 consecutive, previously untreated patients with disease of low or intermediate tumor mass received primary therapy with oral melphalan and intermittent, high-dose dexamethasone (MD), repeated monthly. Within 5 months, 84 responding patients were assigned at random to maintenance treatment with alpha-interferon (3 mU s.c. 3 x weekly) or dexamethasone (20 mg/m<sup>2</sup> p.o. each morning for 4 days) repeated monthly until relapse. Upon relapse, MD was resumed for 2 cycles and second responses were maintained with 4-day courses of melphalan-dexamethasone until second relapse. Initial response was achieved in 88 patients (51%) after a median 0.7 month and no more than 3 courses of MD, a frequency of response similar to that observed previously with dexamethasone alone. There were identical median remissions of 10 months with interferon or dexamethasone, both maintenance regimens being associated with infrequent, mild, and reversible side effects. Significantly more patients responded again to resumption of MD after disease relapse to interferon (82%) than to dexamethasone (44%) ( $P = 0.001$ ). The median remission from randomization to melphalan-resistant second relapse was 32 months for patients maintained initially on interferon compared to 19 months for those on dexamethasone ( $P = 0.01$ ). These findings supported an advantage for interferon in remission maintenance by increasing the frequency of tumor recontrol with later treatment that included dexamethasone.

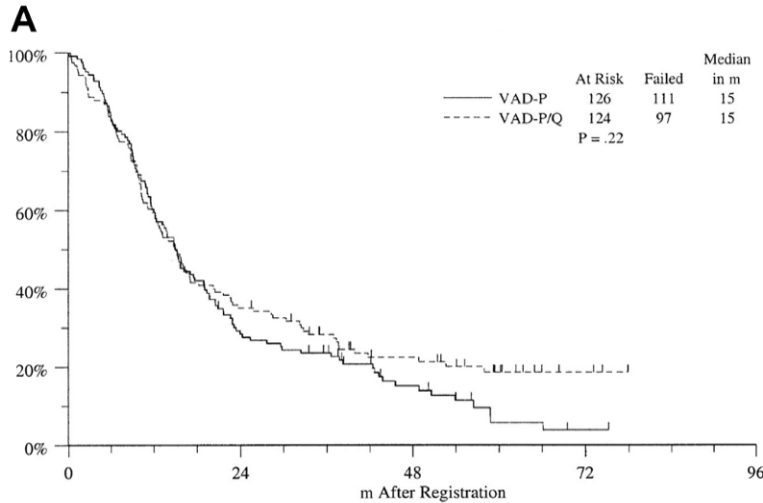


# MM'da interferon idamesi- özet:

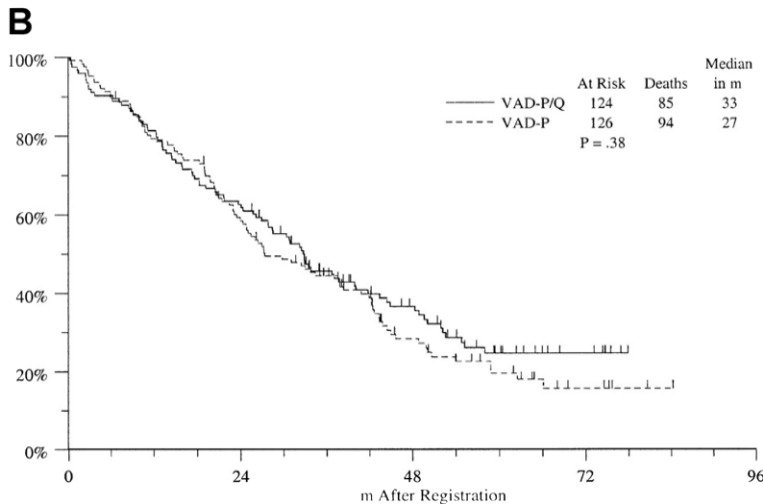
- **Interferon (IFN):**

- 3mÜ/gün, haftada 3 kez, 6 – 12 ay süre ile
- IFN ile ilerlemesiz sağ kalım (PFS) ve genel sağ kalım (OS) IFN'siz kola göre daha uzun (5 ay ve 26 ay).
- Tolerans zor, yaşam kalitesi olumsuz etkilenir.

# Multipl Miyelomda VAD sonrası Prednizolon İdamesi ile PFS ve OS Değişmemektedir.

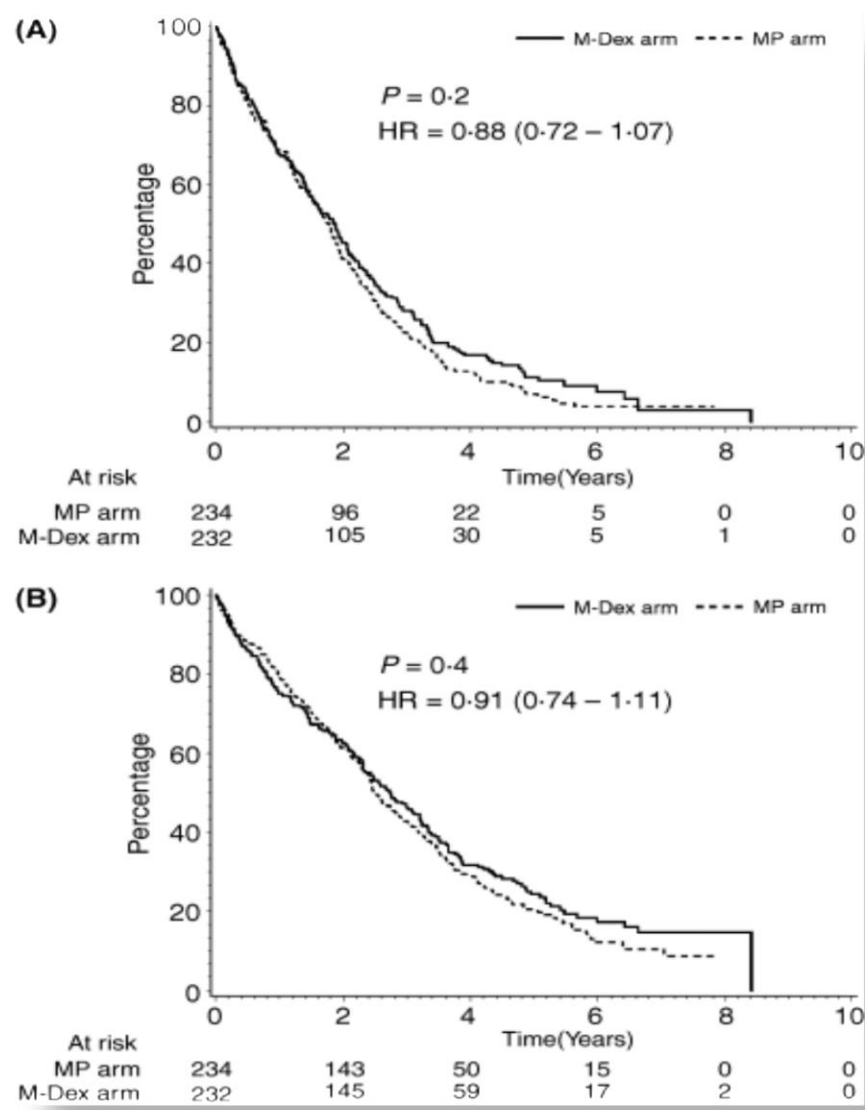


**VAD-P / VAD-PQ**  
**Prednizolon: 10mg veya 50mg/gün aşırı**



**Median PFS benzer**

# Multipl Miyelomda MP veya MD sonrası dekzametazon idamesi ile PFS ve OS Değişmemektedir



Dekzametazon

40mg /gün, 4 gün/ay

# Multipl miyelomda thalidomid

## idamesi

Induction

MRC IX çalışması

Meta-analiz

Maintenance

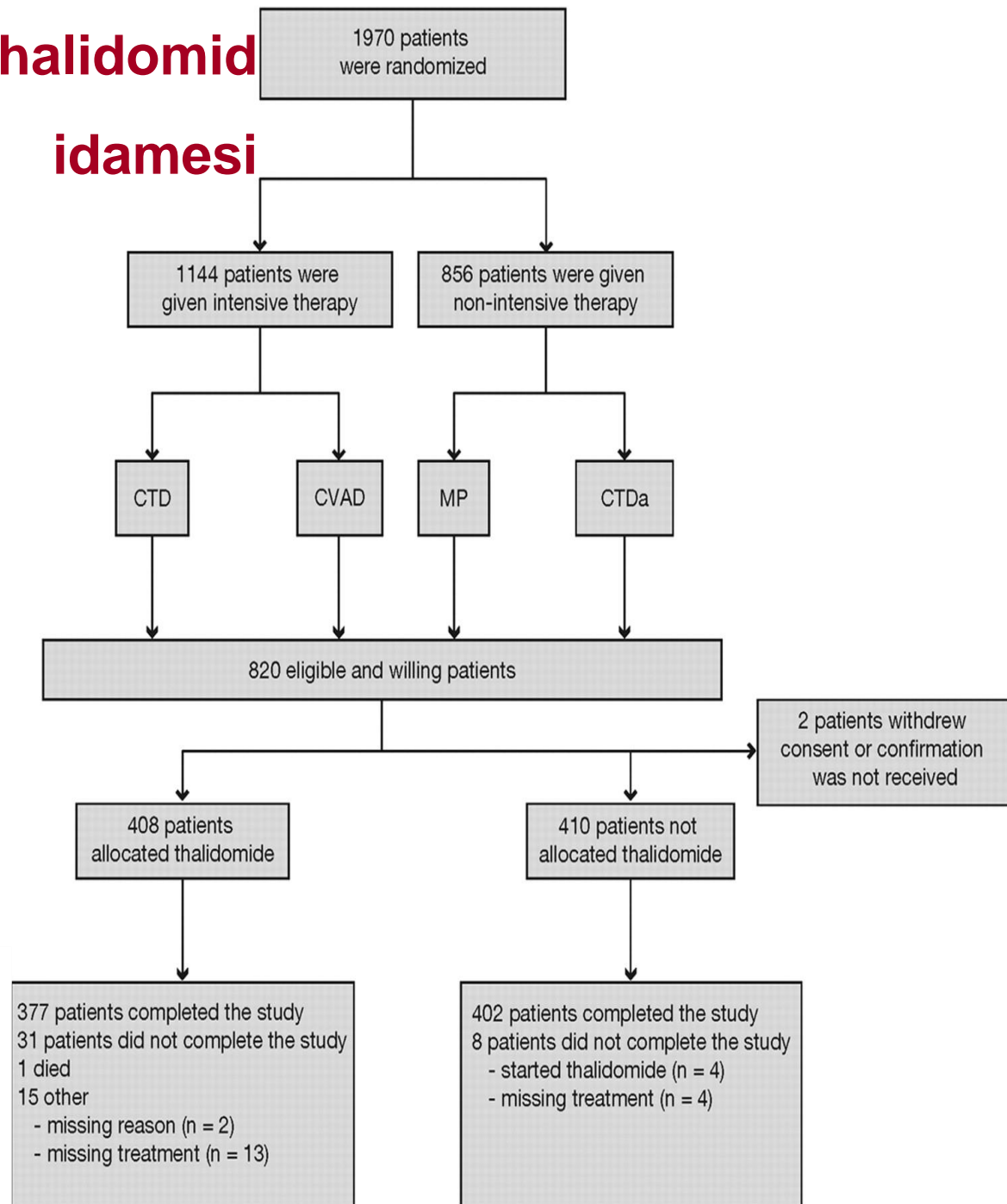
Maintenance  
ITT population

**Thalidomid:**

50mg/g; 4 hf sonra 100mg/g

tolere edebildiği sürece ilerlemeye

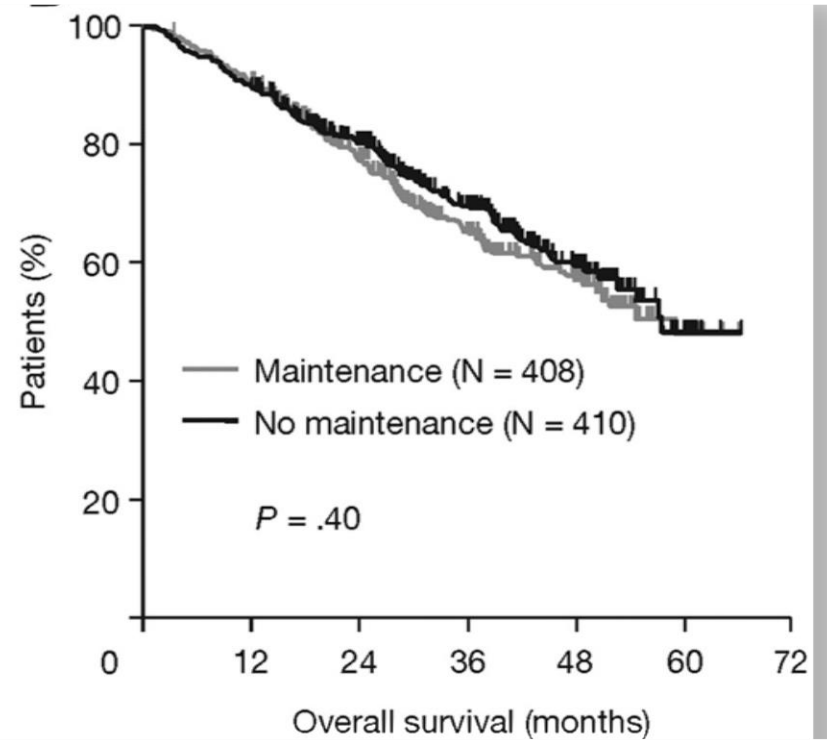
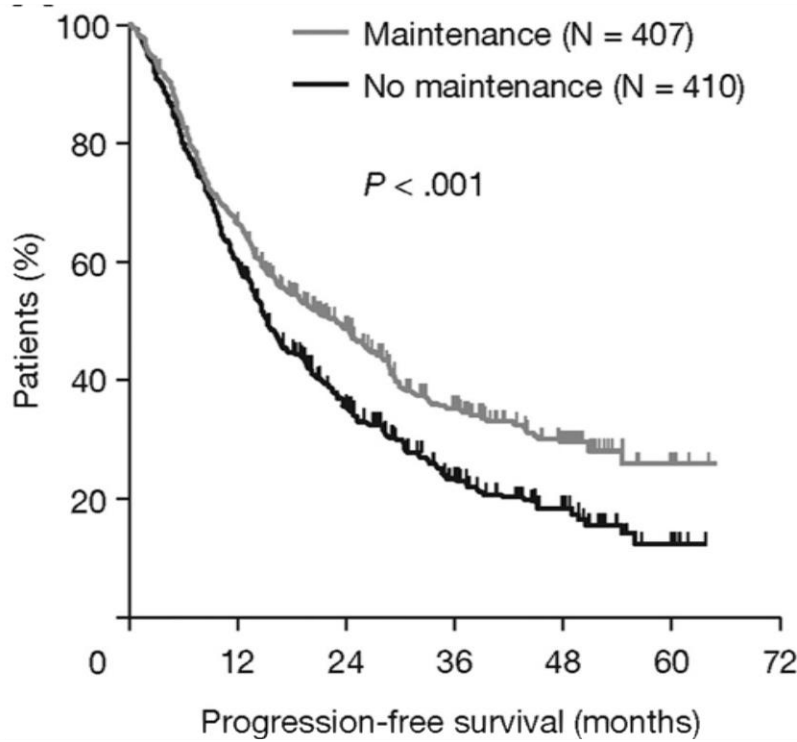
kadar



# Multipl Miyelomda Thalidomid İdamesi ile OS

## Değişmemektedir.

median PFS daha uzun (23/15ay), nüks yanıtlı;  
geç OS iyileşmektedir.

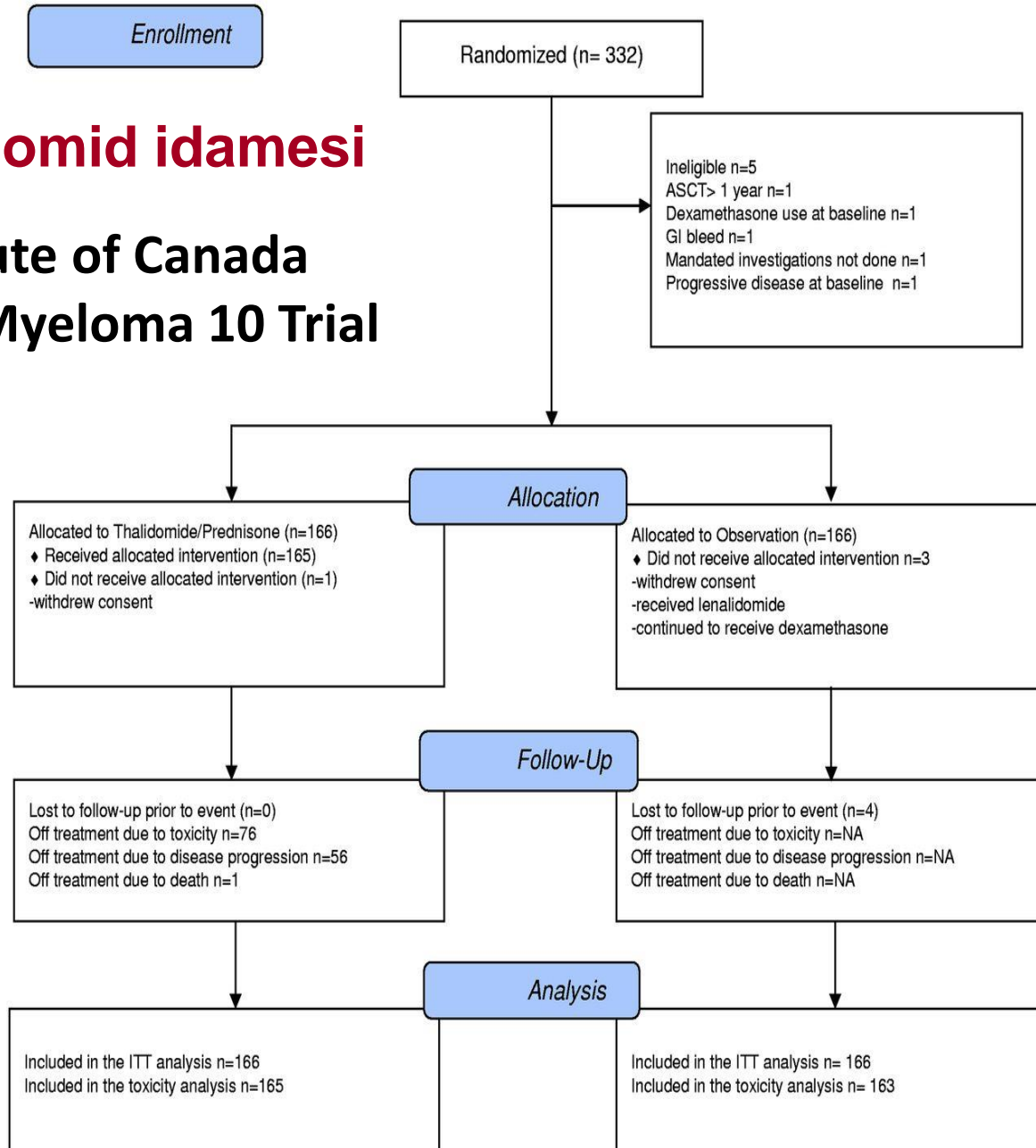


FISH ile yüksek riskli grupta median PFS faydalanımı sağlanamamaktadır.

# Multipl miyelomda thalidomid idamesi

## National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial

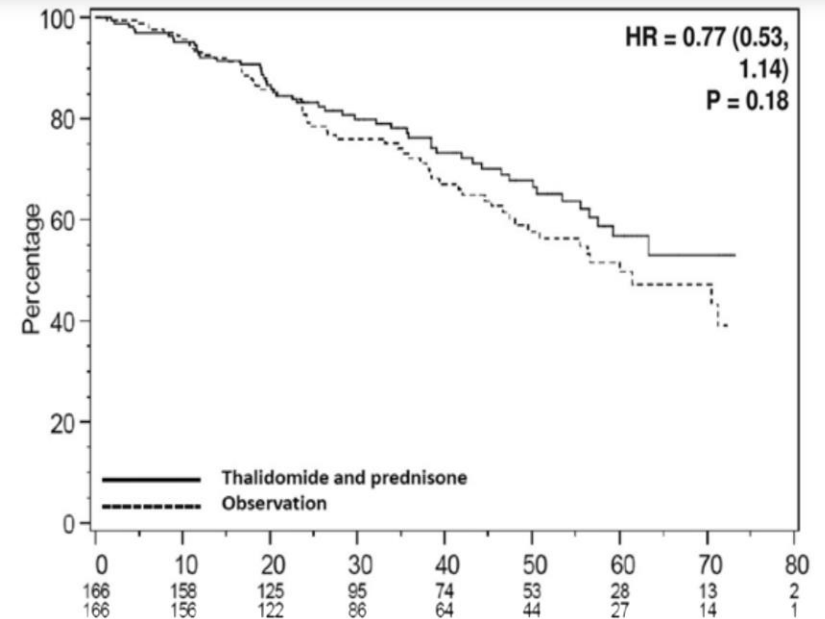
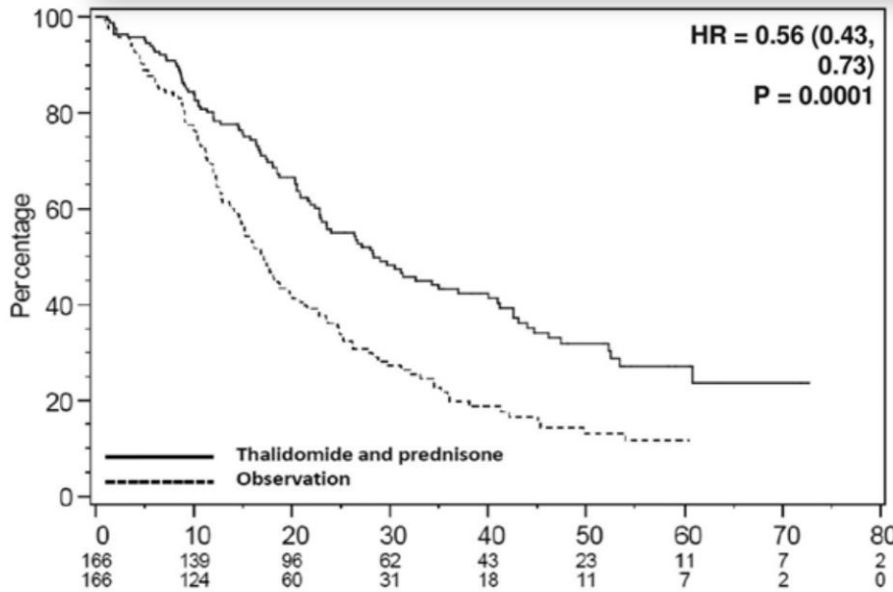
**Thalidomid 200mg/gün ,  
Prednizon 50mg/gün aşırı**



# Multipl Miyelomda Thalidomid İdamesi ile OS değişmemektedir.

4 yıl izlem

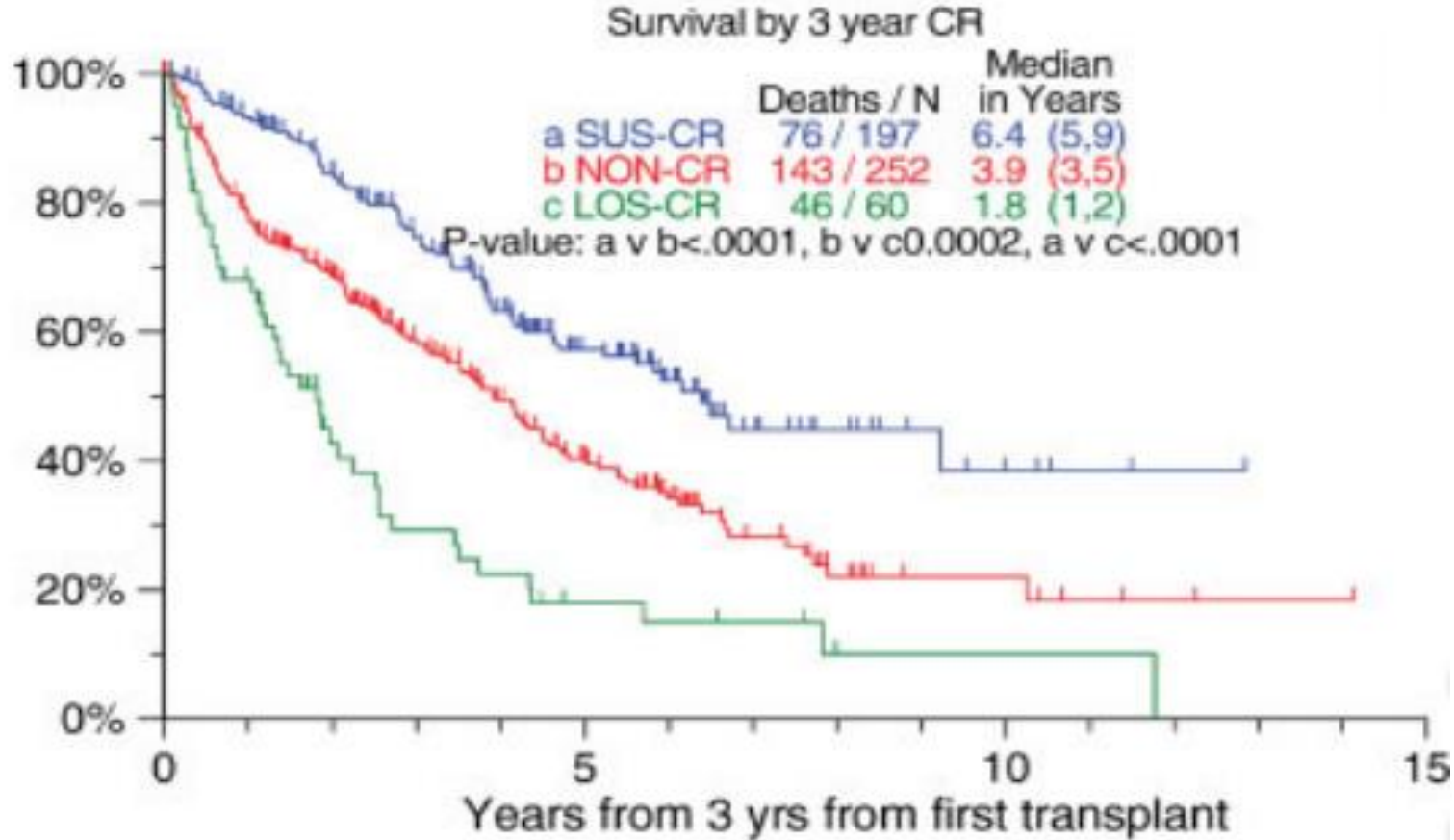
PFS: %32 / %14, OS: %68 / %60





# Tam yanıt elde edilmesinden daha önemlisi tam yanıtın sürmesidir.

Total terapi veya diğer tedavi fark etmeksizin CR erken kaybı kötü seyirlidir



**Tedavi sonrası arda kalan tümör yükü; *minimal rezidüel hastalık durumu [MRD] yanıt kalıcılığını belirler***

Standart CR tanımlama kriterleri CR kalıcı /kalıcı olmayan CR arasındaki  
« farkı » tespitte yetersizdir.

**Transplant uygun veya değil CR'da MM hastası**

**→ %40'ı nüks edecektir.**

**→ %20'i 4 yıl içinde ölecektir.**

# MM Hastalarında Lenalidomid İdamesi ile başlıca çalışmalar

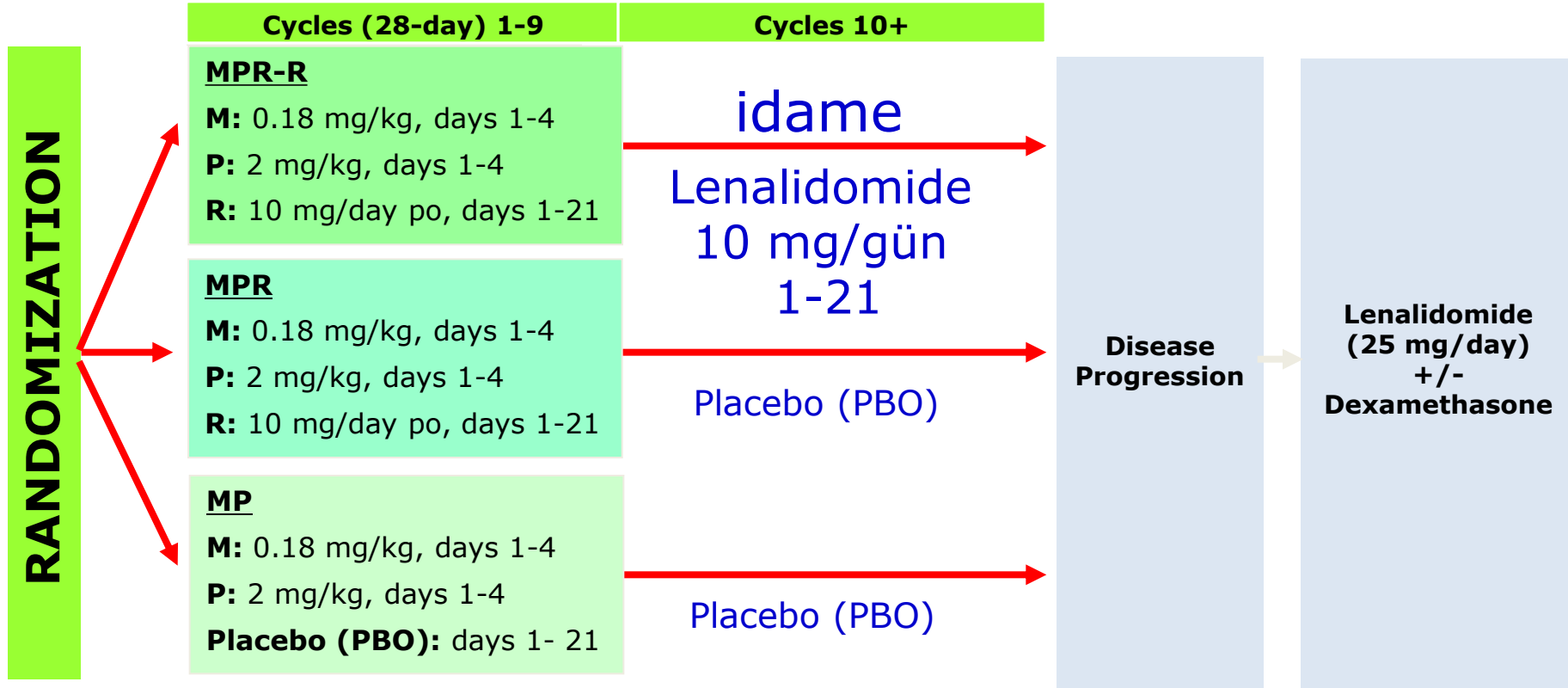
**Transplant uygun  
olmayan hasta  
grubu**

- MM-015
- FIRST
- E1A06
- HOVON87/NMSG18

# Transplant uygun olmayan MM Hastalarında Lenalidomid İdamesi

MM-015; 82 Avrupa merkezi (N = 459)  
2007 -2008

Open-Label  
Extension Phase



Double-Blind Treatment Phase

- (**≤75 ve >75 yıl**) ve **Evre (ISS I/II ve III)**

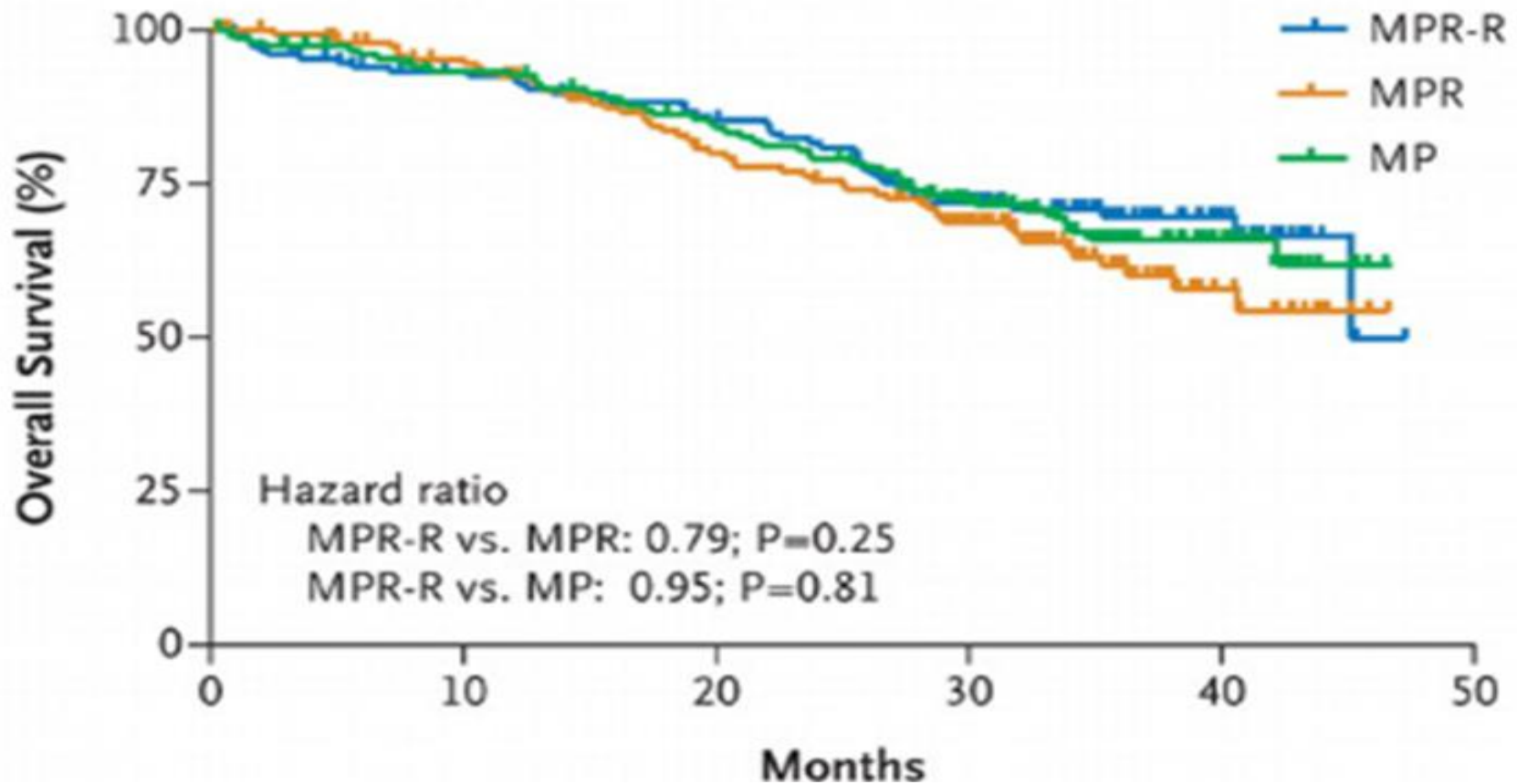
With permission from Palumbo A et al. *Proc ASH* 2011;Abstract 475.



# The NEW ENGLAND JOURNAL of MEDICINE

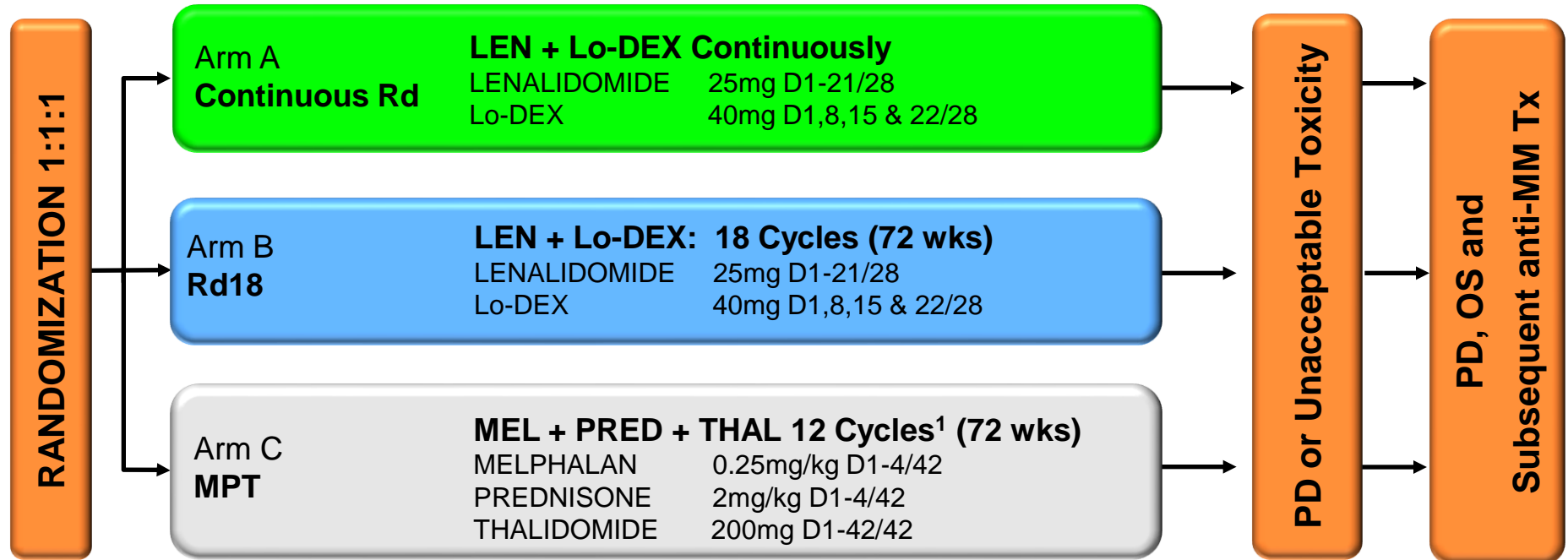
N Engl J Med 2012; 366:1759-1769

## Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma



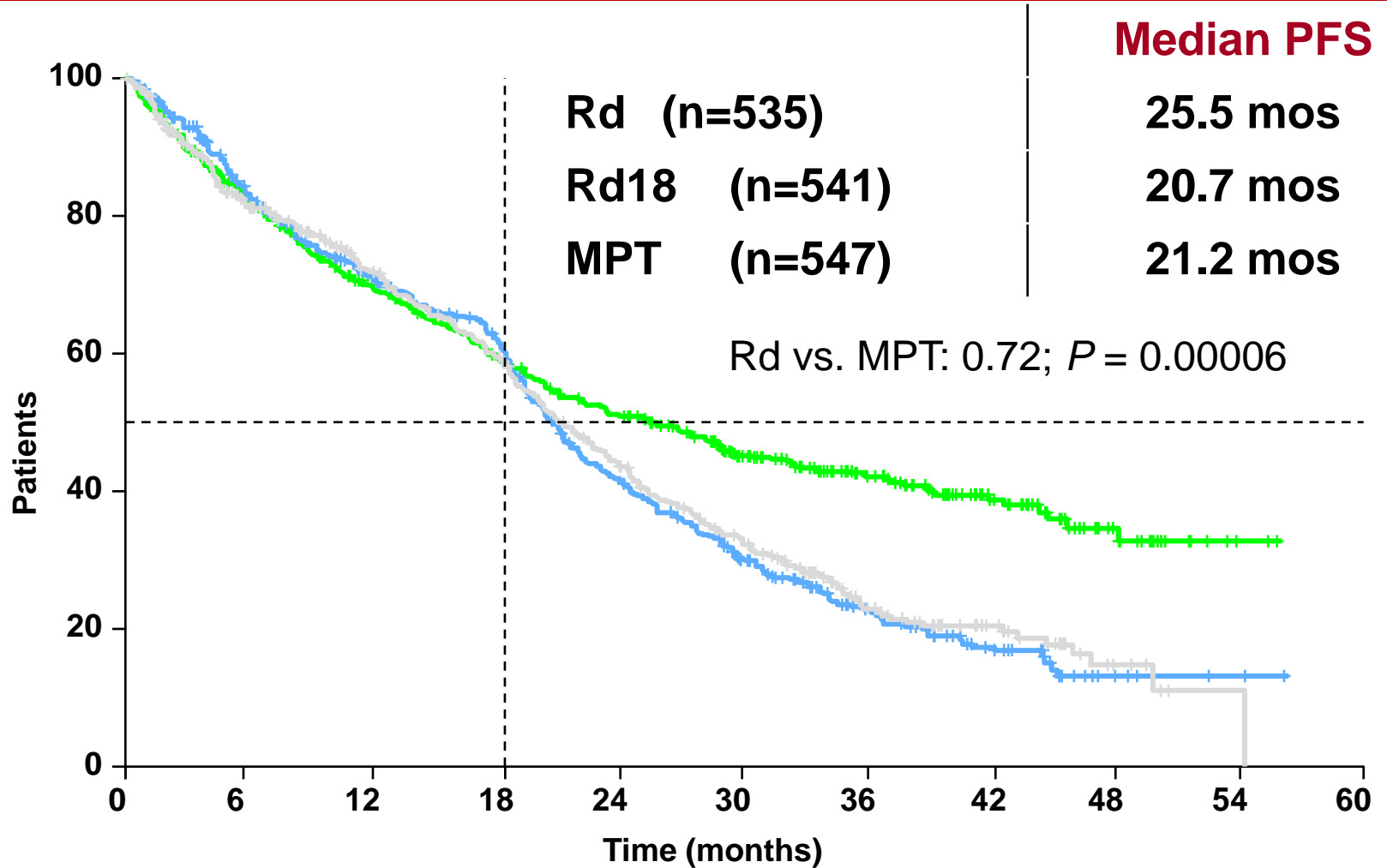
OS faydalanımı gözlenmedi

# Transplant Uygun Olmayan MM Hastalarında Lenalidomid İdamesi



## FIRST Trial

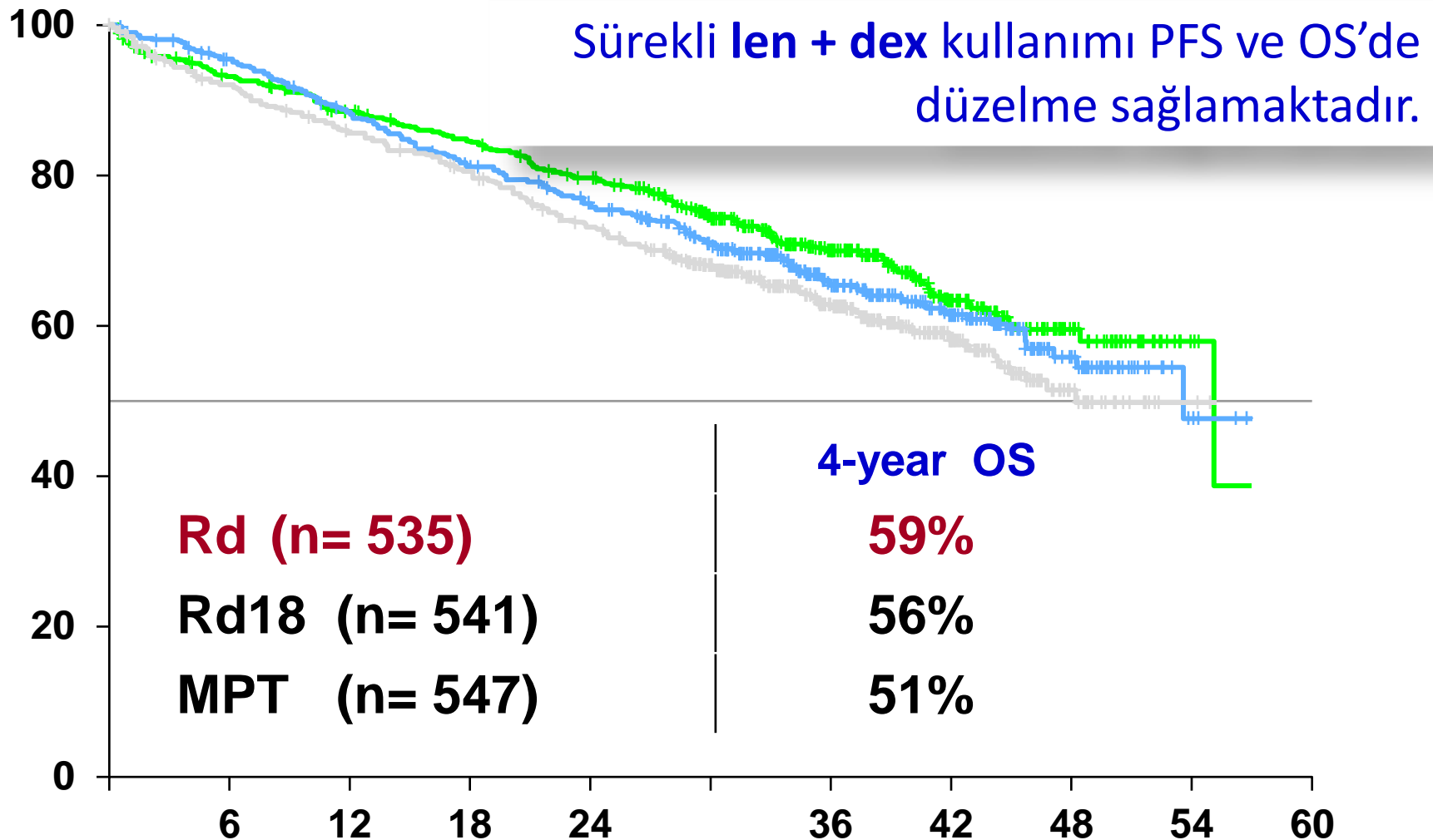
# Transplant Uygun Olmayan MM: FIRST çalışması



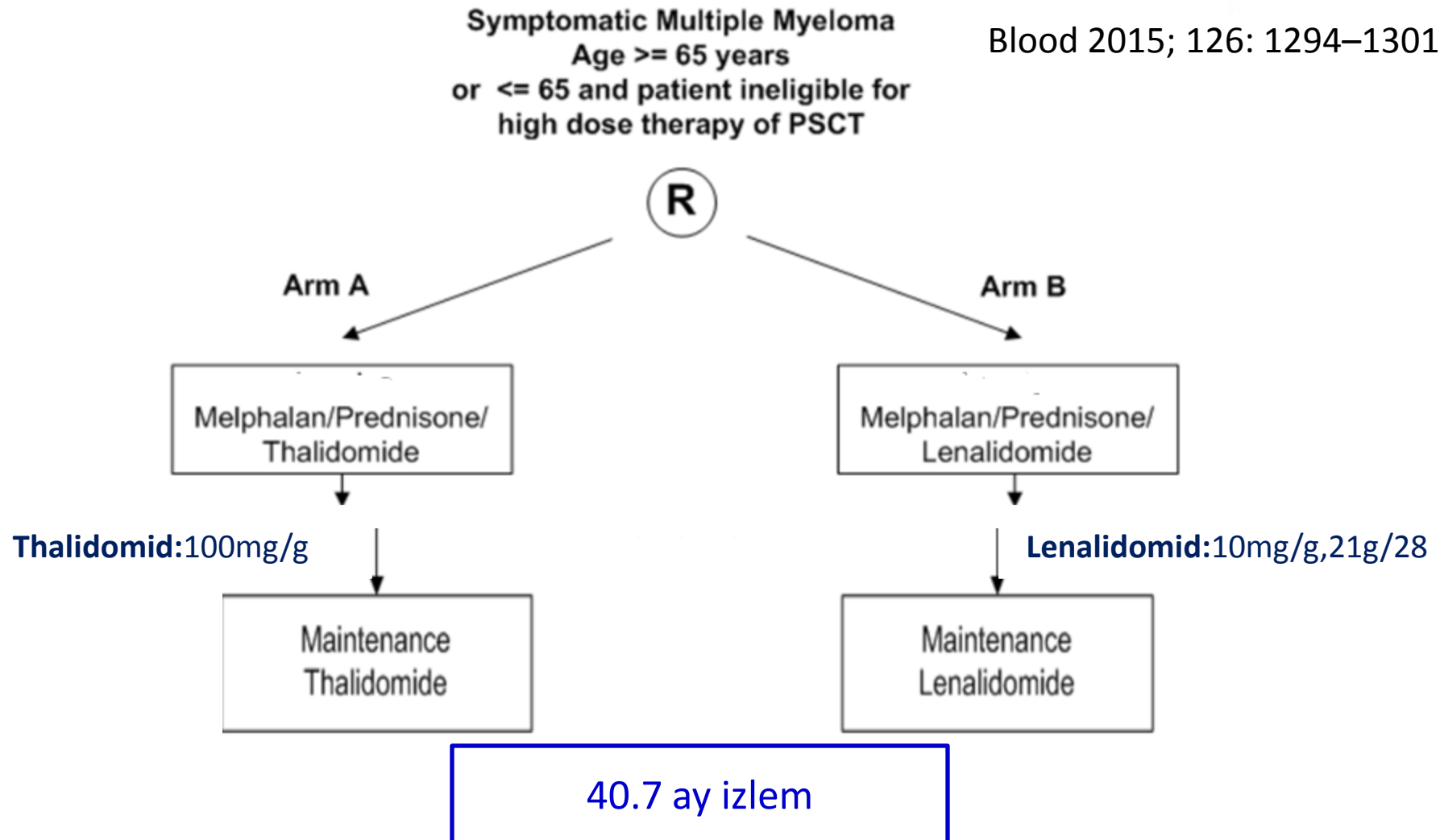
Sürekli **len + dex** kullanımı PFS'de düzelme sağlamaktadır.



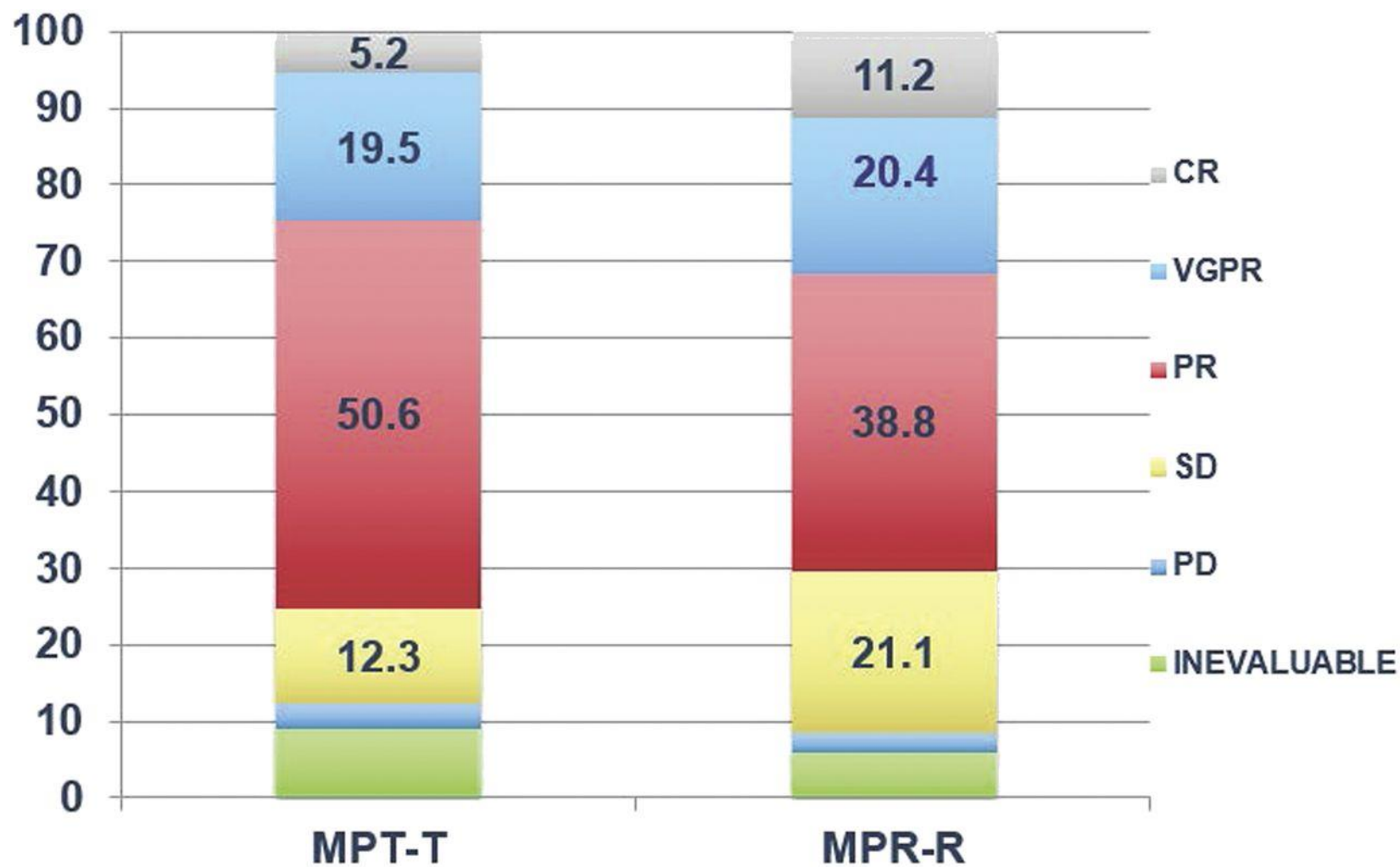
# Transplant Uygun Olmayan MM: FIRST çalışması



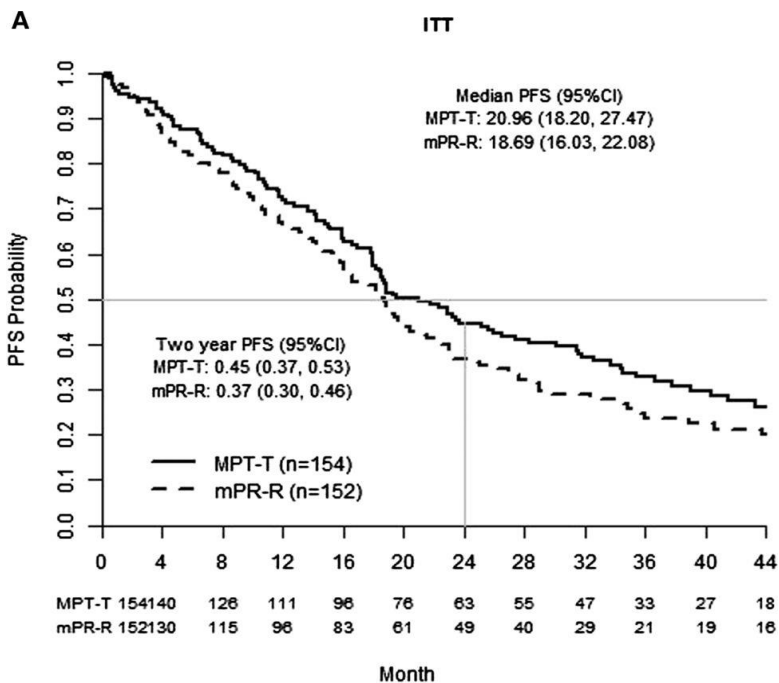
# Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma.



## Investigator-adjudicated response rates.

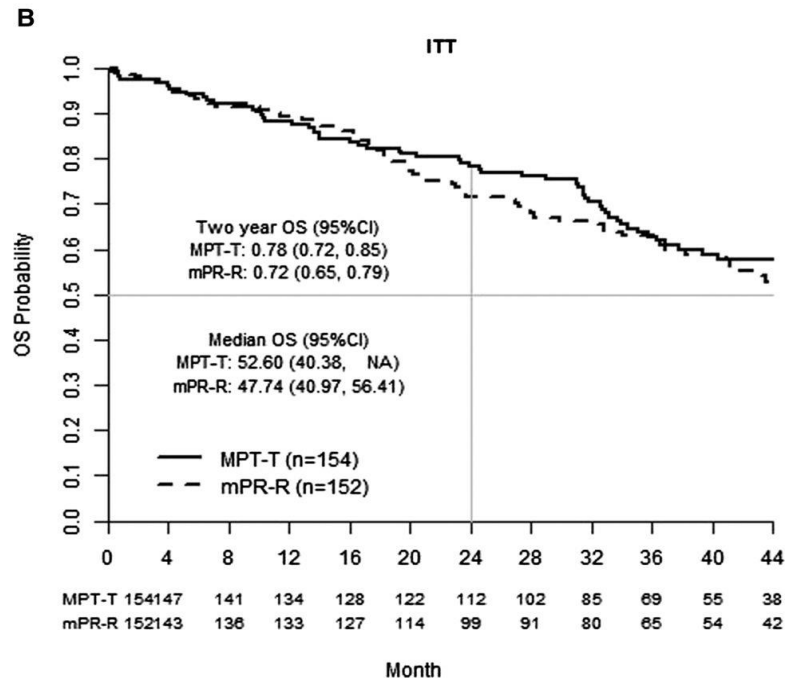


A. Keith Stewart et al. Blood 2015;126:1294-1301



**MPT-T / MPR-R karşılaştırılması;**

**PFS, OS farklı değil**

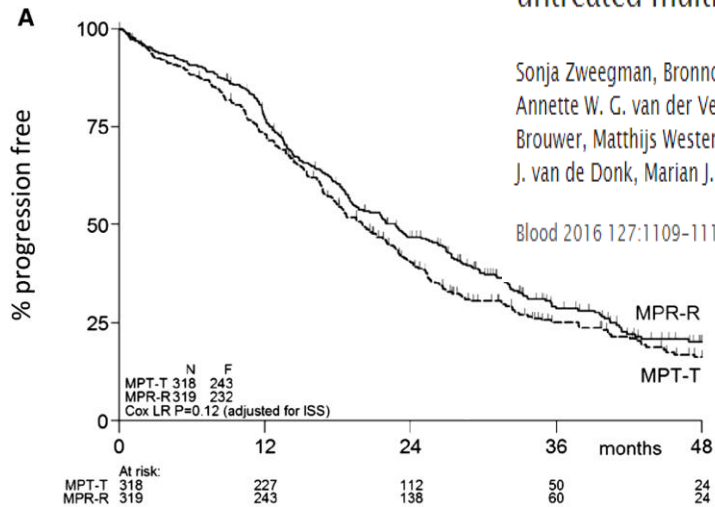


# Transplant Uygun Olmayan MM: MPT-T vs MPR-R

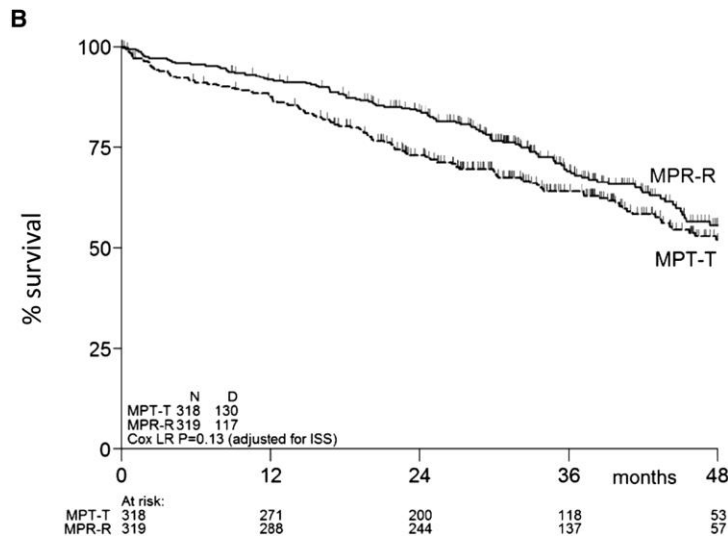
Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma

Sonja Zweegman, Bronno van der Holt, Ulf-Henrik Mellqvist, Morten Salomo, Gerard M. J. Bos, Mark-David Levin, Heleen Visser-Wisselaar, Markus Hansson, Annette W. G. van der Velden, Wendy Deenik, Astrid Gruber, Juleon L. M. Coenen, Torben Plesner, Saskia K. Klein, Bea C. Tanis, Damian L. Szatkowski, Rolf E. Brouwer, Matthijs Westerman, M. (Rineke) B. L. Leys, Harm A. M. Sinnige, Einar Haukås, Klaas G. van der Hem, Marc F. Durian, E. (Vera) J. M. Mattijssen, Niels W. C. J. van de Donk, Marian J. P. L. Stevens-Kroef, Pieter Sonneveld and Anders Waage

Blood 2016 127:1109-1116; doi:10.1182/blood-2015-11-679415



36 ay izlem



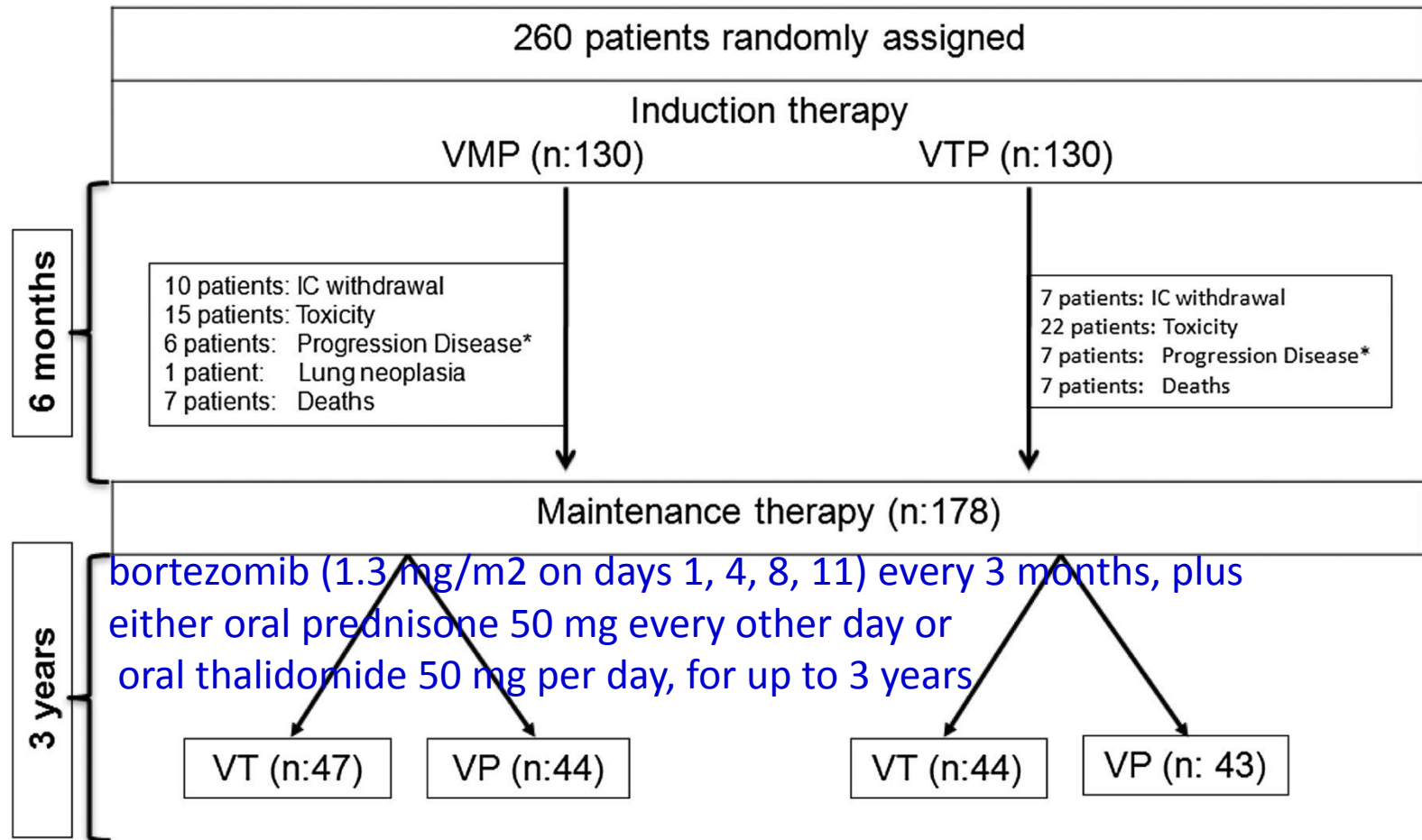
MPT-T ve MPR-R: PFS ve OS açısından farklı değil  
Thalidomid kolunda ilaç kesilmesi daha sık

# MM Hastalarında bortezomib İdamesi ile başlıca çalışmalar

**Transplant uygun  
olmayan hasta  
grubu**

- **GEM-2005MAS65**
- **GIMEMA MM03-05**
- **UPFRONT**

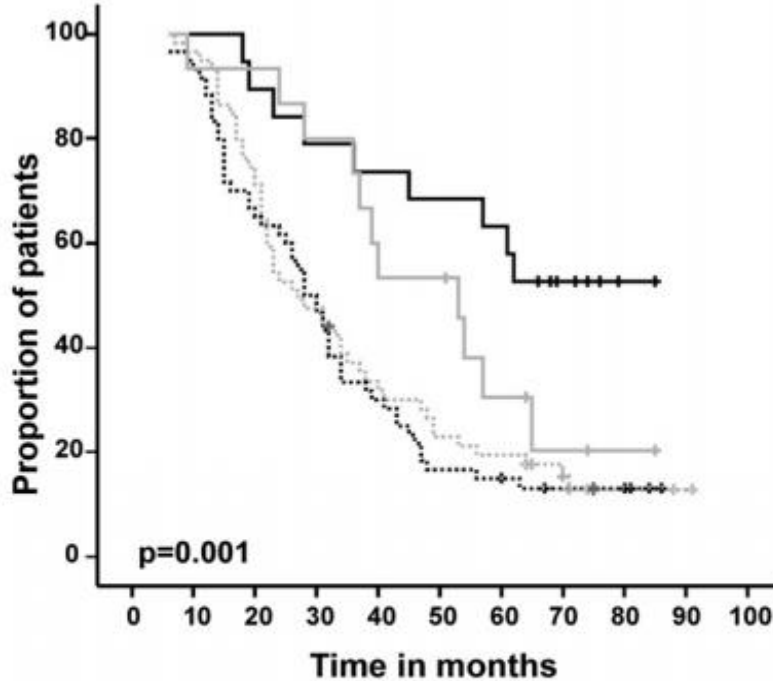
# GEM2005MAS65: VMP/VTD



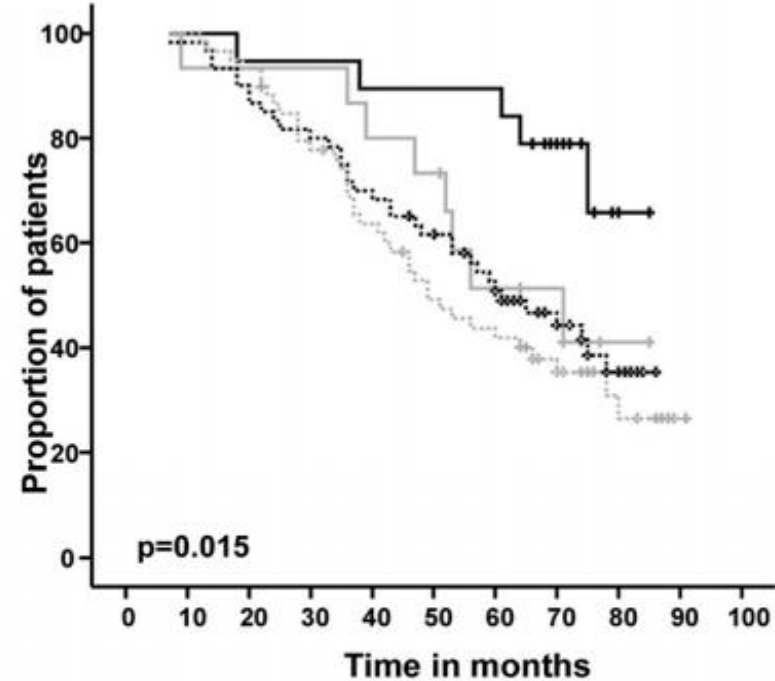
\*Four patients in VMP and VTP arms progressed under induction therapy and two and three patients in VMP and VTP arms, respectively, progressed just before the initiation of maintenance phase



# MM Hastalarında VT / VP idamesi indüksiyondan itibaren VMP ve VTD kolunda PFS ve OS yönünde farklı değil



- VMP, MRD- median PFS: not reached
- VTP, MRD- median PFS: 53 months
- ..... VMP MRD+ median PFS: 28 months
- ..... VTP MRD+ median PFS: 27 months



- VMP, MRD- median OS: not reached
  - VTP, MRD- median OS: 73 months
  - ..... VMP MRD+ median OS: 62 months
  - ..... VTP MRD+ median OS: 51 months
- }  $p=0.062$

Tam yanıt ve MRD durumu VMP ve VTD sağ kalımı etkilemekte;

## MM Hastalarında bortezomib idamesi ile PFS artışı

### GIMEMA MM-03-05/Palumbo *et al.*

- *VMP vs VMPT*
- *idame:*
- *VMP → idame yok*
- *VMPT → VT*

	<b>VMP (n = 254)</b>	<b>VMPT-VT (n = 257)</b>
CR	%24	%38
Median PFS	38ay	55ay

# MM Hastalarında bortezomib idamesi

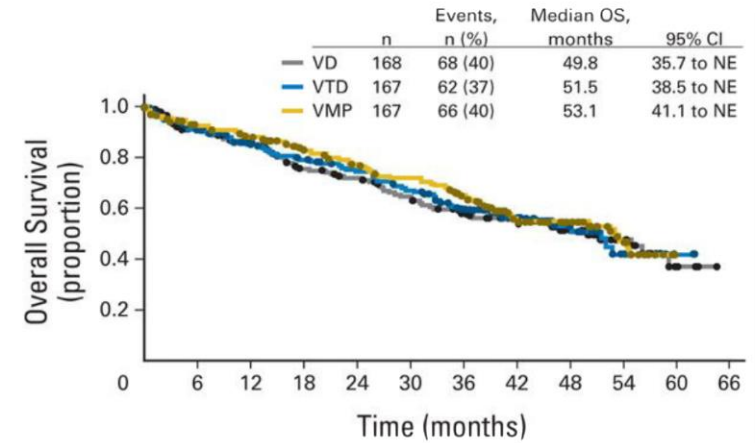
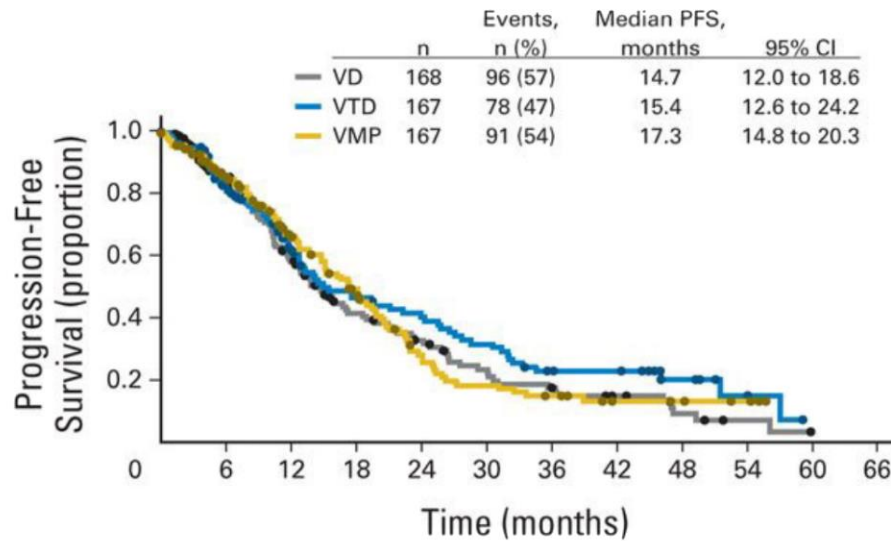
## JOURNAL OF CLINICAL ONCOLOGY

..... Official Journal of the American Society of Clinical Oncology

### Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens

1. VD; (n = 168) iv bortezomib 1.3 mg/m<sup>2</sup>, 1, 4, 8, 11dys + oral dexamethasone 20 mg, 1, 2, 4, 5, 8, 9, 11, 12 [cycles 1 - 4], or 1, 2, 4, 5 [cycles 5 to 8]),
  2. VTD; (n = 167); VD + thalidomide 100 mg, 1 - 21),
  3. VMP; (n = 167; bortezomib + oral melphalan 9 mg/m<sup>2</sup> + oral prednisone 60 mg/m<sup>2</sup>, 1 - 4, every other cycle), 25 weeks
- bortezomib maintenance (1.6 mg/m<sup>2</sup>, days 1, 8, 15, and 22).

# MM Hastalarında bortezomib idamesi



**%40 ancak bortezomib idamesi alabilmiş  
%89'unda yanıt sürmüş.**

# Transplant uygun MM Hastalarında Lenalidomid İdamesi

**Transplant uygun  
hasta grubu**

- IFM 2005-02
- CALGB 100104
- RV-MM-P12094
- CRD
- IFM /DFCI

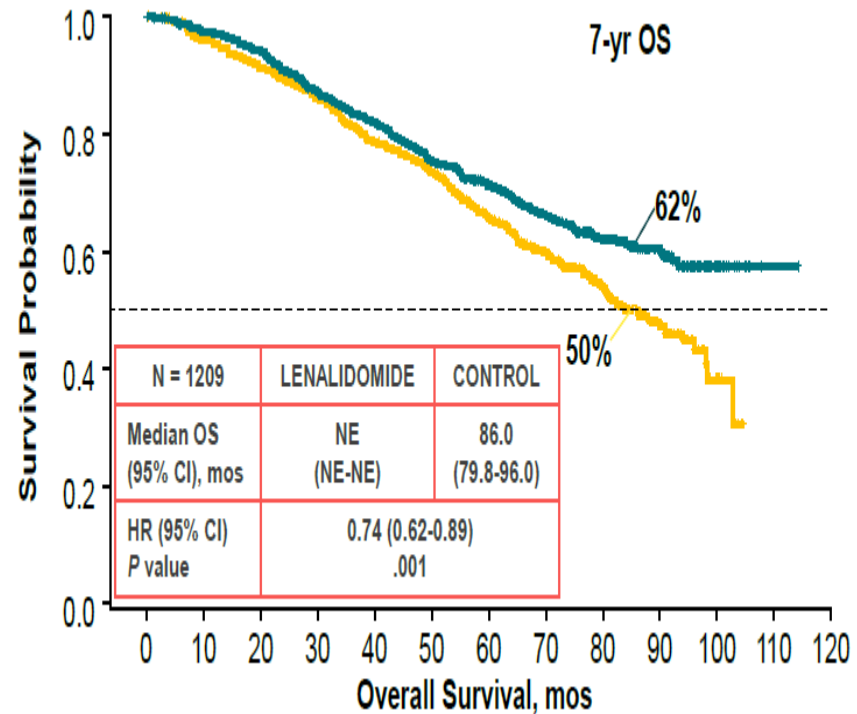
# Transplant uygun MM Hastalarında Lenalidomid İdamesi PFS'i artırmaktadır

	İdame	mPFS	OS	SPM
IFM 2005.02	TX +6.ay Len 10 x3ay Len 15 x2yıl	46/24 ay	Ulaşılmadı/ 90ay	%2.3/%1/ yıl
CALGB100104	Tx +100.g Len 10 x3ay Len 15 x2yıl	mTTP 53/26 ay	Ulaşılmadı /76ay	%10.8 %4.5/yıl
RVMMP1209	Len10 sürekli	41.9 /21.6ay	3yıllık %88 /80	İdame seyrinde +

OS 'da sadece CALGB çalışmasında iyileşme gözlenmiştir

# MM'da lenalidomid idamesi

- **Meta-analiz, median izlem süresi: 80 ay**
- 3 çalışma
- Ölüm riskinde %26 azalma
- Tahmini 2.5yıllık ortanca sağ kalımda artış
- İkinci kanser gelişimi dikkat çekici (CALGB ve IFM çalışmaları)





# Transplant Uygun MM Hastalarında Bortezomib İdamesi

**Transplant uygun  
hasta grubu**

- **HOVON-65/GMMG-HD4**

# Transplant Uygun MM Hastalarında Bortezomib İndüksiyon ve İdamesi CR, PFS ve OS'ı iyileştirmektedir

J Clin Oncol. 2012 Aug 20;30(24):2946-55. doi: 10.1200/JCO.2011.39.6820. Epub 2012 Jul 16.

## **Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial.**

Sonneveld P<sup>1</sup>, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, Weisel KC, Wittebol S, Bos GM, Stevens-Kroef M, Scheid C, Pfreundschuh M, Hose D, Jauch A, van der Velde H, Raymakers R, Schaafsma MR, Kersten MJ, van Marwijk-Kooy M, Duehrsen U, Lindemann W, Wijermans PW, Lokhorst HM, Goldschmidt HM.

VAD /PAD → SCT →

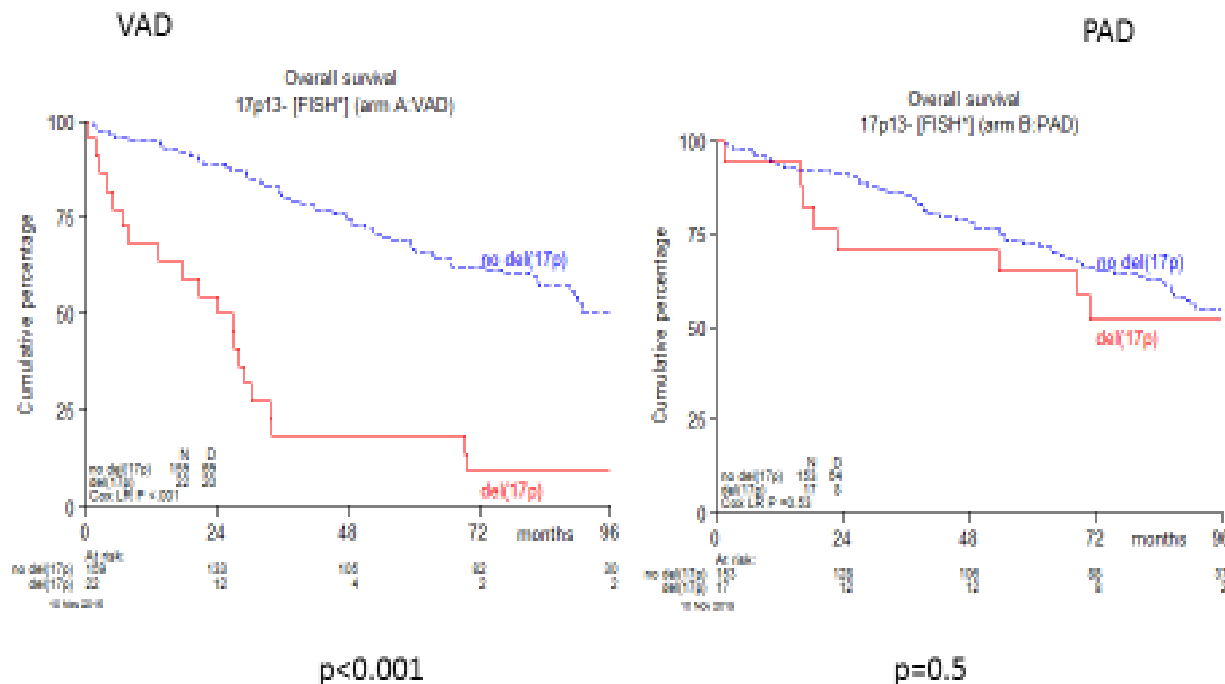
İdame: thalidomide 50 mg (VAD) veya bortezomib 1.3 mg/m(2) (PAD)/2 hafta, 2 yıl  
41 ay izlem

	<b>VAD</b>	<b>PAD</b>
CR	%24	%38
	<b>VAD-T</b>	<b>PAD-bortez</b>
CR	%39	%49
PFS	28ay	35ay

# Bortezomib idamesi del17p'li hastalarda OS avantajı sağlar

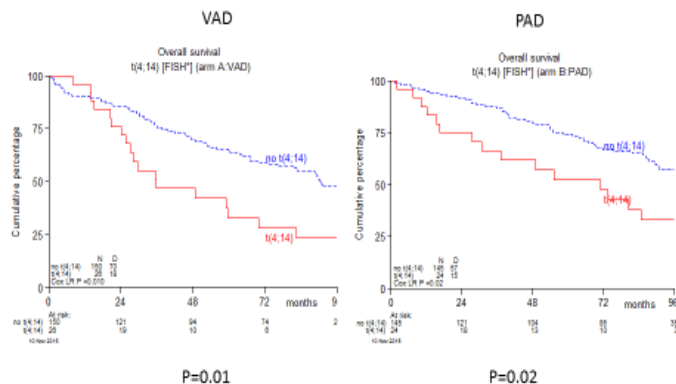
## HOVON-65/GMMG-HD4: OS by treatment arm Subgroup with del(17/17p) and double ASCT

median follow-up: 91.4 months



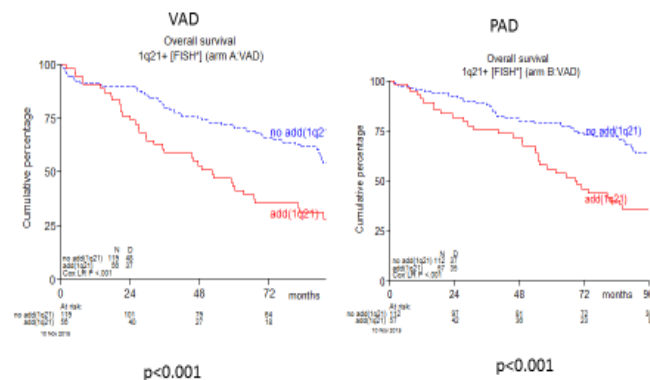
# Bortezomib idamesi t(4;14) veya +1q 'lu hastalarda OS'ı etkilemiyor

HOVON-65/GMMG-HD4: No OS advantage for t(4;14) even with double ASCT



Sonneveld P, et al. ASH 2015 (data as of November 10, 2015)

HOVON-65/GMMG-HD4: No OS advantage for gain(1q21) even with double ASCT

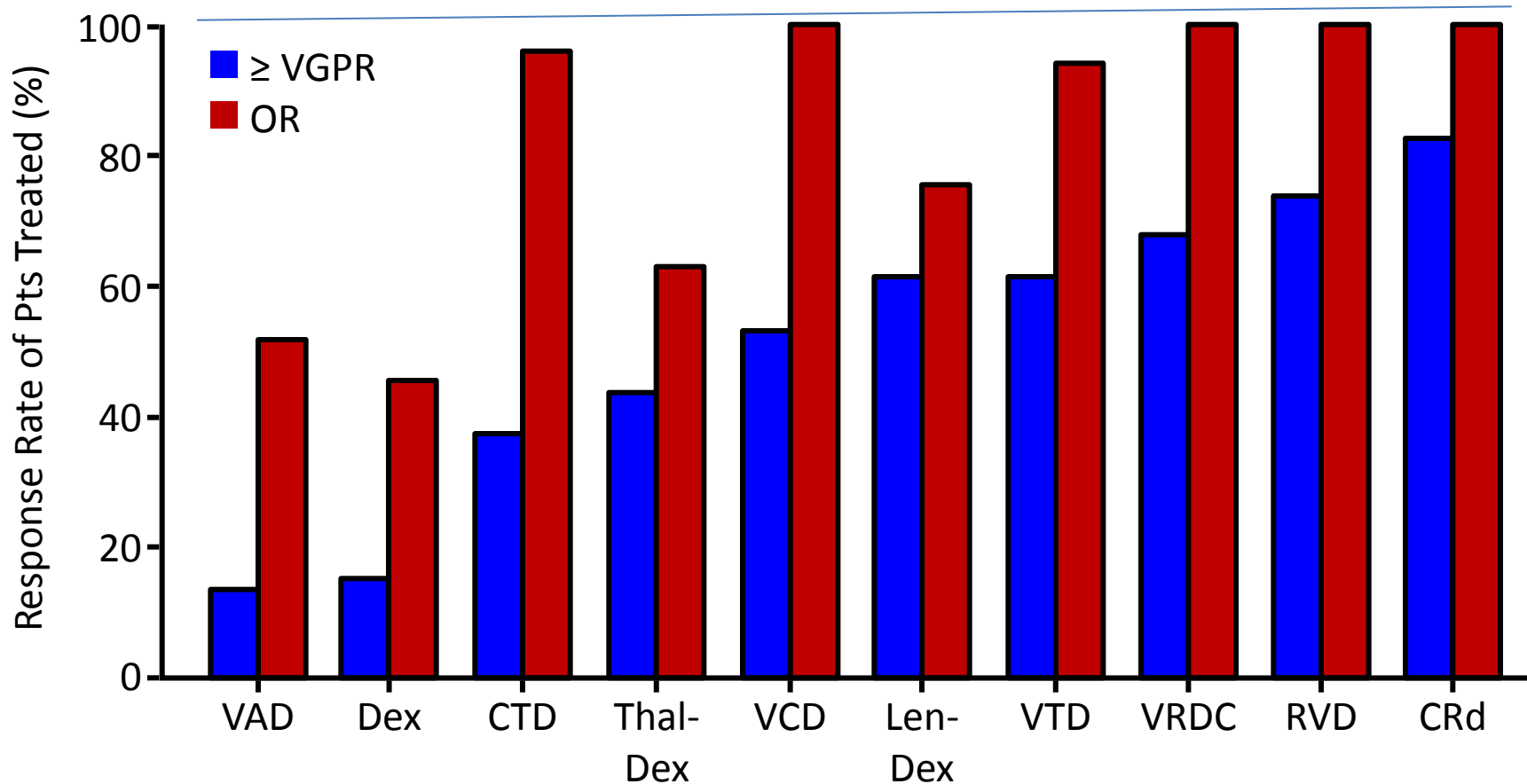


Sonneveld P, et al. ASH 2015 (data as of November 10, 2015)

# Sonuç olarak

- Thalidomide idamesi (tercihen prednison ile) kötü sitogenetik risk grubunda olmayan ancak VGPR'a ulaşmamış hastalarda 1-2 yıl önerilebilir.
- Lenalidomide idamesi PFS ve OS avantajı sağlamaktadır; standart risk hasta grubunda ikincil malignite riski bilgisi ile kullanılabilir.
- Bortezomib idamesi özellikle del17p'li hastalarda uygundur.
- Yeni ajanlar ile idame çalışmaları mevcuttur: carfilzomib, daratumumab, ixazomib

# Yeni MM ilaçları ile derin yanıt oranı giderek artmaktadır

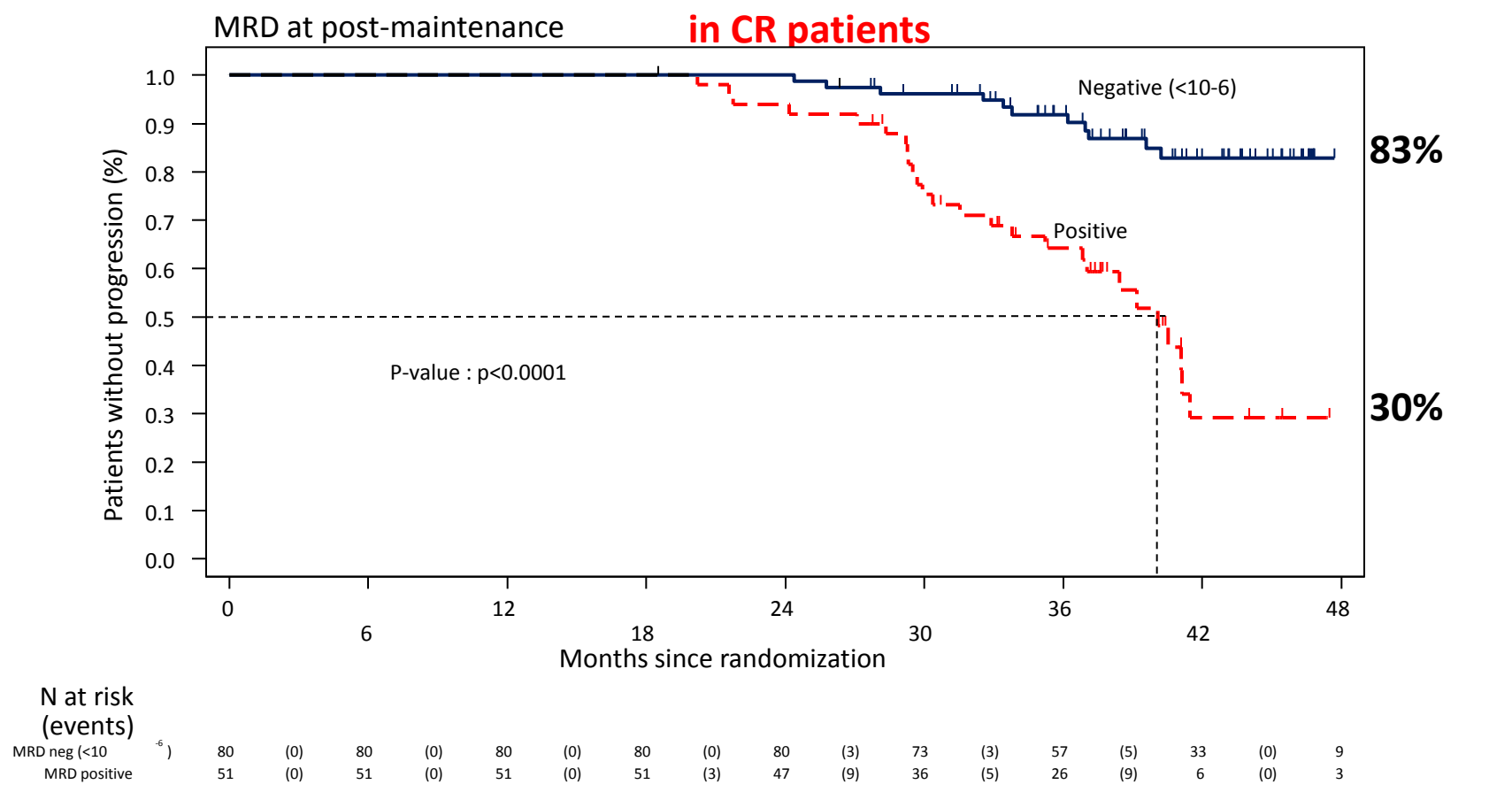


# IFM/DFCI 2009 Study. Newly Diagnosed MM patients. RVDx3.

RVD x 2. RVD x 5. Revlimid 12 mos

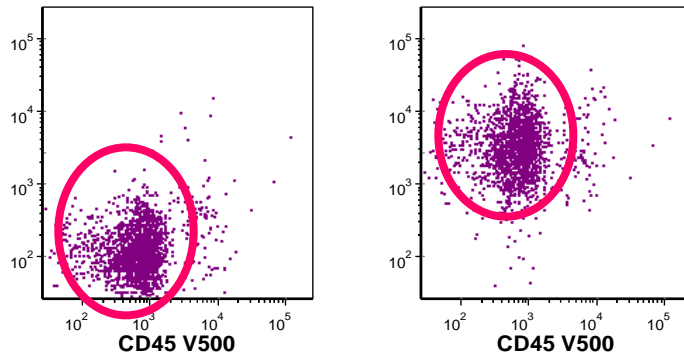
## NGS /CR

NGS ile CR'daki hastaların %39 MRD pozitif

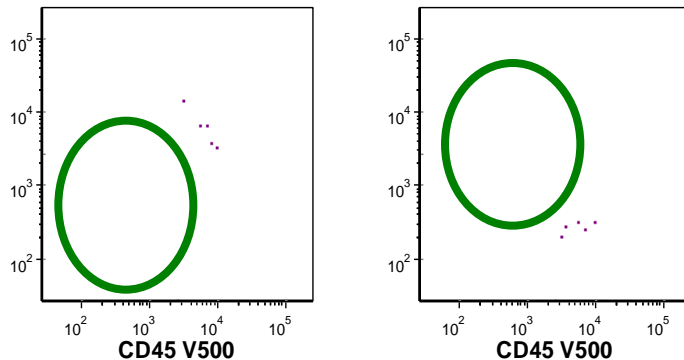


# Yeni tanı MM'da CRd ile MRD durumu

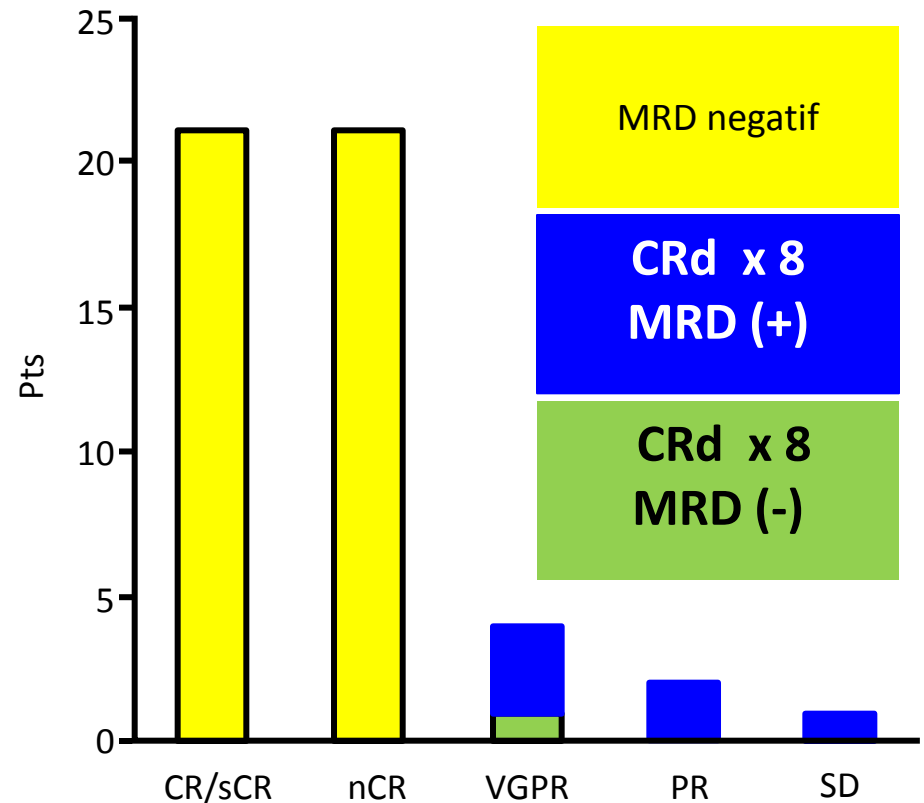
Pt #7CRd öncesi : Abnormal PCs CD19-, CD45 dim, CD56dim+



CRd sonrası: Normal PCs CD19+, normal CD45, CD56-



N=27 nCR/sCR\* MFC; n=27 MRD (-)



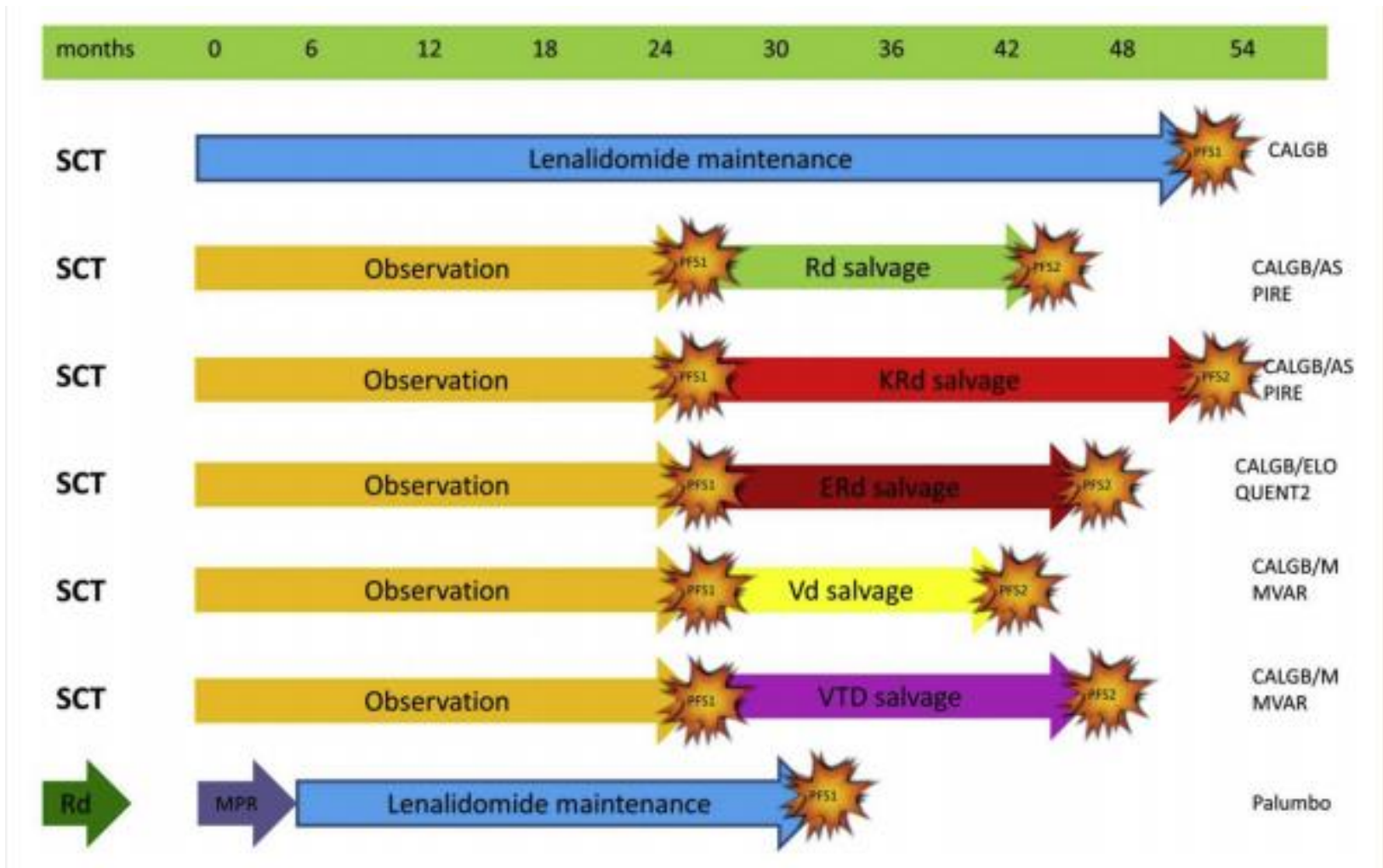
\*2 pts (1 sCR and 1 nCR) not available for interpretation.

Korde N, et al. ASH 2014. Abstract 2105.

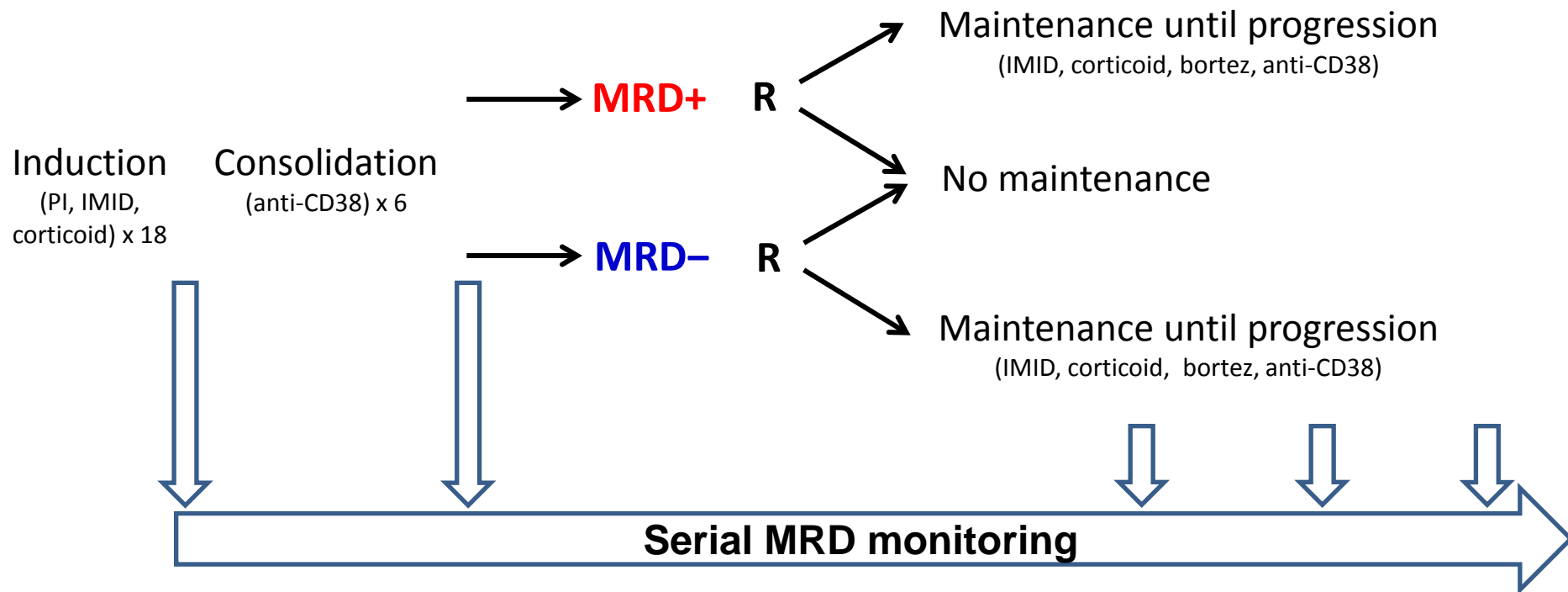
Jama 2015 Sep;1(6):746-54



# Faz III çalışmalar ve PFS



# Redefining remission in MM with MRD monitoring to improve patients' care



## In patients with persistent MRD+ after 2y of treatment what is the best option:

- To stop tx because it could be an indolent clone
- To continue tx because it will control the residual clone
- To change drugs since the same continuous tx is not able to eradicate/control the residual clone

## In patients with continuous MRD- after 2y of treatment what is the best option:

- To continue tx because of late relapses
- To stop tx for a period of time until MRD reappearance (e.g.: 3y – 5y)
- To stop tx because many patients will be operationally cured (>10y PFS of therapy)

*Teşekkürler*