Myeloma: Are We on the Brink of a Cure?

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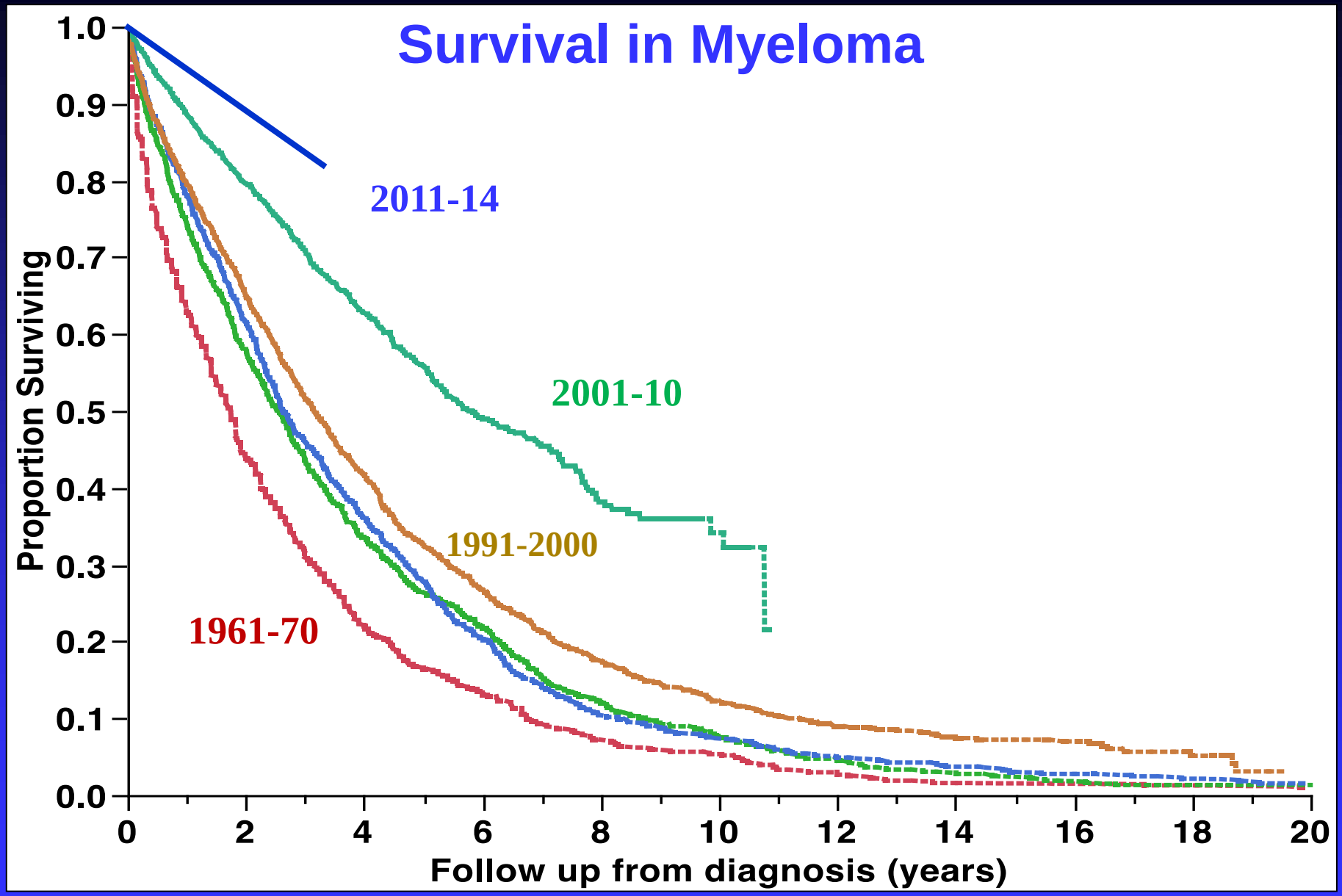


Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

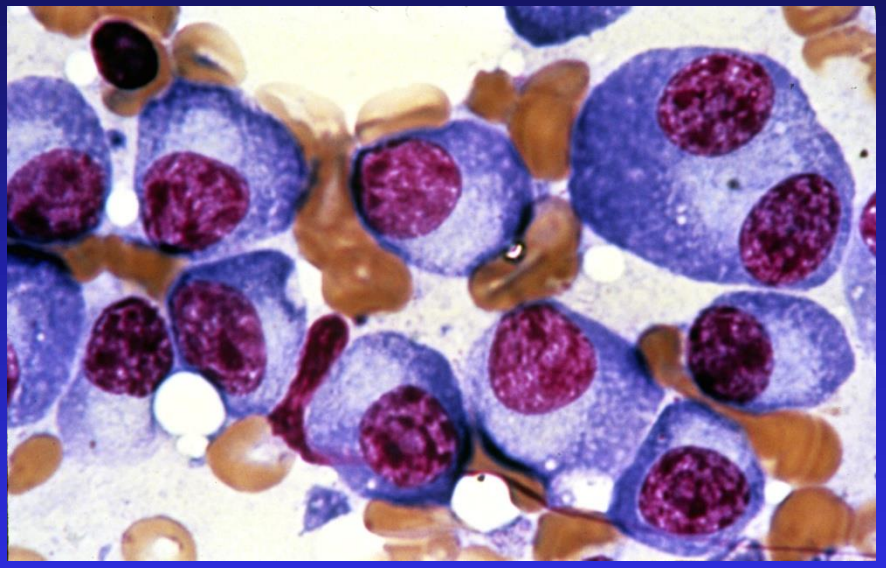
Multiple Myeloma (MM)

- Approximately 30,330 new cases in 2016.
- 95,874 currently with MM
  - Accounts for 1% of all malignancies and about 10% of hematological cancers
  - Accounts for 2% of deaths from all cancers and 20% of deaths from hematological cancers
- Slightly more common in men than women
- Incidence in African Americans is about twice that of whites
- Median age at diagnosis is 66 years
  - Age <50 years: 10%
  - Age <40 years: 2%

American Cancer Society. *Cancer Facts and Figures 2007.* Atlanta, GA: American Cancer Society; 2007; Kufe. *Cancer Medicine.* 6th ed. 2003:2219; Clinical and laboratory manifestations of MM. UpToDate Web site. Available at: http://www.utdol.com/utd/content/topic.do?topicKey=plasma/2083&type=A&selectedTitle=2~80. Accessed January 2, 2007.

Myeloma

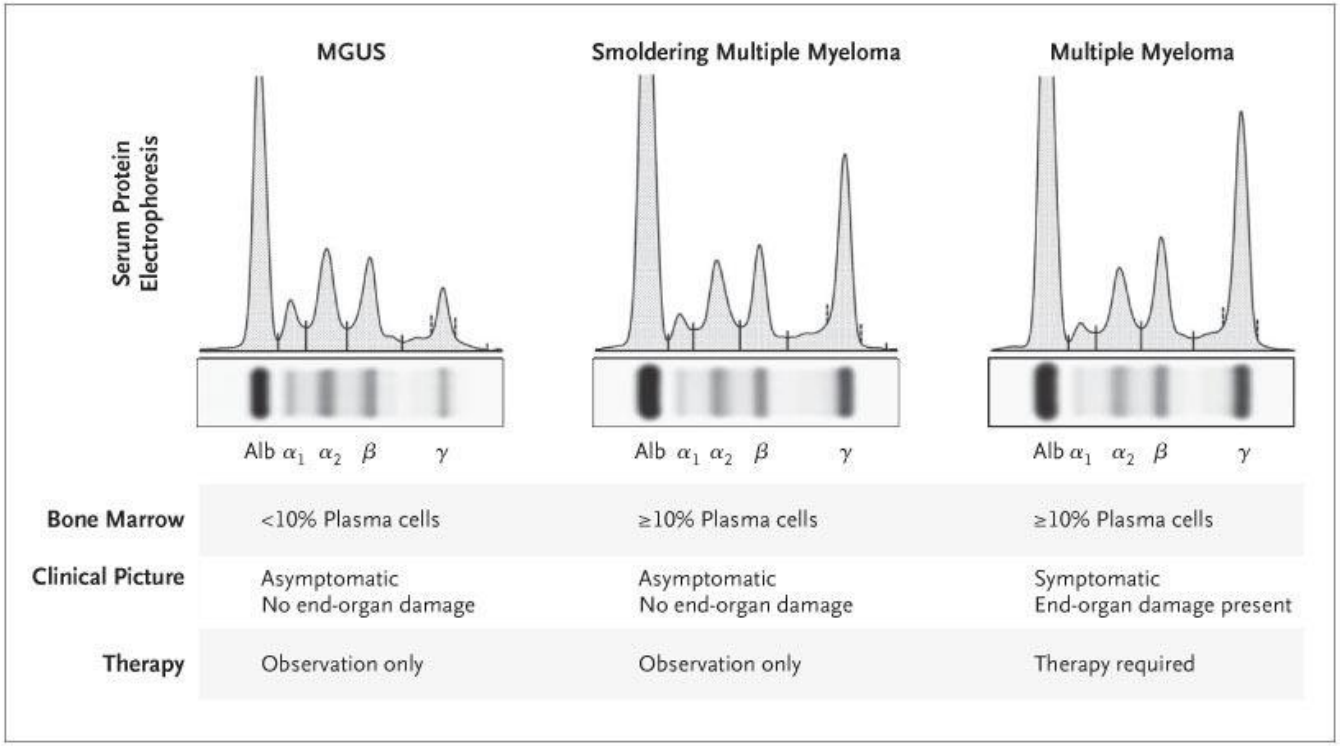
- MM is characterized by:
  - Excessive numbers of abnormal plasma cells in the bone marrow
  - Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD) or free antibody light chains
  - concomitant drop in other immunoglobulins
  - CRAB Criteria
    - HyperCalcemia
    - Renal
    - Anemia
    - Bone Lesions



Reproduced with permission from the Multiple Myeloma Research Foundation Web site. Available at: http://www.multiplemyeloma.org/about_myeloma/index.html

Kufe. *Cancer Medicine*. 6th ed. 2003:2219.

Characteristics of Active Multiple Myeloma and Its Precursors



	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma
Bone Marrow	<10% Plasma cells	≥10% Plasma cells	≥10% Plasma cells
Clinical Picture	Asymptomatic No end-organ damage	Asymptomatic No end-organ damage	Symptomatic End-organ damage present
Therapy	Observation only	Observation only	Therapy required

Kyle R et al. N Engl J Med 2007;356:2582-2590

The NEW ENGLAND JOURNAL of MEDICINE

Historical Criteria for Diagnosis of Myeloma

MGUS

- < 3 g/dL M spike
- < 10% plasma cells

AND NO CRAB* features
or end-organ damage

SMM

- ≥ 3 g/dL M spike
- ≥ 10% plasma cells

AND NO CRAB* features
or end-organ damage

Active MM

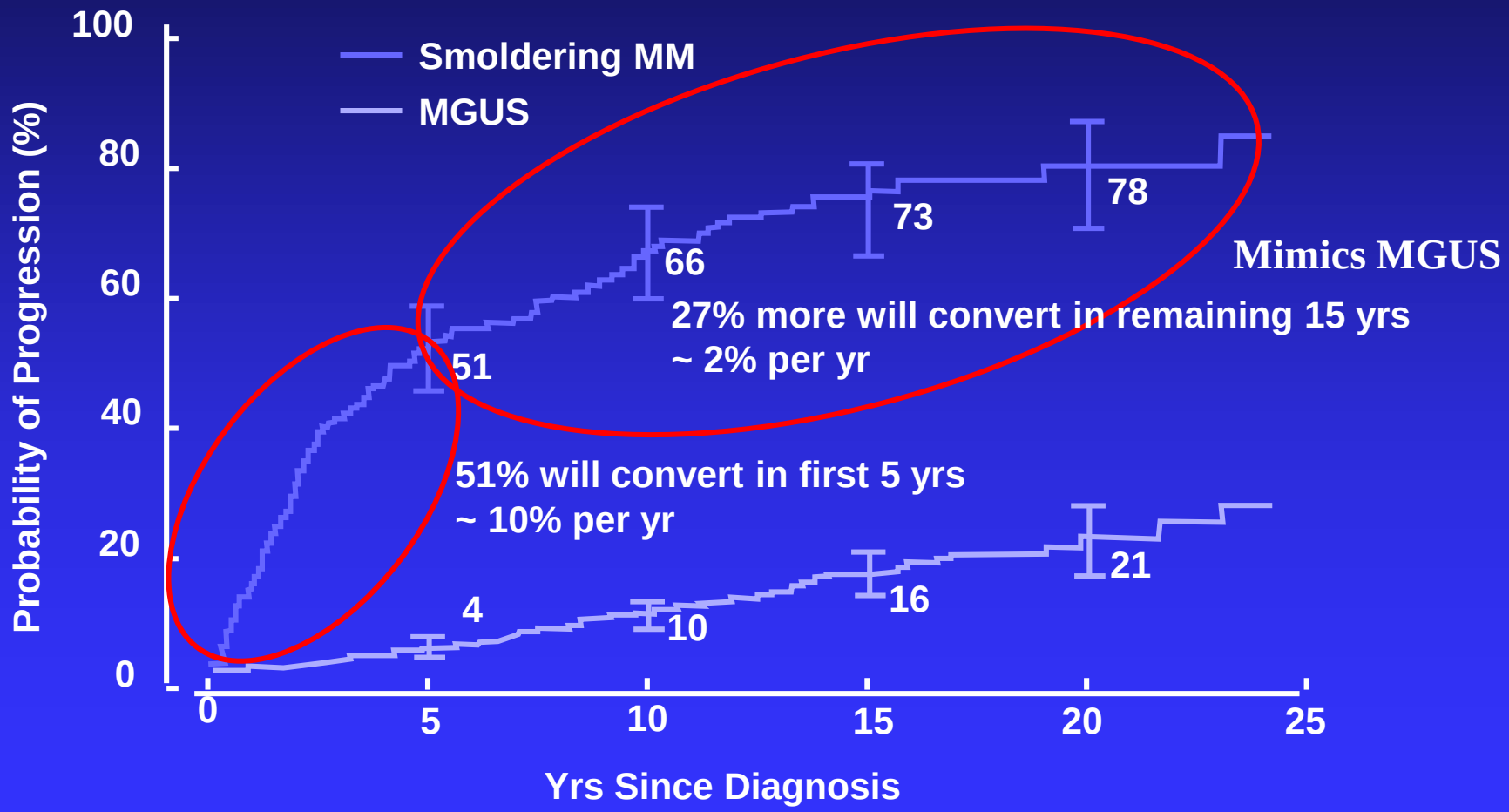
- ≥ 10% plasma cells
- M spike + in serum and/or urine

AND CRAB* features

*C: Calcium elevation (> 10.5 mg/L or ULN)
R: Renal dysfunction (serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g < normal)
B: Bone disease (lytic lesions)

IMWG. Br J Haematol. 2003;121:749-757. Kyle RA, et al. Leukemia. 2009;23:3-9.
Durie BG, et al. Hematol J. 2003;4:379-398.

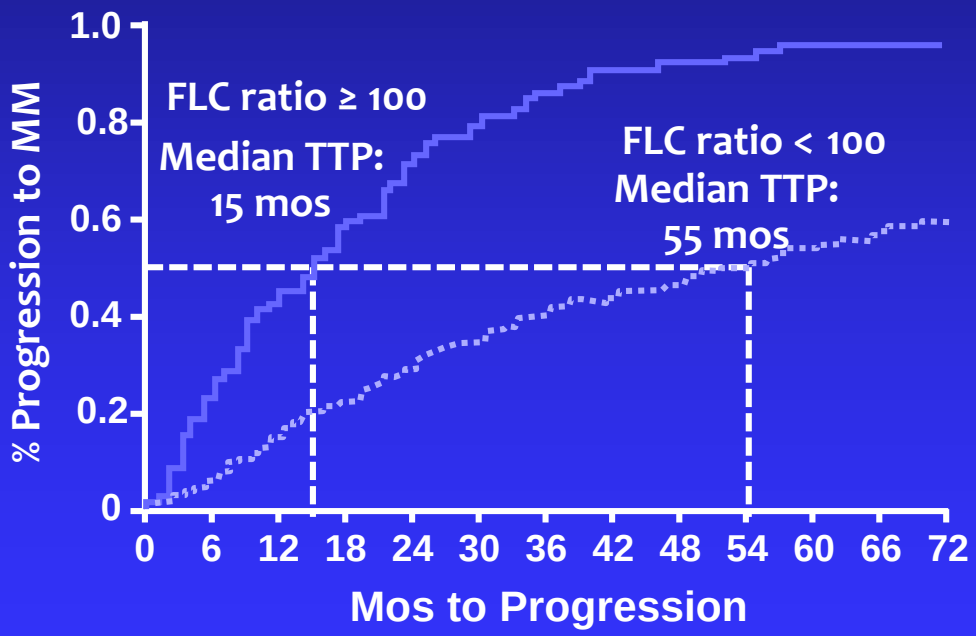
Smoldering Multiple Myeloma

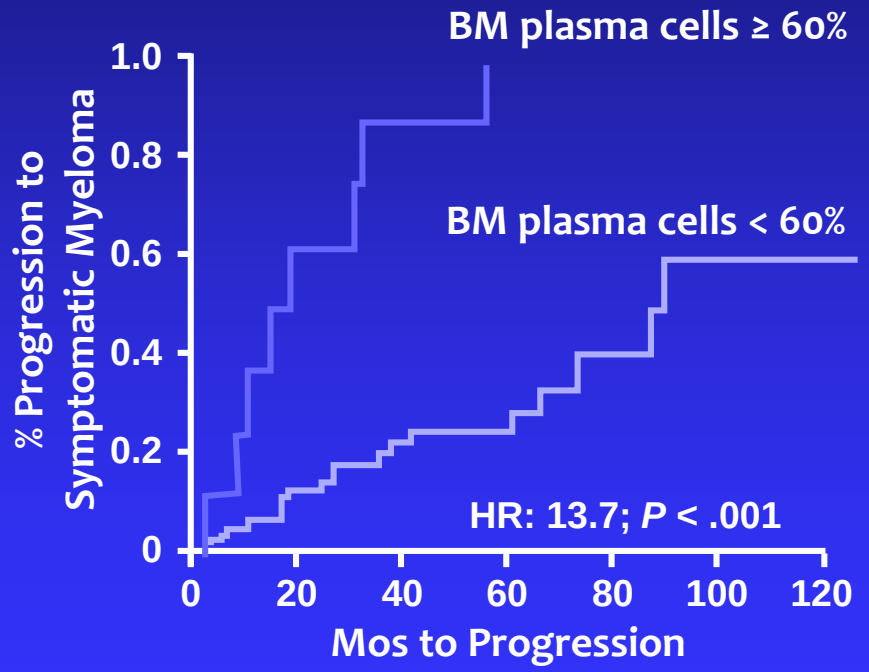


Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Biomarkers to Predict Risk of Progression

- FLC ratio ≥ 100 predicts risk ($P < .0001$)
- Clonal plasma cells in BM predicts risk ($P < .001$)





Larsen JT, et al. Leukemia. 2013;27:941-946. Kastritis E, et al. Leukemia. 2013;27:947-953.

Pre-existing MGUS (Monoclonal Gammopathy of Undetermined Significance)

PLCO Study
Landgren, et.al.

- 100% of patients with samples 2 years prior had MGUS
- 82.4% with samples 8 years prior had MGUS
- 97.1% of all patients had MGUS from 2 to 8 or more years prior

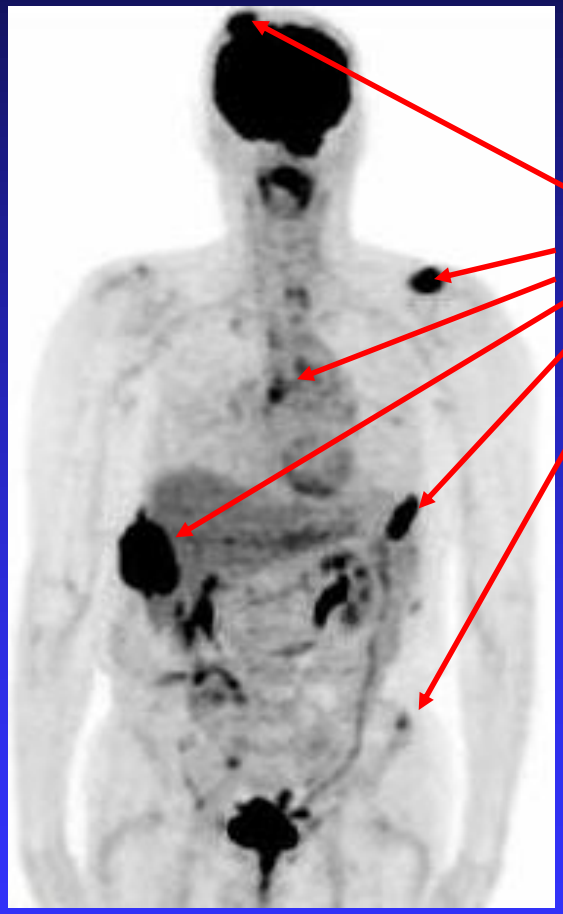
Walter Reed Study

Weiss et.al.

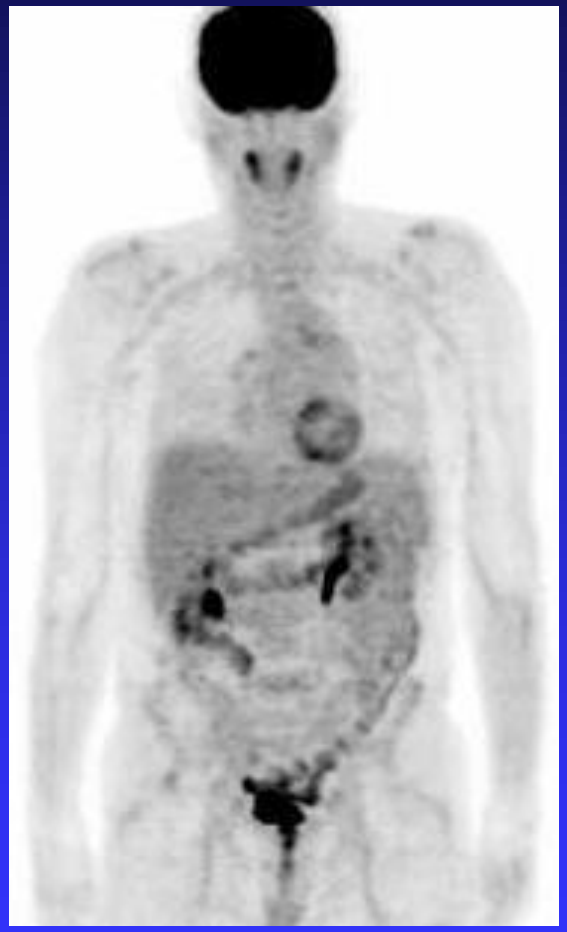
- Samples available for 30/90
- Median number of samples available 3.5 (1-14)
- PPCD detected in 27/30
  - +SPEP and/or IFE 21
  - + sFLC 6
- First detected
  - sFLC alone 6
  - IFE alone 1
  - SPEP + IFE 5
  - IFE + sFLC 1
  - All three 14

Imaging

Bortezomib +/- Dex:
Confirmation of Remission: PET Scan



Pretreatment



After 4 Cycles

Imaging

- Either
  - PET/low dose whole body CT
  - MRI of spine and pelvis
  - New: Combined WB PET/MRI
- Must be used
  - To confirm sCR and MRD neg CR
  - To confirm smoldering myeloma

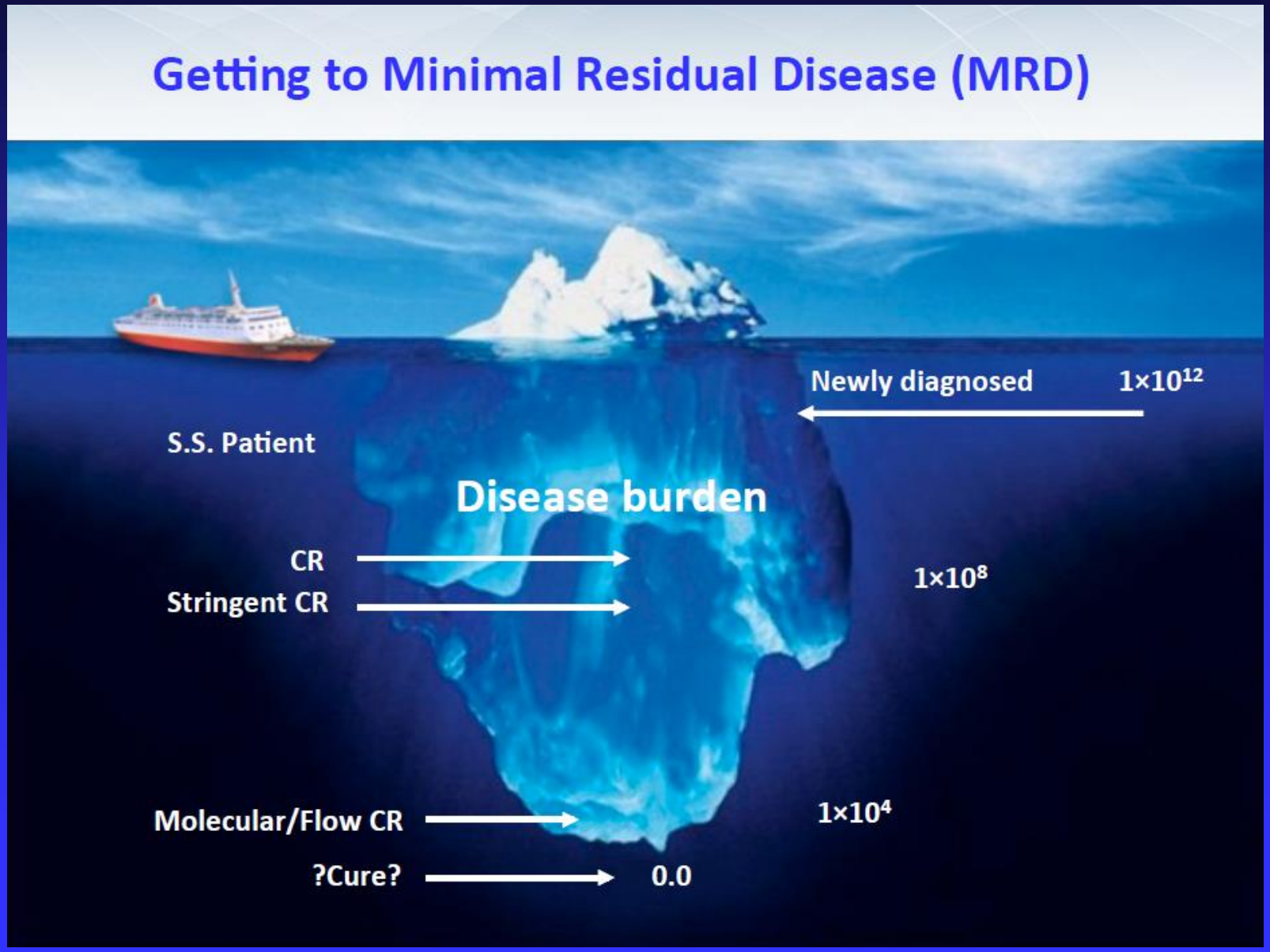
Measurement of the Disease

- Measurement of protein
  - Immunoelectropheresis (IEP) or Immunofixation (IF or IFE)
  - Serum Protein Electropheresis (SPEP) with M-spike (M-protein)
  - Quantitative immunoglobulins (IgG. IgA. IgD, IgM)
  - Free light chain analysis replacing urine studies, including Bence-Jones and 24 hour total protein
  - MRD – Flow or NGS

Measurements of Response

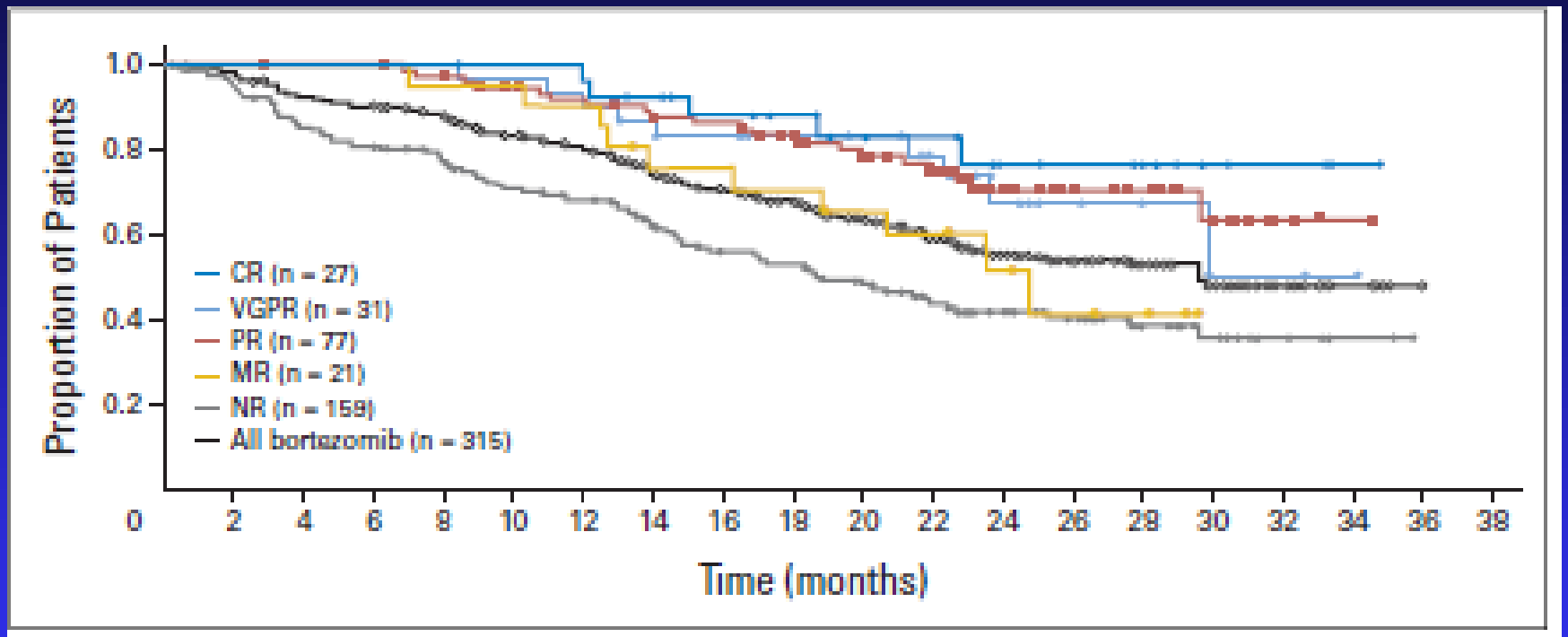
- IMWG Criteria
  - SD = <25% reduction
  - MR = 25% - 49% reduction
  - PR = 50 % or greater reduction
  - VGPR = 90% reduction in protein spike (includes nCR)
  - nCR = pos IEP
  - CR = neg IEP
  - sCR = nml free lite and absence of clonal cells in BM
  - **MRD neg CR**
  -

The Iceberg


Getting to Minimal Residual Disease (MRD)
Newly diagnosed
1×10¹²
S.S. Patient
Disease burden
CR
Stringent CR
1×10⁸
Molecular/Flow CR
1×10⁴
?Cure?
0.0

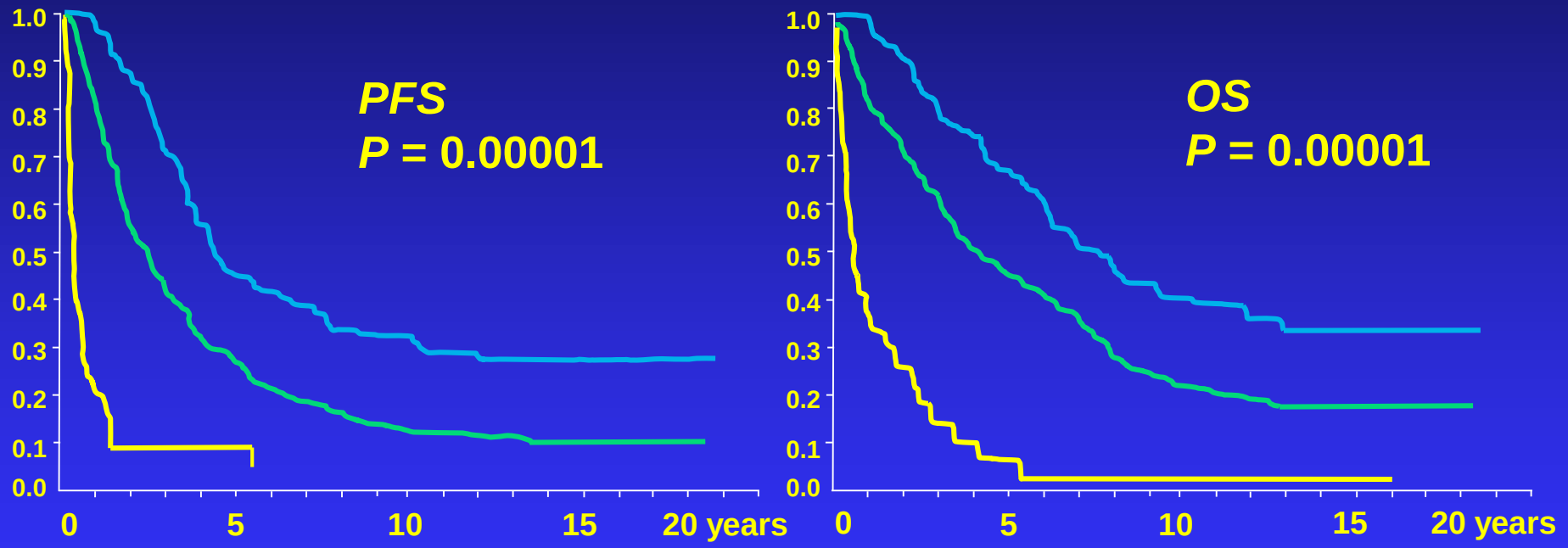
Evidence that CR Matters

APEX Trial: OS (Velcade vs Dex)



CR vs nCR / VGPR / PR vs Less

Prognostic effect of CR patients vs those in nCR or VGPR or PR vs patients with SD or PD after HDT/ASCT



CR (n=63)

nCR (n = 66) + VGPR (n = 54) + PR (n = 114)

SD (n = 12) + PD (n = 14)

Martinez-Lopez J, et al. *Blood*. 2011;118:529-534.

Minimal Residual Disease (MRD)

Flow

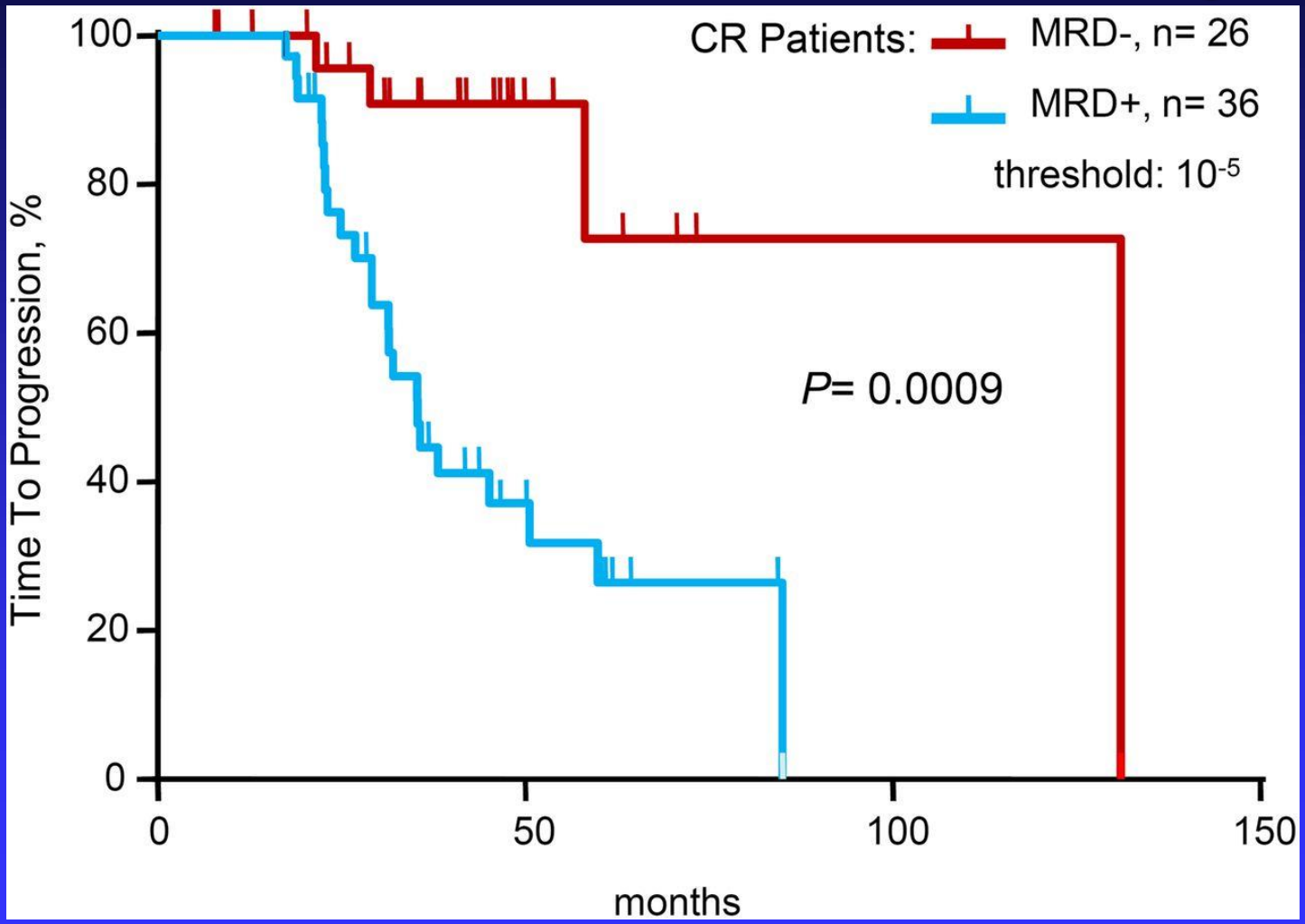
Next Generation Sequencing

Measurement of MRD

- Black Swan (Spanish) Flow
  - 8-12 color
- Characteristics
  - 10^5
  - No need for ID specimen
  - Must do it on fresh specimen

- Clonoseq (Adaptive)
  - NGS
- Characteristics
  - 10^6
  - Requires ID specimen
  - 8 % failure to identify clone

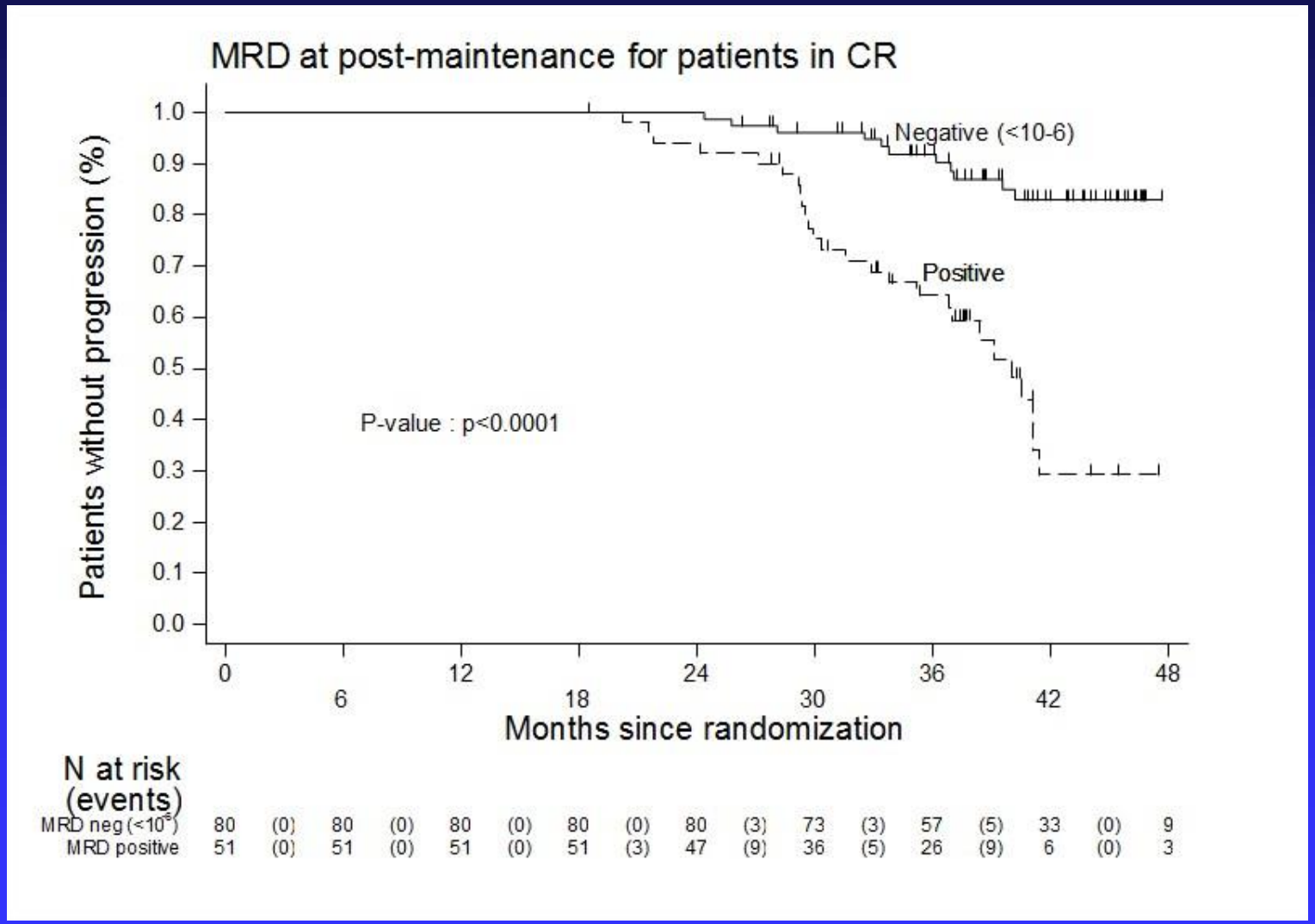
Time to progression for patients achieving conventional complete remission (CR), according to minimal residual disease (MRD) status as determined by deep sequencing.



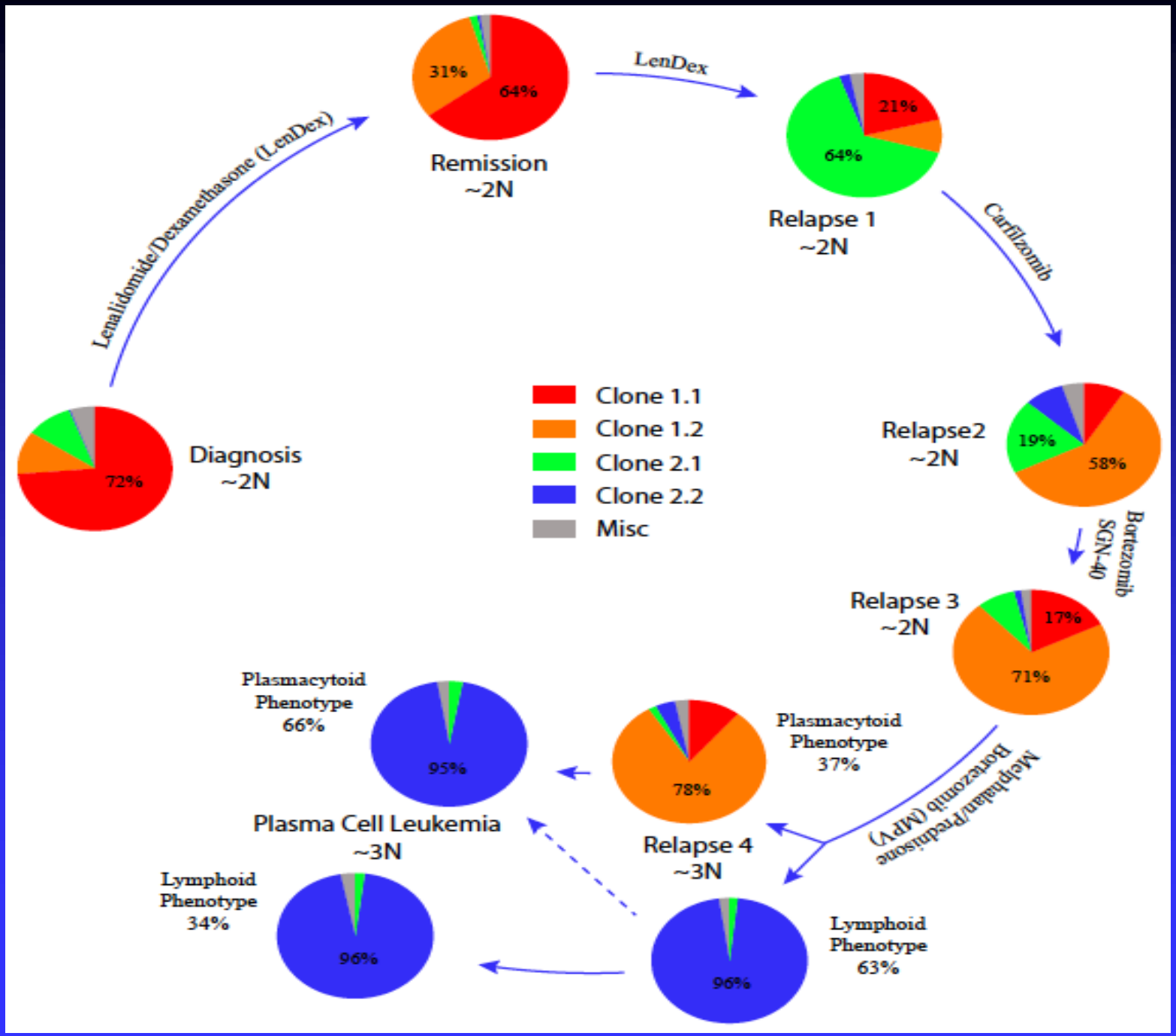
Martinez-Lopez J et al. Blood 2014;123:3073-3079

blood

IFMDFCI 2009 MRD



Why are we Failing to Obtain Long Periods of Disease Control in 25% of Patients?

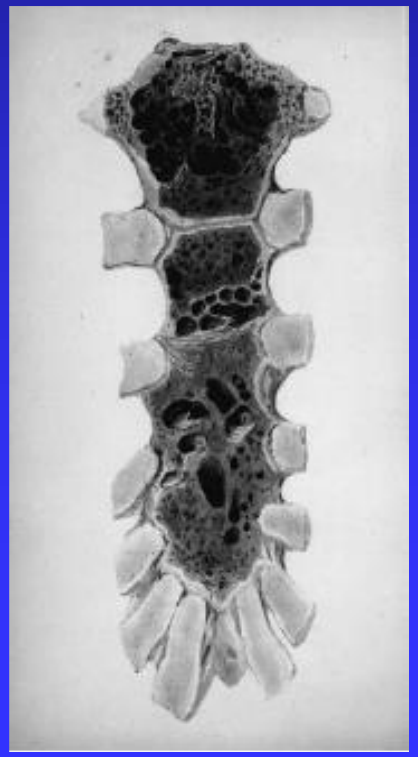

Lenalidomide/Dexamethasone (LenDex)
31%
64%
Remission
~2N
LenDex
21%
64%
Relapse 1
~2N
Carfilzomib
Clone 1.1
Clone 1.2
Clone 2.1
Clone 2.2
Misc
72%
Diagnosis
~2N
Relapse2
~2N
19%
58%
Bortezomib
SGN-40
Relapse 3
~2N
17%
71%
Melphalan/Prednisone
Bortezomib (MPV)
Plasmacytoid
Phenotype
66%
95%
Plasma Cell Leukemia
~3N
78%
Plasmacytoid
Phenotype
37%
Relapse 4
~3N
Lymphoid
Phenotype
34%
96%
96%
Lymphoid
Phenotype
63%

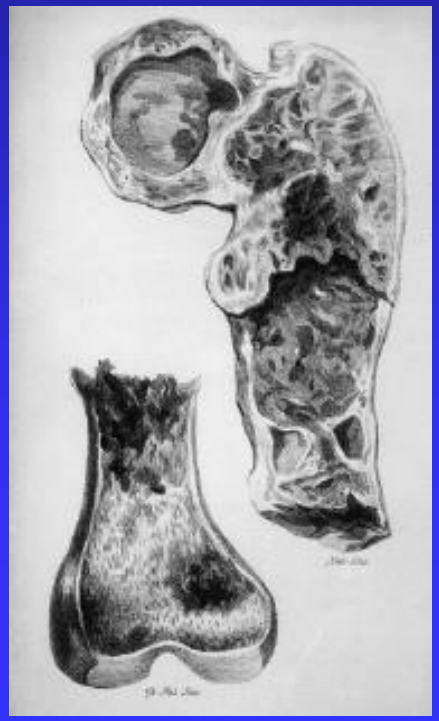
Evolution of Myeloma Therapy

Patient Case:

39 y.o. female with months of severe back pain, right leg pain, and lower extremity weakness. Subsequently she developed clavicular fractures and spine and lower extremity deformities.

Admitted to her local hospital, April 15, 1844





Solly, Med Chirur Trans London 1844

Treatment

- wine
- arrow-root
- a mutton chop
- a pint of porter daily
- an infusion of orange peel
- a rhubarb pill when necessary
- opiates

Conclusion

“earthy matter of the bone is absorbed and thrown out by the kidneys”

Myeloma Therapy (1961-1970)

CP1143748-23

Myeloma Therapy (1971-1990)

- Steroids
- Alkylators
  - Cyclophosphamide (Cytoxan)
  - Melphalan (low dose)
- OS = 2 years

Myeloma Therapy (1991-2000)

- VAD (Vincristine, adriamycin, decadron)
- Autologous PSC-T(peripheral stem cell transplant) (use of high dose melphalan)
- +/- Allogeneic PSC-T
- +/- Interferon

- OS = 3-4 years for good risk, lower stages
  = 2 years for everyone else

Myeloma Therapy (2001-2010)

- Thalidomide
- Bortezomib (Velcade) (5/2003)
- Lenalidomide (Revlimid) (12/27/05)
- Pegylated liposomal doxorubicin (Doxil) (2007) ((in combo with bortezomib)

- Continued auto PSC-T
- Began combinations with new agents and old
  - RVd
  - CyBorD

Myeloma Therapy (2011 – 2013)

- Carfilzomib (Kyprolis) (7/20/12)
- Pomalidomide (Pomalyst) (2/8/13)

- Role of "Maintenance" Therapy defined
- Develop combinations for induction followed by transplantation
- OS = 8-10 years for standard risk

Myeloma Therapy (2014-2016)

- Panobinostat (Farydak) (2/23/15)
- Daratumumab (Darzalex) (11/16/15)
- Ixazomib (Ninlaro) (11/20/15)
- Elotuzumab (Empliciti) (11/30/15)

- Concept of post transplant consolidation
- Adding in newer agents (Carfilzomib) to induction
- Doublets and triplets for “High Risk” maintenance
- Use of Minimal Residual Disease testing
- Further confirmation of the role of auto PSC-T

Decisions at Diagnosis

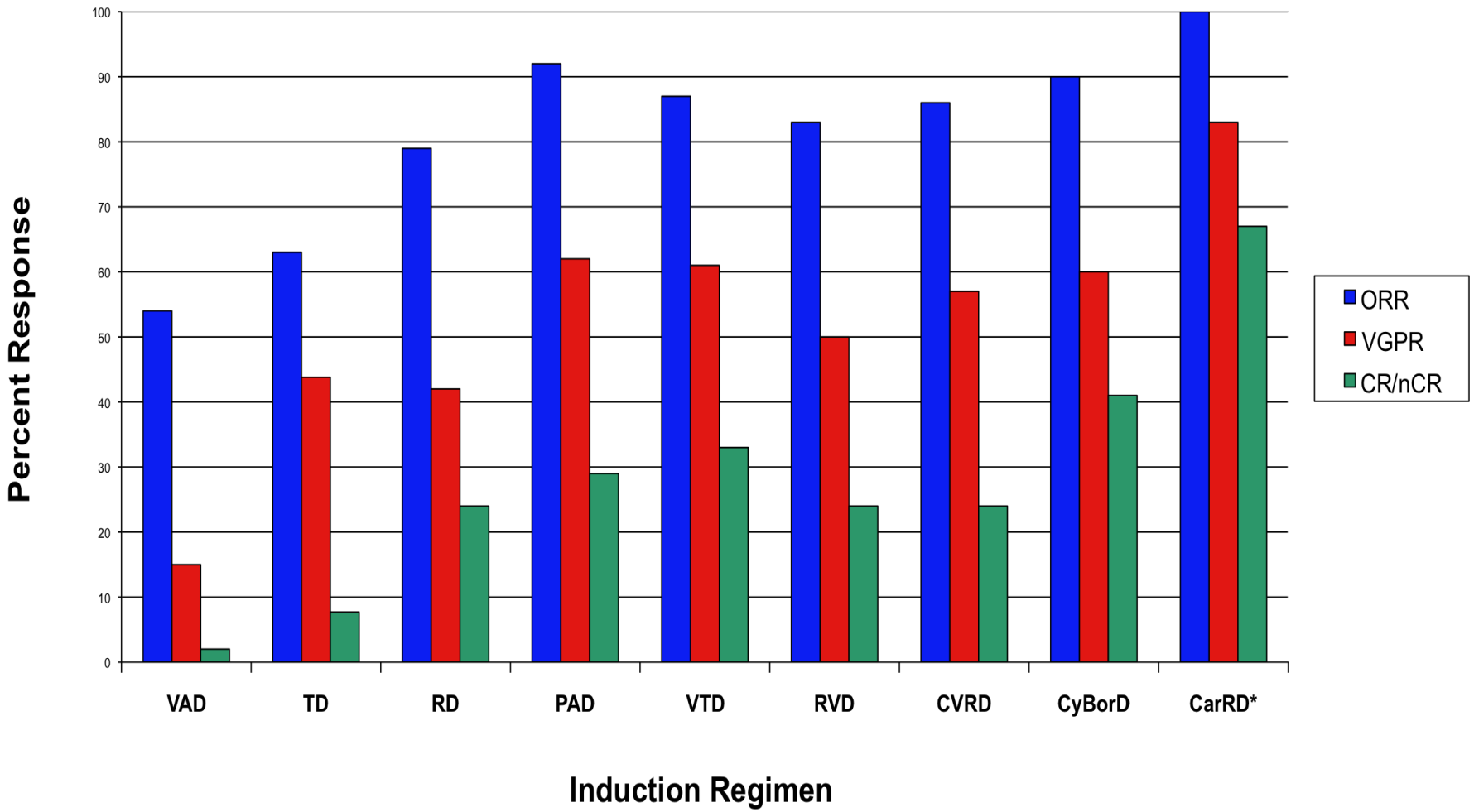
- Does this patient need treatment at all? Smoldering?
  - Use of PET/CT
  - Studies of Revlimid and other agents in smoldering

- Transplant candidate vs not (Melphalan issue)
  - Not necessarily still true
    - Nobody (except in Europe) uses frontline melphalan
    - There are combinations that work for both groups
    - We now have Plerixafor

Initial Induction Therapy for Patients Eligible for Transplant

NO MELPHALAN

Improving Response Rates with Combination Therapies

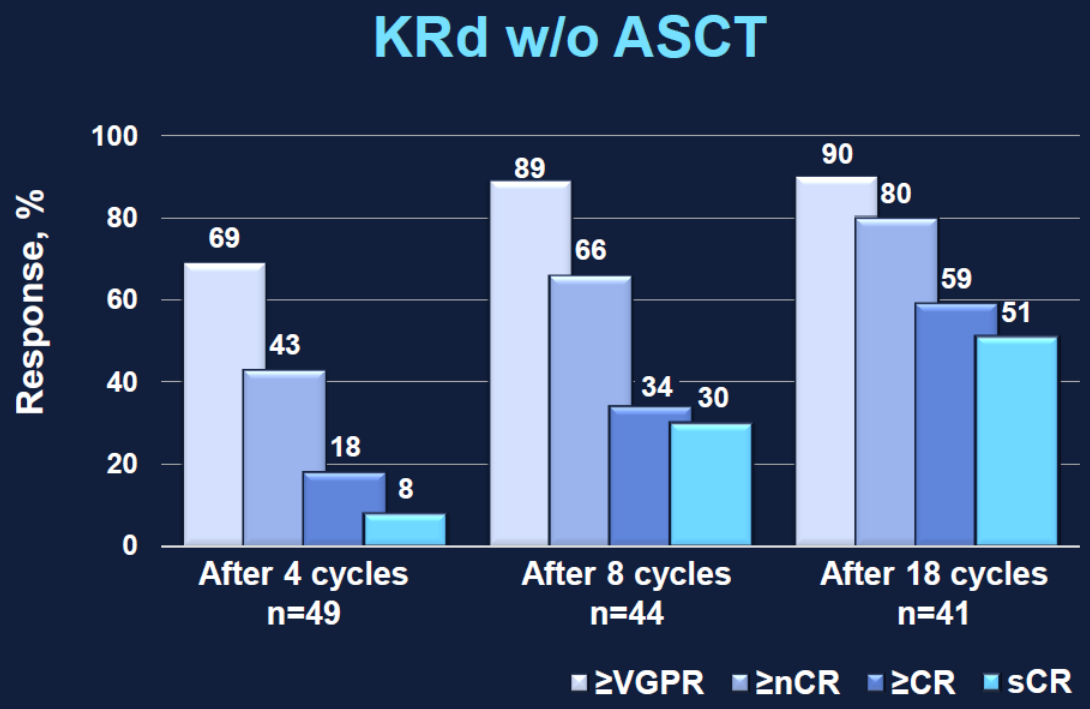


Carfilzomib (Kyprolis)

KRd (? Improvement over RVd?)

Jakubowiak, 2015

Response Rates Over the Course Treatment

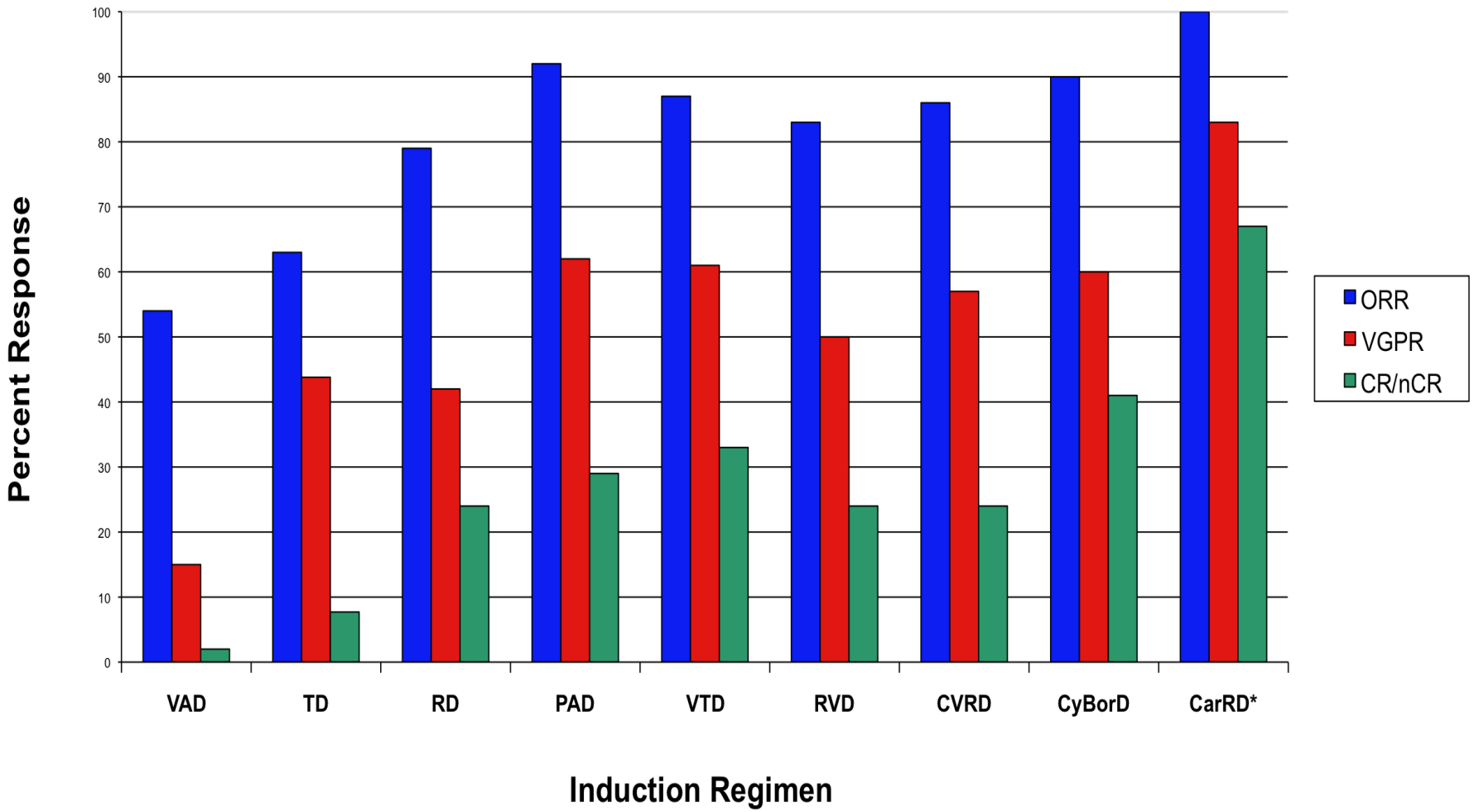


nCR, near complete response; VGPR, very good partial response

Frontline Therapy for Patients Ineligible for Transplant

Melphalan OK

Improving Response Rates with Combination Therapies



Stem Cell Transplantation

There is still a role!!!

The Debate… ASCT: Up-Front or at Relapse
DFCI/IFM 2009 Trial

Len-Bz-Dex ×3

↓

Stem collection

↓

ASCT

↓

Len-Bz-Dex ×2

↓

Len ×12m (IFM)

Len until relapse (US)

Len-Bz-Dex ×3

↓

Stem collection

↓

Len-Bz-Dex ×5

↓

Len ×12m (IFM)

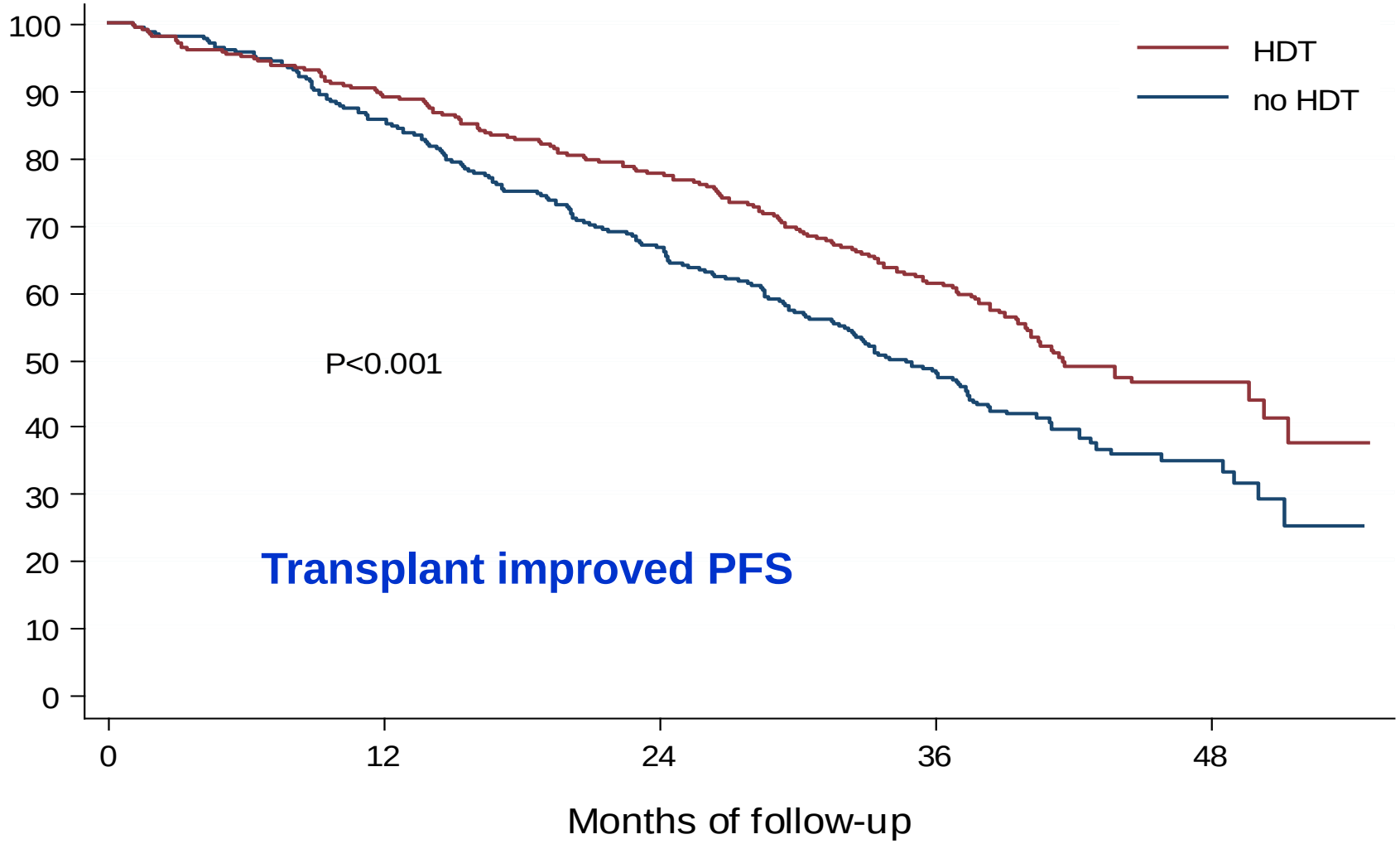
Len until relpase (US)

⋮

ASCT at relapse

NCI Clinical Trial Identifier NCT01191060.

IFM/DFCI 2009



N at risk

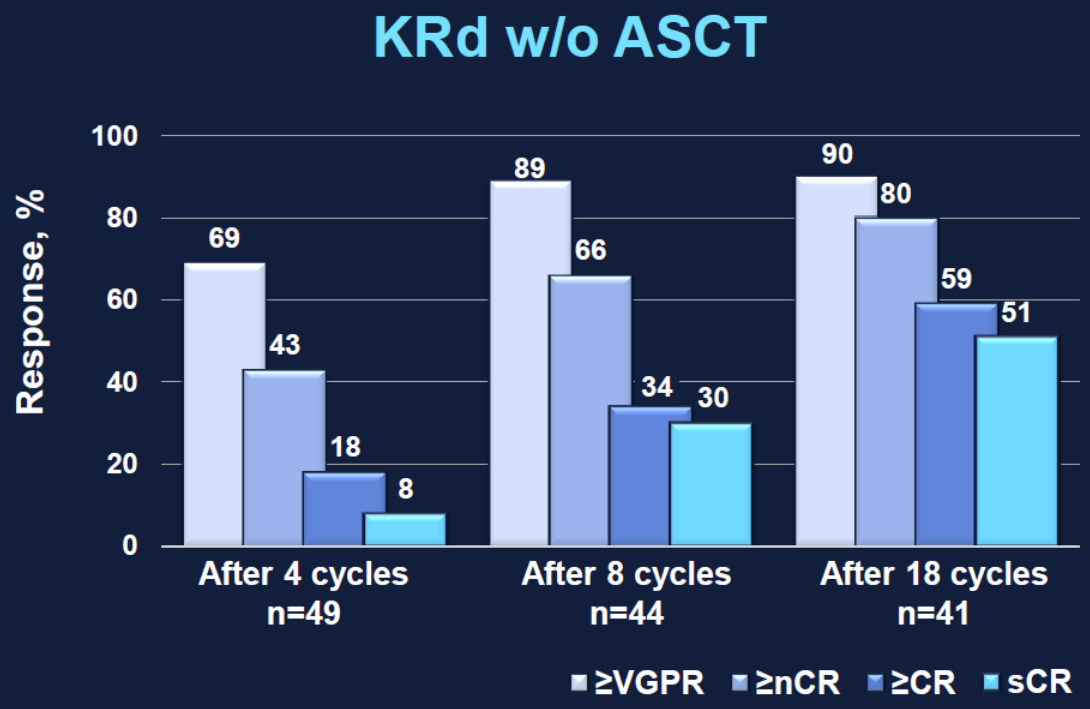
HDT	350	309	261	153	27
no HDT	350	296	228	128	24

Further Evidence for Role of Auto ASCT

KRd (? Improvement over RVd?)

Jakubowiak, 2015

Response Rates Over the Course Treatment

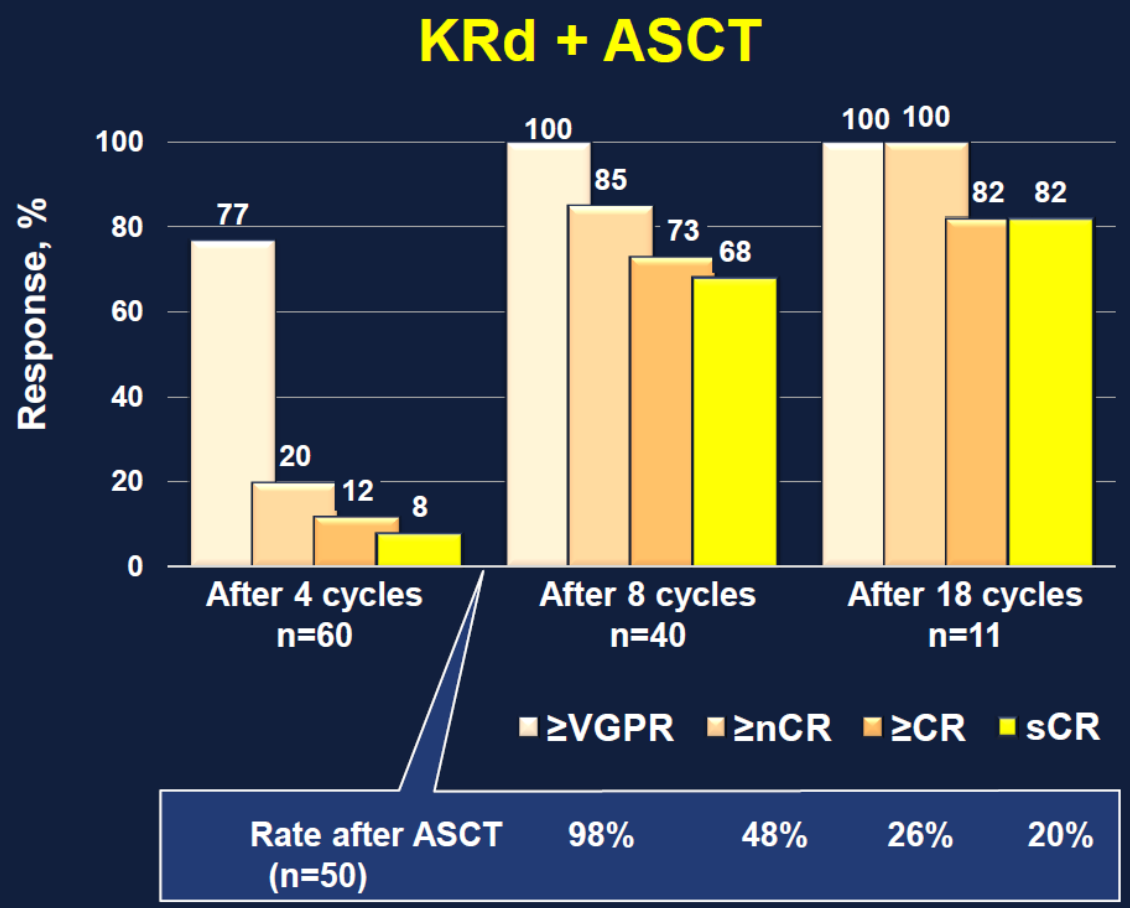


nCR, near complete response; VGPR, very good partial response

KRd + ASCT

Zimmerman, 2016

Response Rates Over the Course Treatment



nCR, near complete response; VGPR, very good partial response

Maintenance Therapy (continuation therapy)

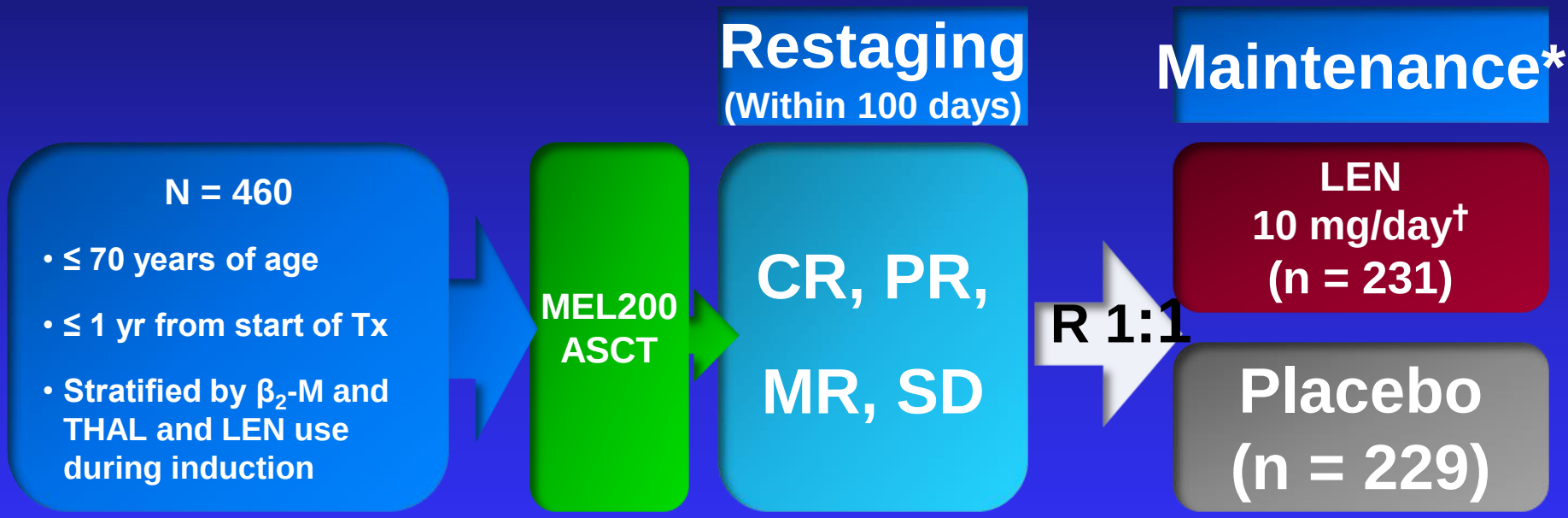
CALGB 100104: A Phase III Randomized, Double-Blind Study of LEN vs. PBO Maintenance Therapy Following ASCT for MM

McCarthy P., et al

McCarthy PL. *N Engl J Med*. 2012;366:1770-1781.

CALGB 100104: Study Design and Endpoints

- Primary endpoint: TTP (time from ASCT to PD/death)
- Secondary endpoints: OS, post-ASCT response, long-term LEN feasibility

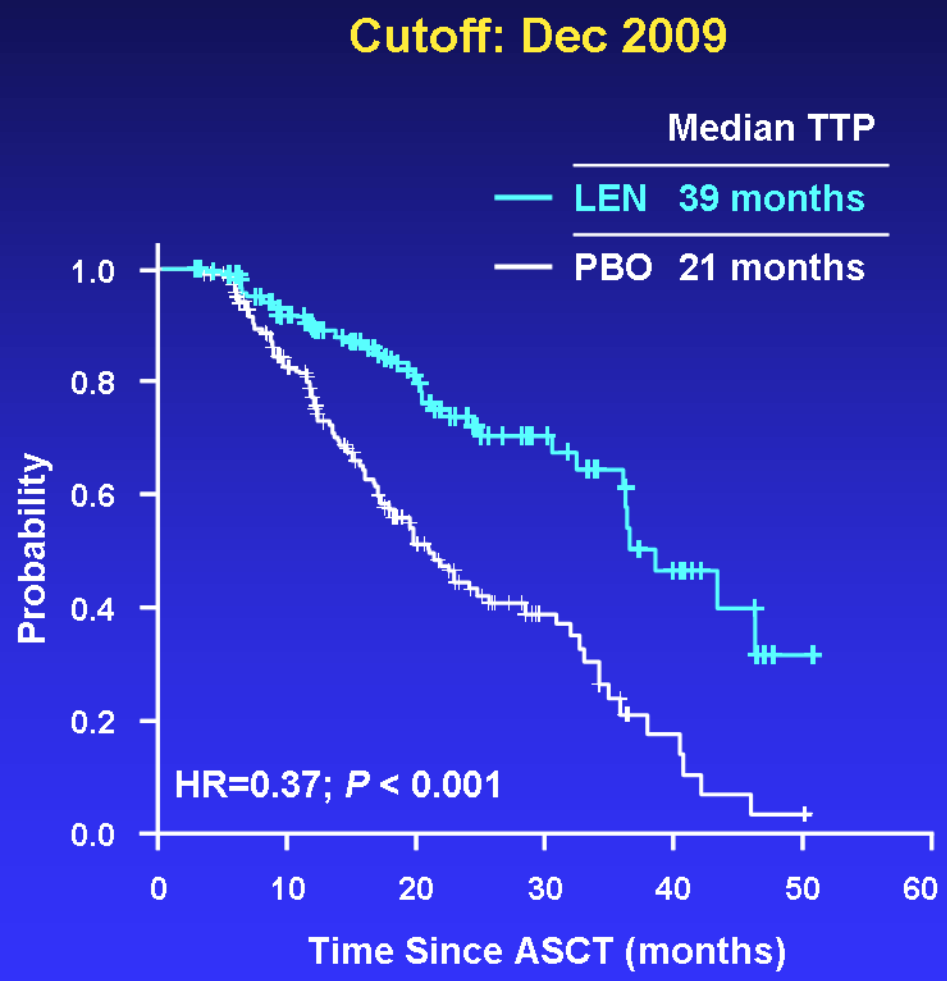


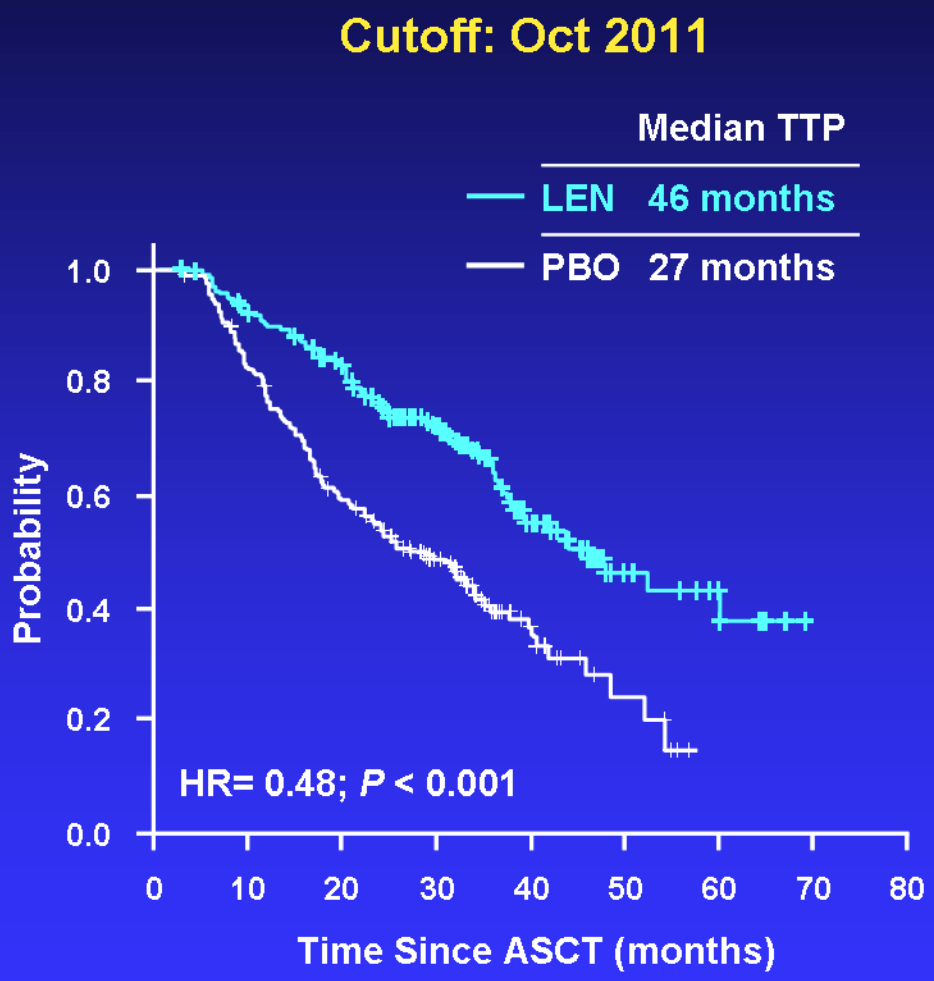
* All patients received thromboprophylaxis; † LEN dose adjustments between 5-15 mg permitted.

ASCT: autologous stem cell transplant; β_2-M: β_2-microglobulin; CALGB: Cancer and Leukemia Group B; CR: complete response; LEN: lenalidomide; MEL200: melphalan 200 mg/m^2; MR: minimal response; OS: overall survival; PD: progressive disease; PR: partial response; R: randomization; SD: stable disease; THAL: thalidomide; TTP: time to progression; Tx: treatment.

McCarthy PL. *N Engl J Med.* 2012;366:1770-1781.

CALGB 100104: Time to Progression

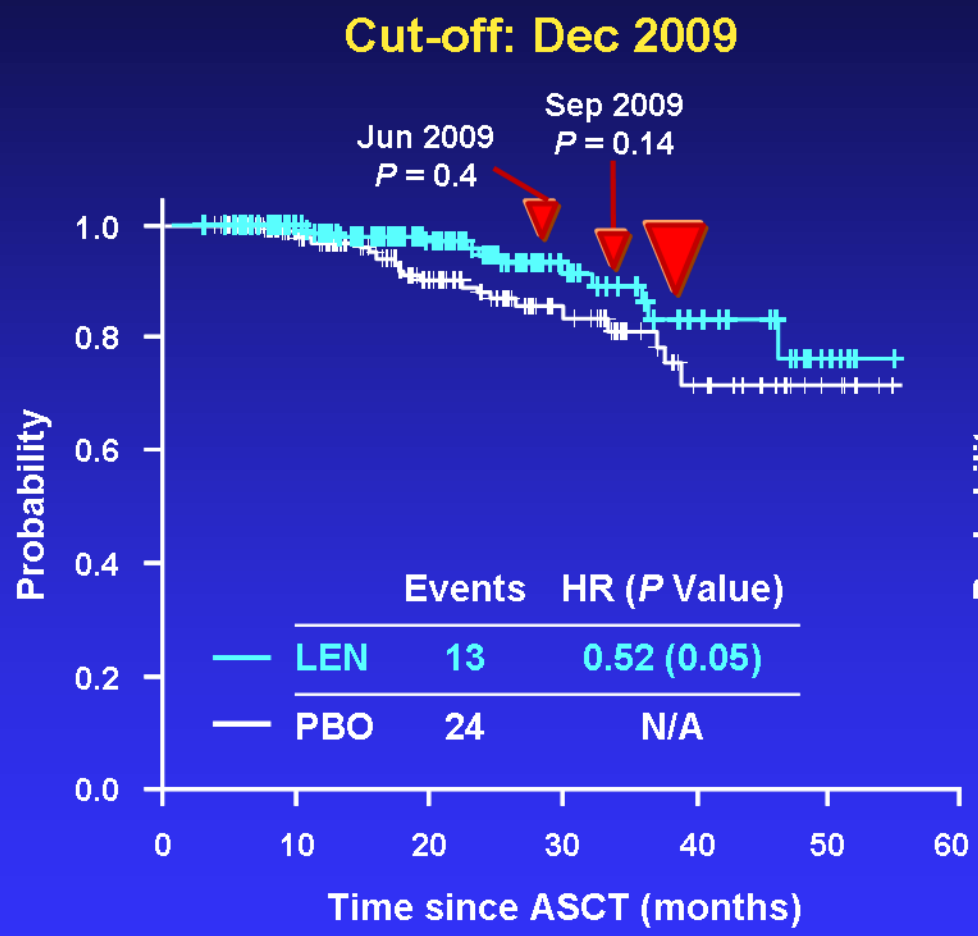


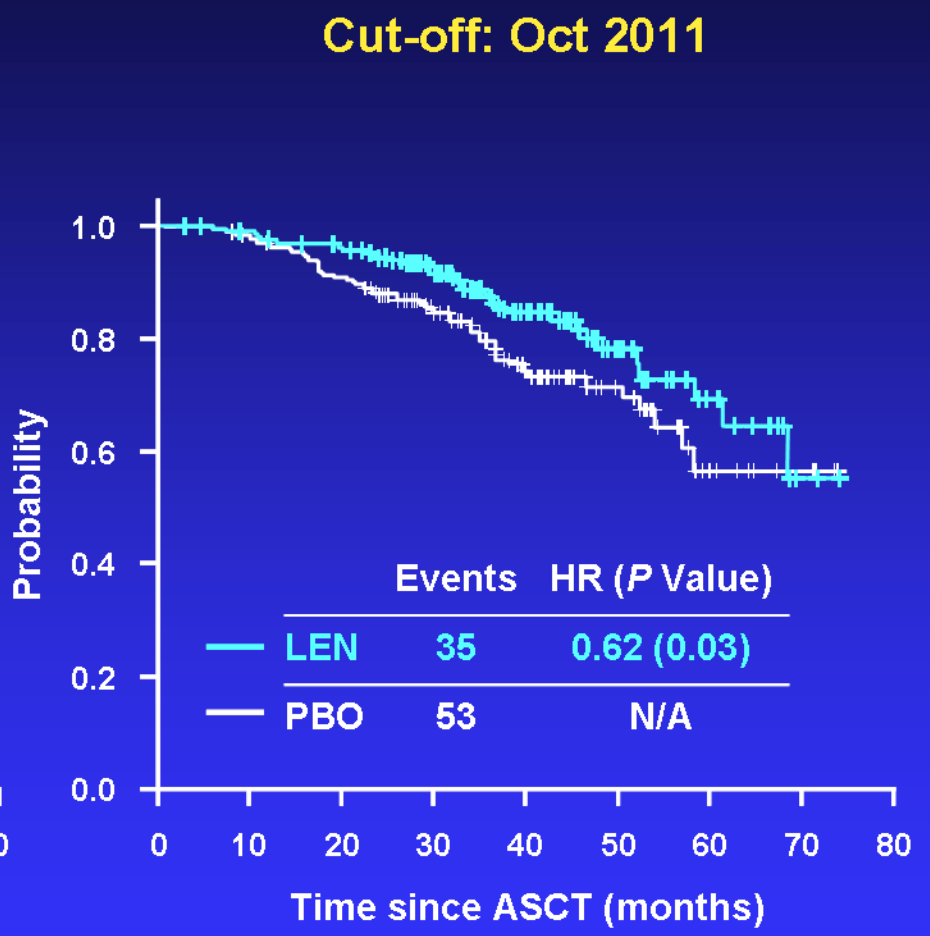


ASCT: autologous stem cell transplant; CALGB: Cancer and Leukemia Group B; HR: hazard ratio; LEN: lenalidomide; N/A: not applicable; PBO: placebo; TTP: time to progression.

McCarthy PL. *N Engl J Med.* 2012;366:1770-1781.

CALGB 100104: Overall Survival





ASCT: autologous stem cell transplant; CALGB: Cancer and Leukemia Group B; HR: hazard ratio; LEN: lenalidomide; N/A: not applicable; OS: overall survival; PBO: placebo.

McCarthy PL. *N Engl J Med.* 2012;366:1770-1781.

New Drugs/New Studies

Ixazomib (Ninlaro)

Panobinostat (Farydak)

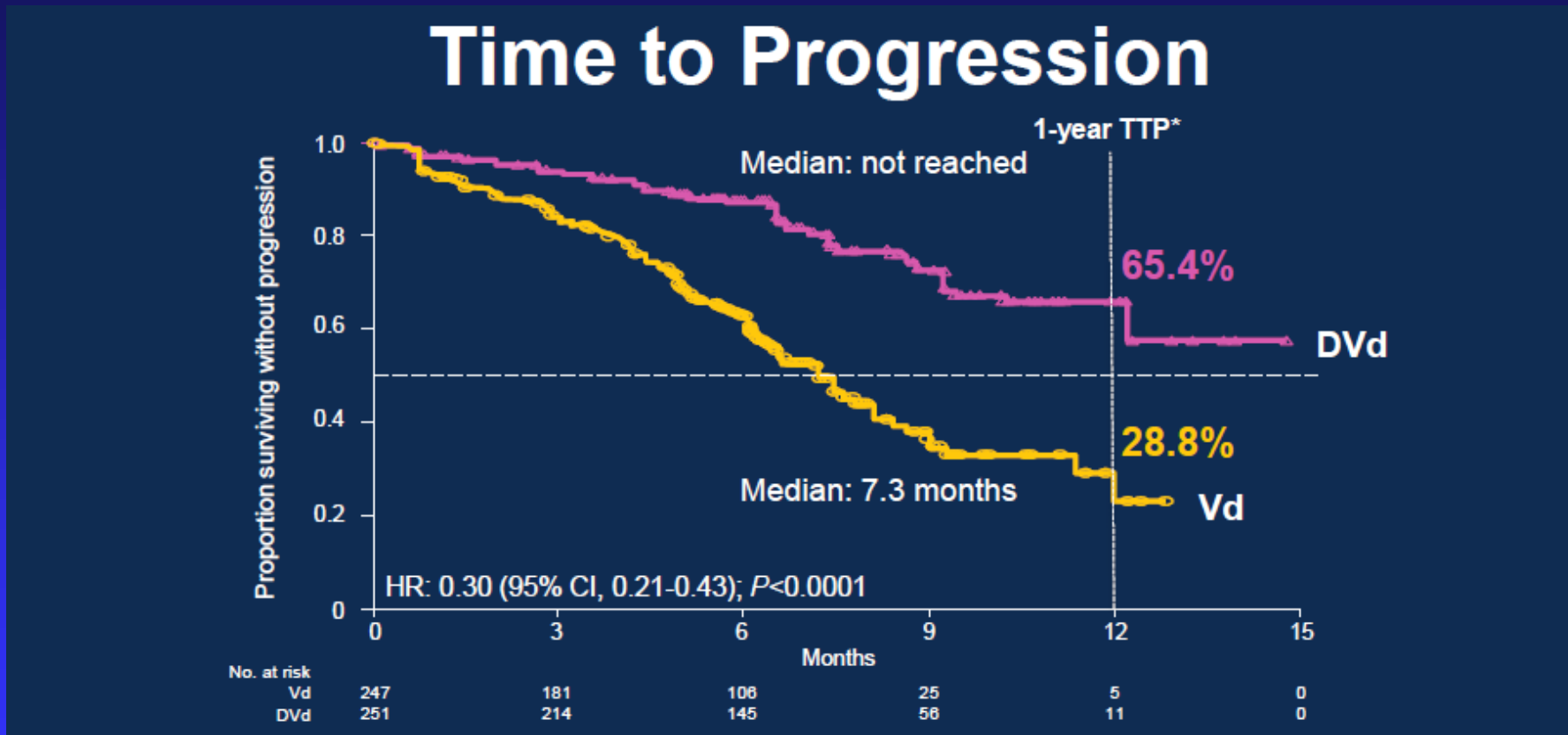
Elotuzumab (Impliciti)

Daratumumab (Darzalex)

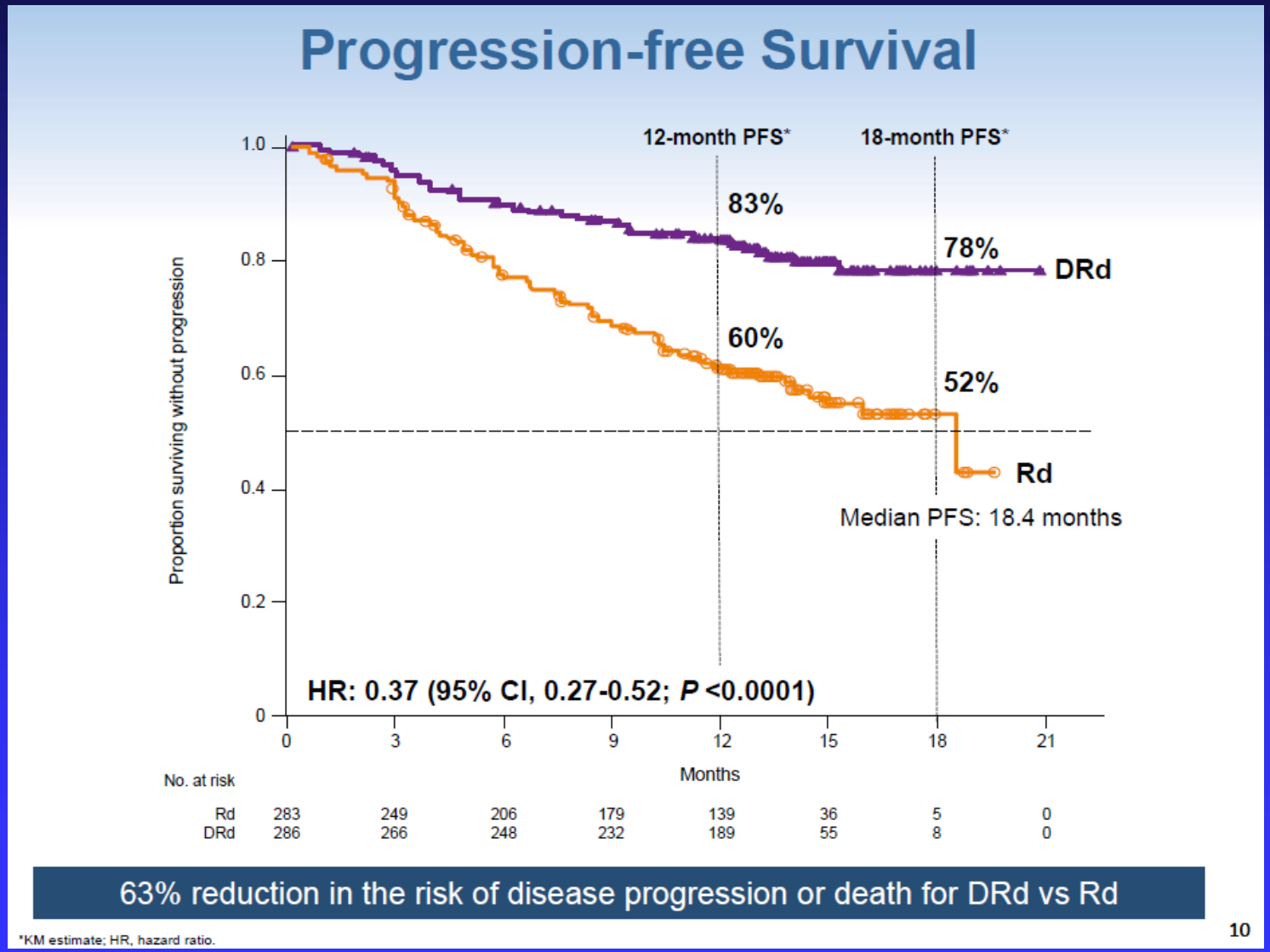
Daratumumab

Anti CD 38

Castor: Vd vs Dara Vd



Pollux: Rd vs Dara Rd



Immunotherapies

Antibodies

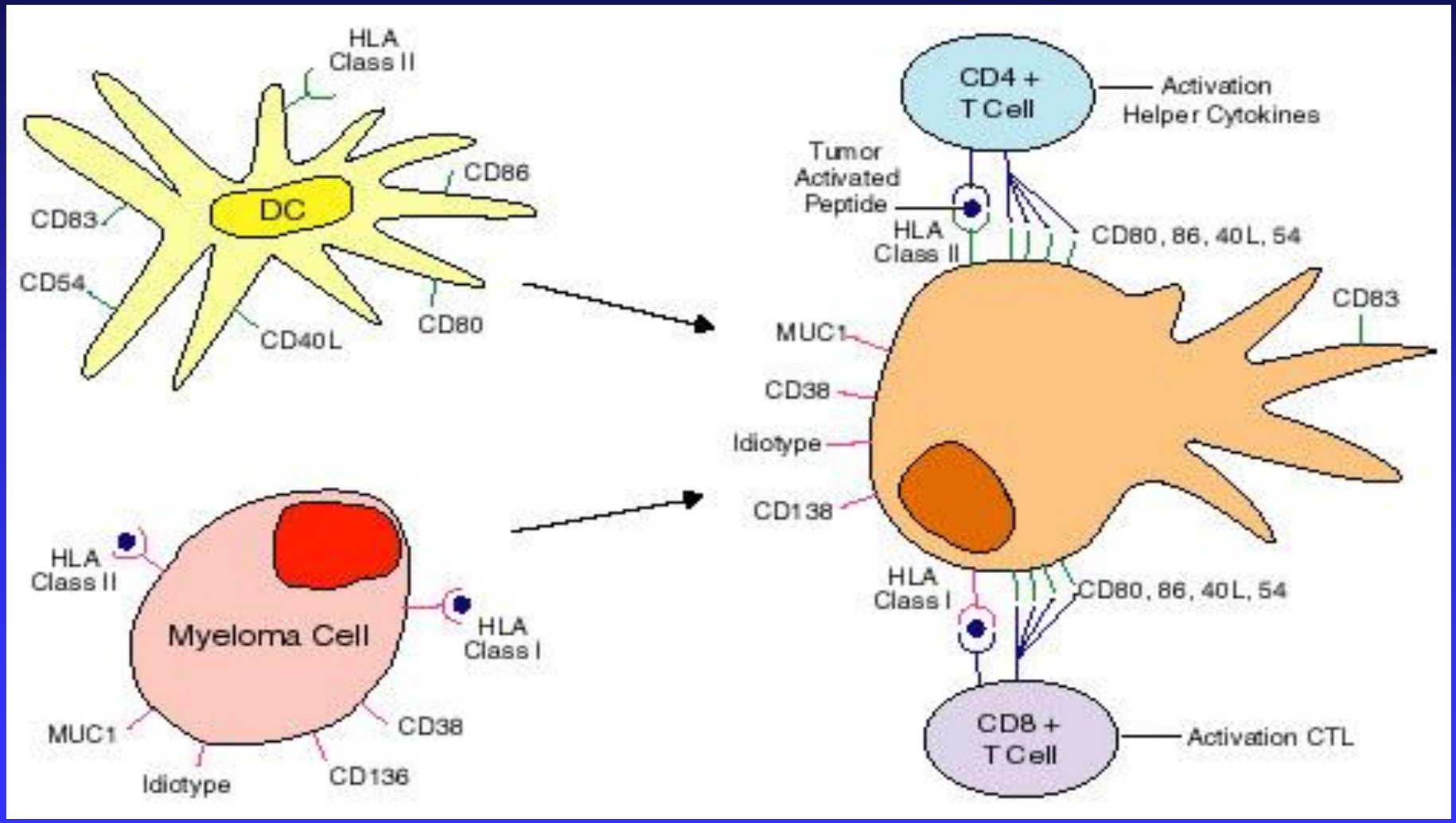
Vaccines

Checkpoint Inhibitors

BiTEs

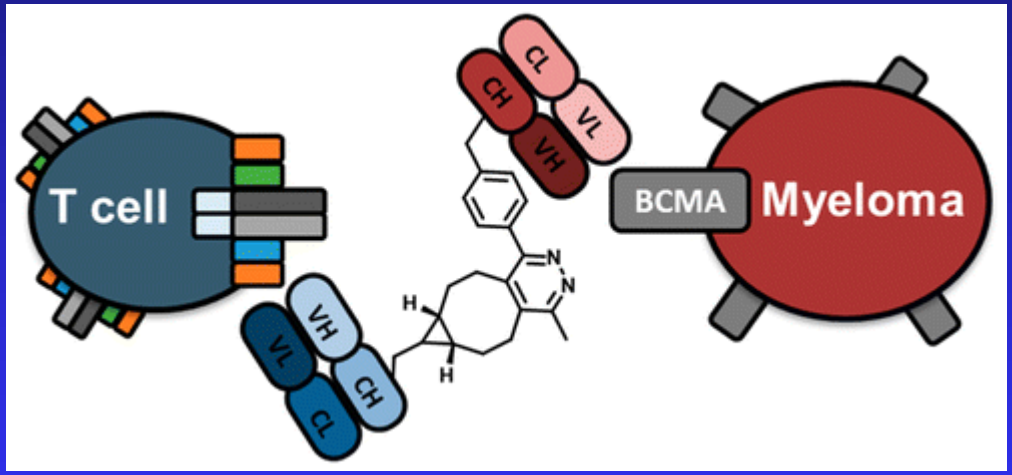
CAR-Ts

Vaccine approaches: DC fusion

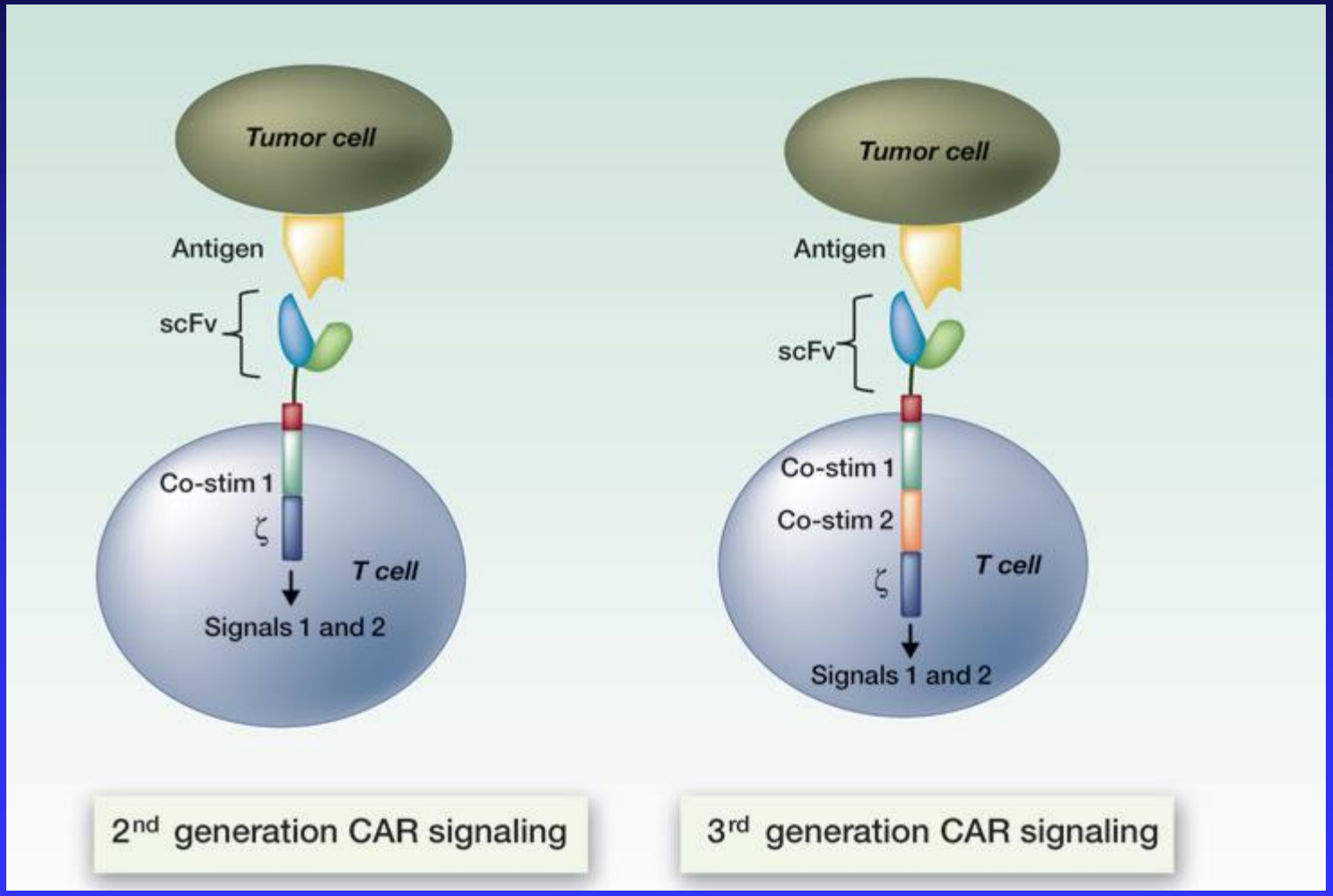


Courtesy of David Avigan

BiTe Therapy



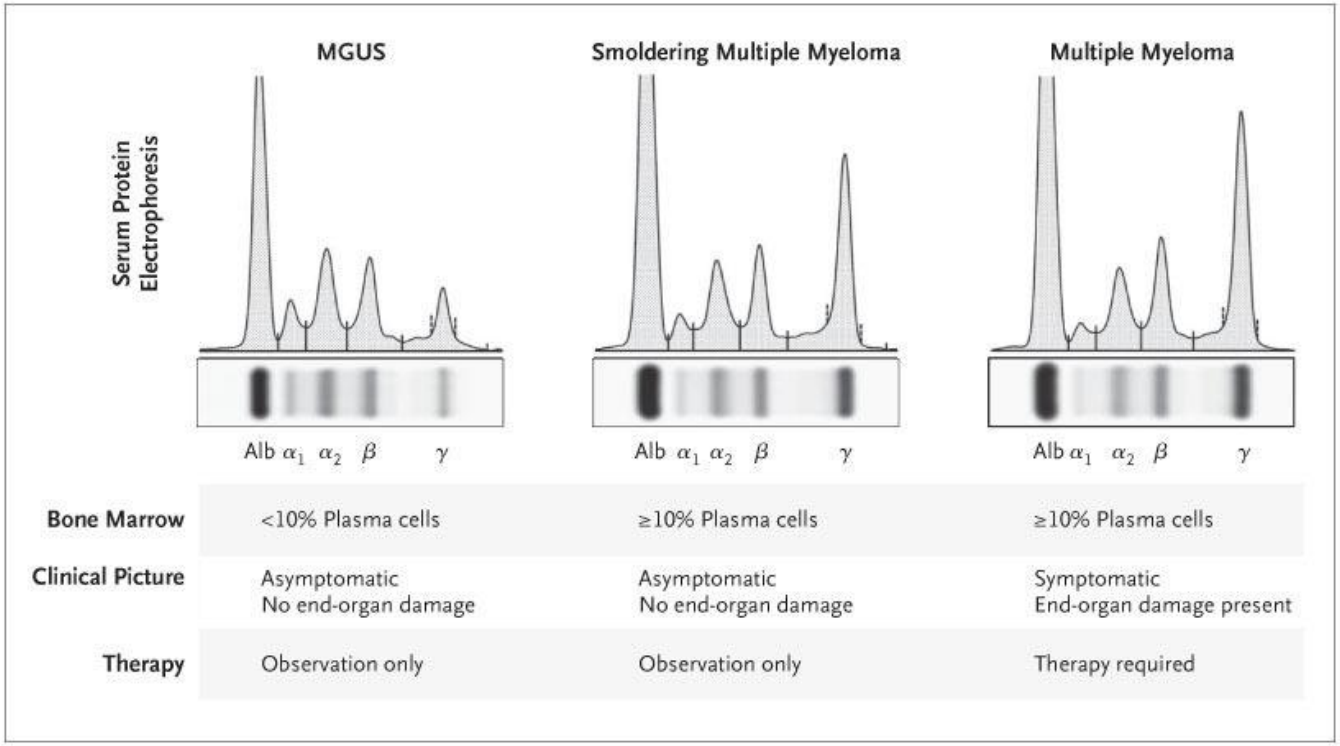
Chimeric Antigen Receptor Effector Cells (CAR-T)



Treatment of High Risk Smoldering Myeloma

Is there a rationale for treating?

Characteristics of Active Multiple Myeloma and Its Precursors



	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma
Bone Marrow	<10% Plasma cells	≥10% Plasma cells	≥10% Plasma cells
Clinical Picture	Asymptomatic No end-organ damage	Asymptomatic No end-organ damage	Symptomatic End-organ damage present
Therapy	Observation only	Observation only	Therapy required

Kyle R et al. N Engl J Med 2007;356:2582-2590

The NEW ENGLAND JOURNAL of MEDICINE

Free Light is Useful for Risk Assessment in SMM

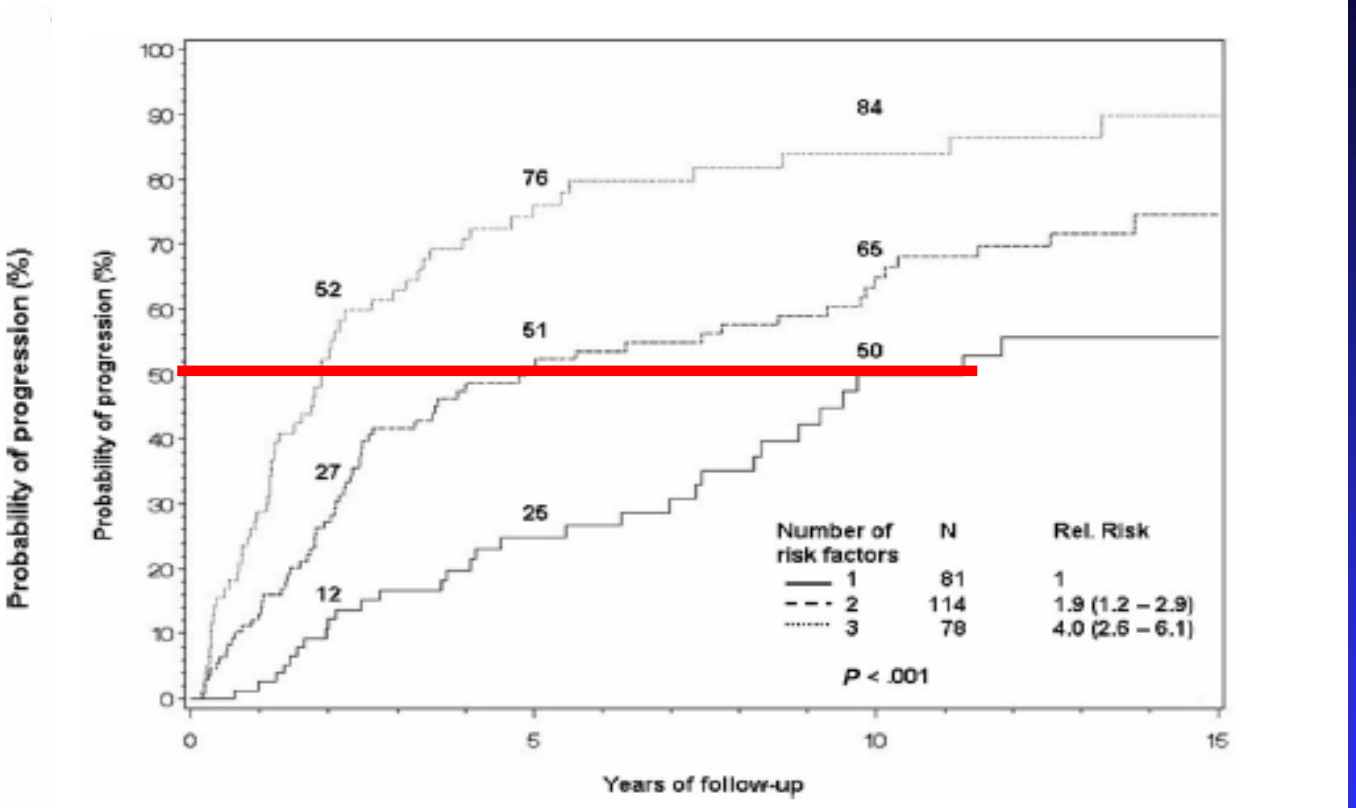


Table 3. Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

Prognostic factor	Hazard ratio (95% CI)	*P*
Bone marrow plasma cells more than 10%	3.1 (1.6-6.3)	< .01
Abnormal FLC ratio less than 0.125 or more than 8	1.9 (1.3-2.7)	< .01
Serum M protein size, more than 30 g/L	1.9 (1.4-2.6)	< .01

Dispenzeri et al Blood 2008

Schedule of therapy (N = 126 pts)

Spanish Myeloma Group

	Treatment arm (n = 60)	Control arm (n = 66)
Induction Nine 4-week cycles	**Lenalidomide** 25 mg/daily during 21d every 28 d **Dexamethasone** 20 mg D1-D4 and D12-D15 every 28 d	**Therapeutic abstention**
Maintenance	**Lenalidomide** 10 mg/daily during 21 d every month*	**Therapeutic abstention**

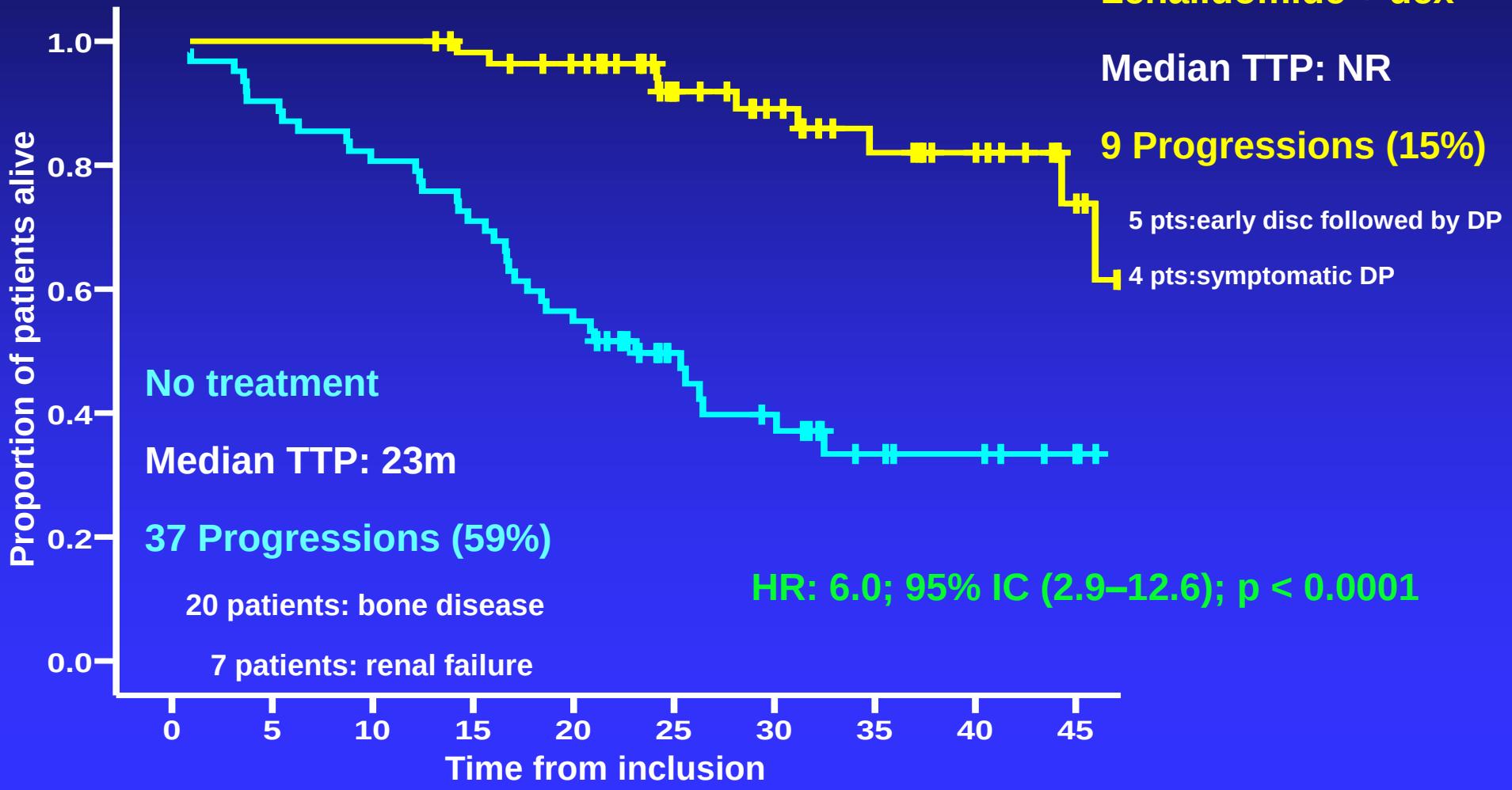
Ammendment on August 2011: Stop treatment at 2 years of treatment

** Low-dose Dex will be added at the moment of biological progression*

Len-Dex vs. No Treatment: TTP to Active Disease

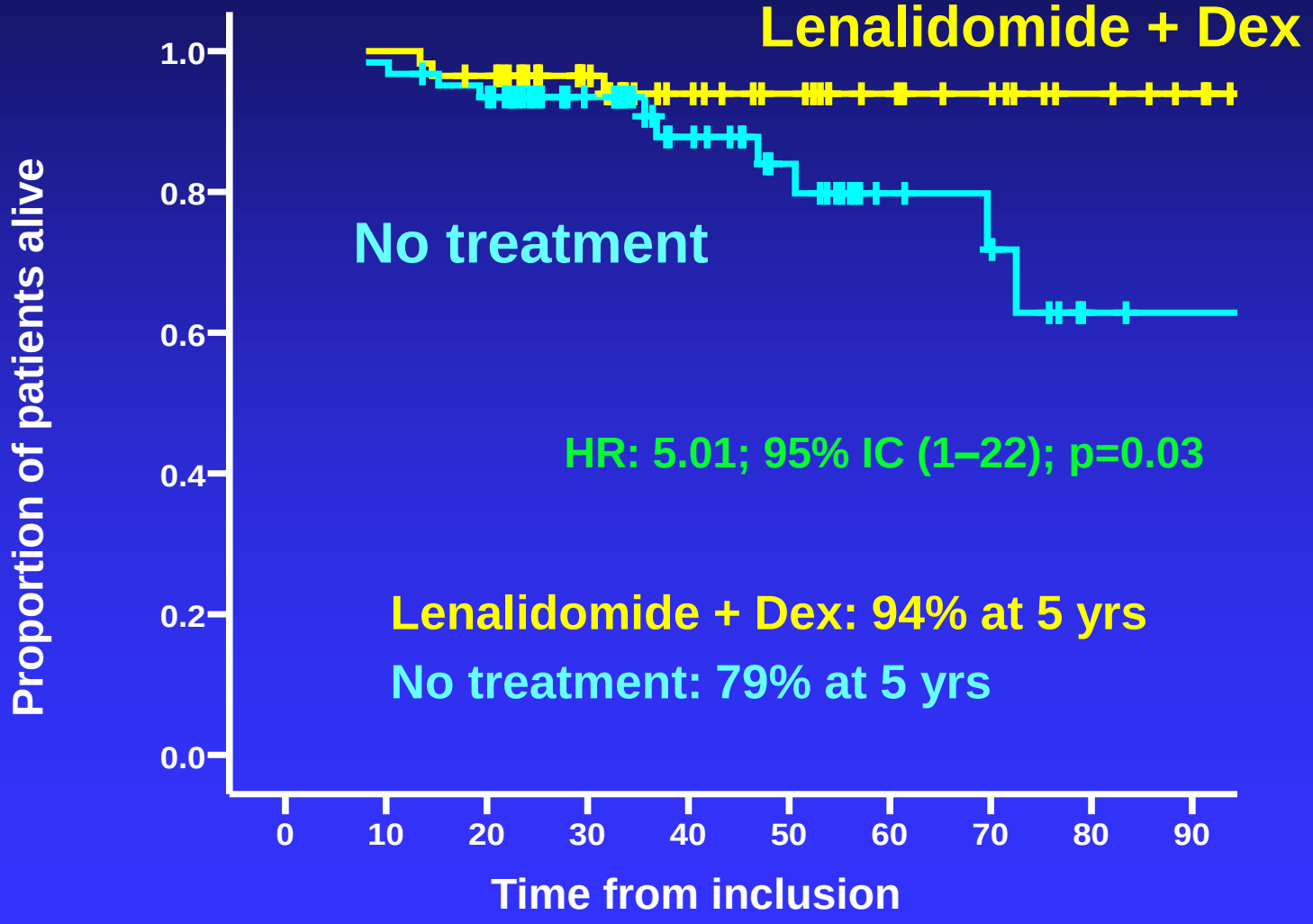
(N = 119)
ITT analysis

Median follow-up: 32 months (range 12–49)

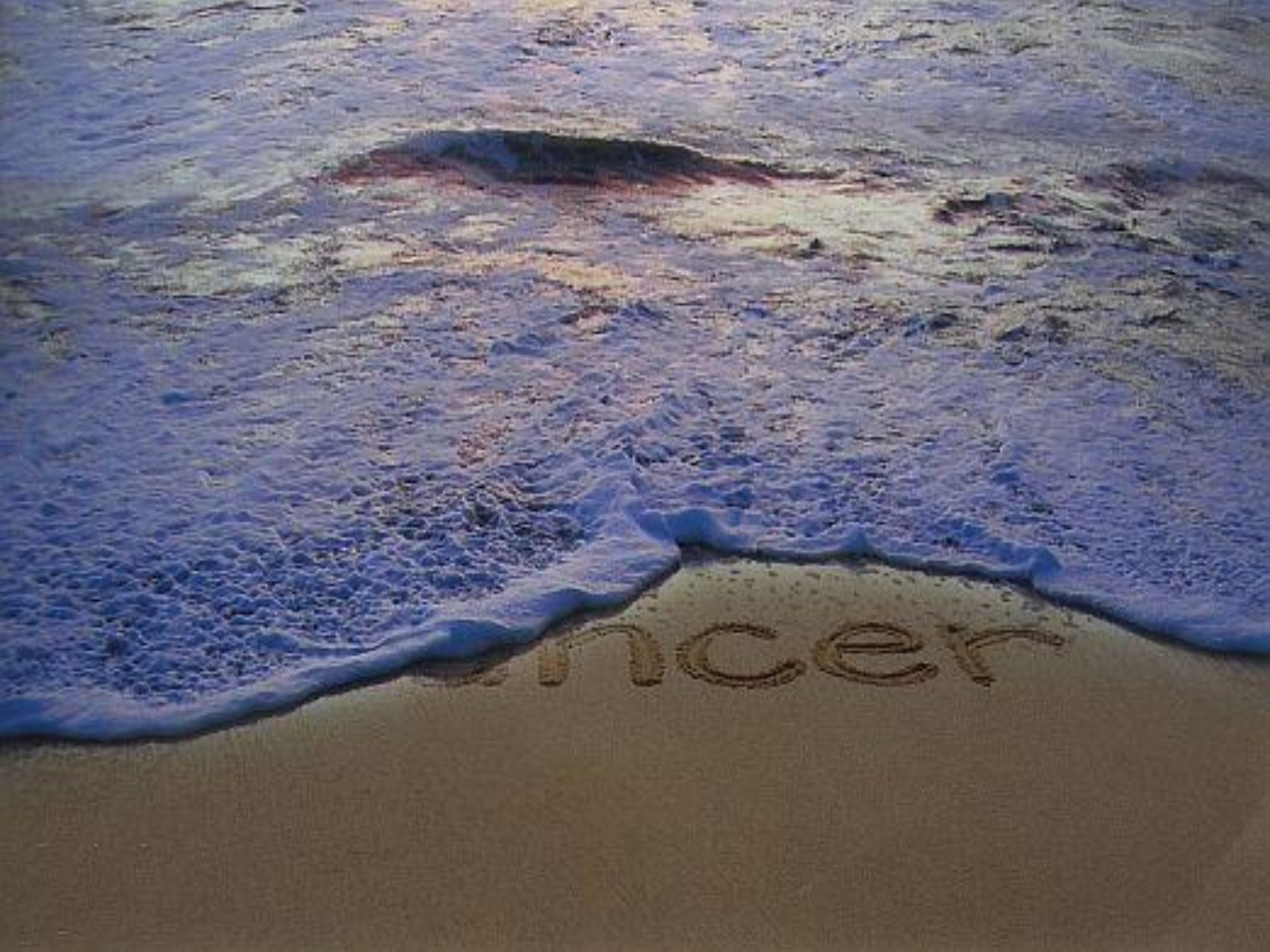


Len-dex vs no treatment: OS from diagnosis (n = 119)

Median follow-up: 38months (range 14–96)




Cancer


cancer

Thank you