MELVIN AND BREN SIMON
CANCER CENTER

INDIANA UNIVERSITY

# Multiple Myeloma
# What is New?

Rafat Abonour, M.D.

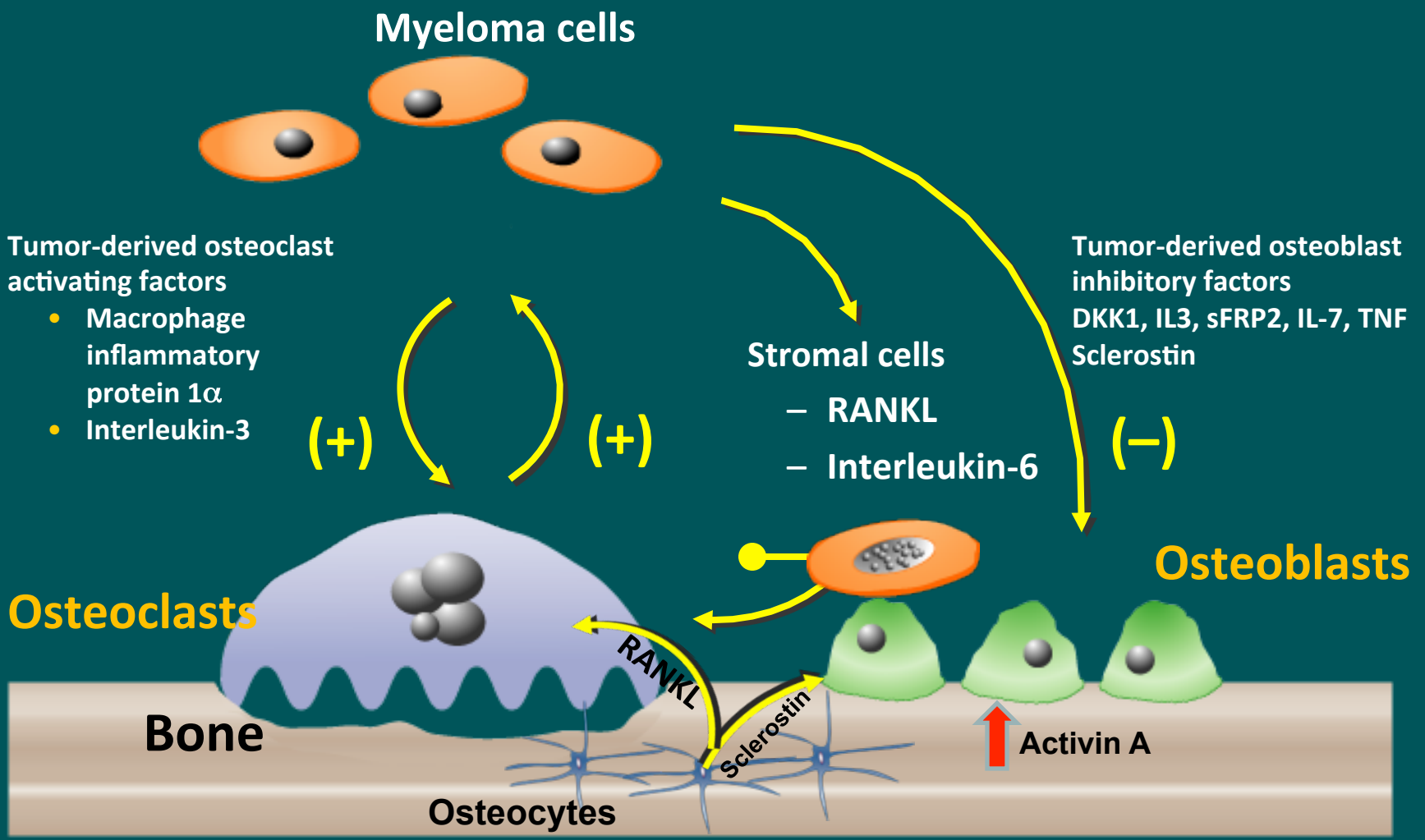
# Multiple Myeloma Facts

- Second most prevalent hematologic neoplasm
- Nearly 24,000 new cases diagnosed in the US per year and 110,000 worldwide
- Median age at diagnosis is 70 years
- Survival is increasing but cure has not been realized
- Based on SEER data the 5 survival of those diagnosed 1990-2005 was only 37.1%

# How to Overcome Multiple Myeloma

- **Understand How Myeloma cells survive.**
- **Understand the Nature of the originating cell**
- **Understand that not all myeloma cells created equally.**
- **Understand the importance of the patients' immune system**

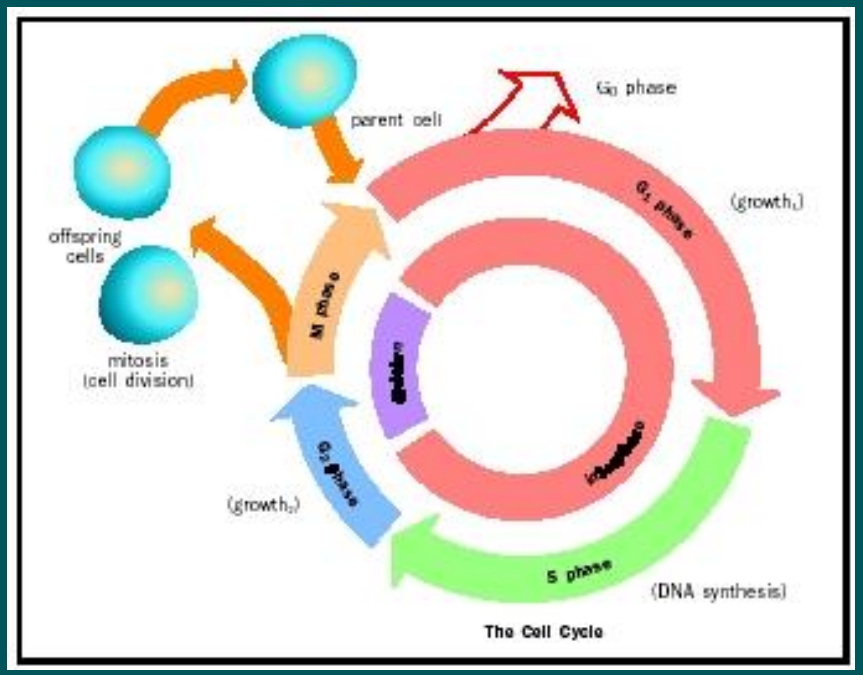
# Myeloma Cells Like their Neighborhood



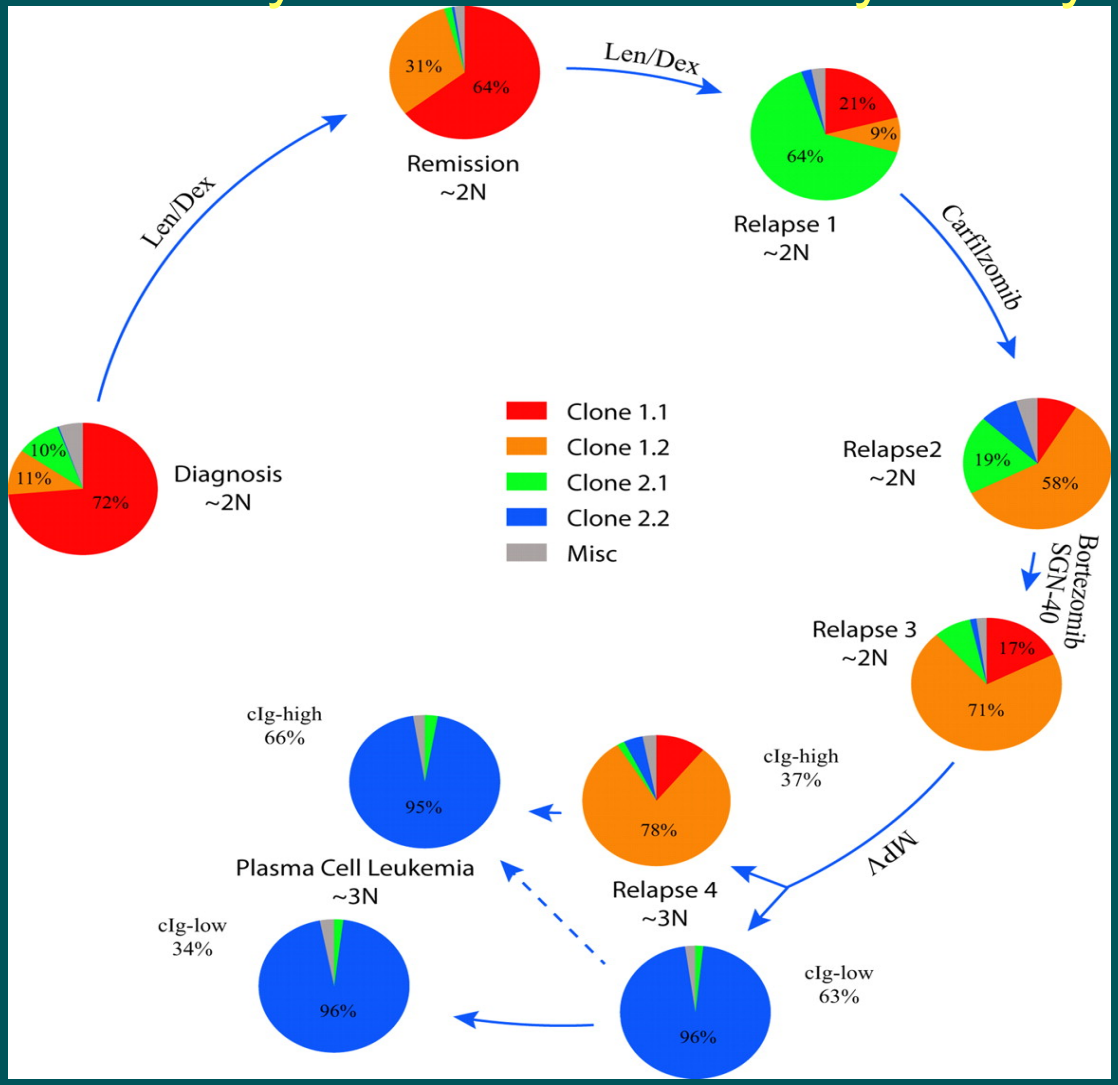

Adapted from Roodman GD. *N Engl J Med*. 2004;350(16):1655-1664.

# The Originating Cell is Stubborn

- myeloma “stem” cell
  - Do not cycle, dormant
  - Very drug resistant
  - Spin off new myeloma cells



# Clonal Heterogeneity Impacts Outcome
# One Nasty Disease: One Nasty Family

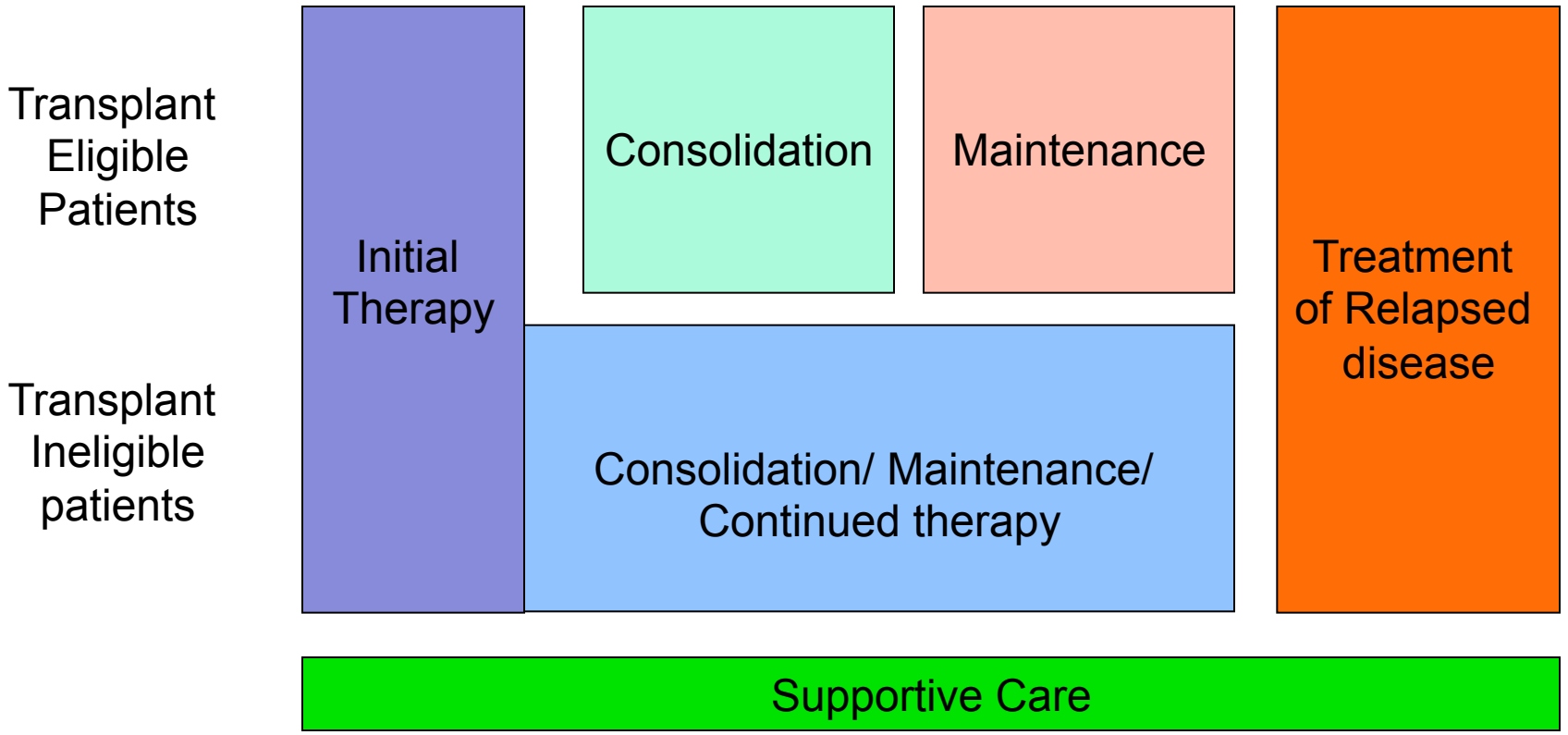



Keats et al. Blood 2012: 120: 1067

# Treatment Goals for MM

- **Symptom Control**
  - **Ameliorate pain and other disease-related symptoms**
  - **Prevent further organ damage**
  - **Preserve and improve performance status and quality of life**
- **Disease Response and Survival**
  - **Rapid cytoreduction to relieve symptoms**
  - **Minimize treatment-related toxicity and Stem Cell damamge**
  - **Prolong survival – Overall Survival**

# Managing myeloma: the components



# Treatment sequence

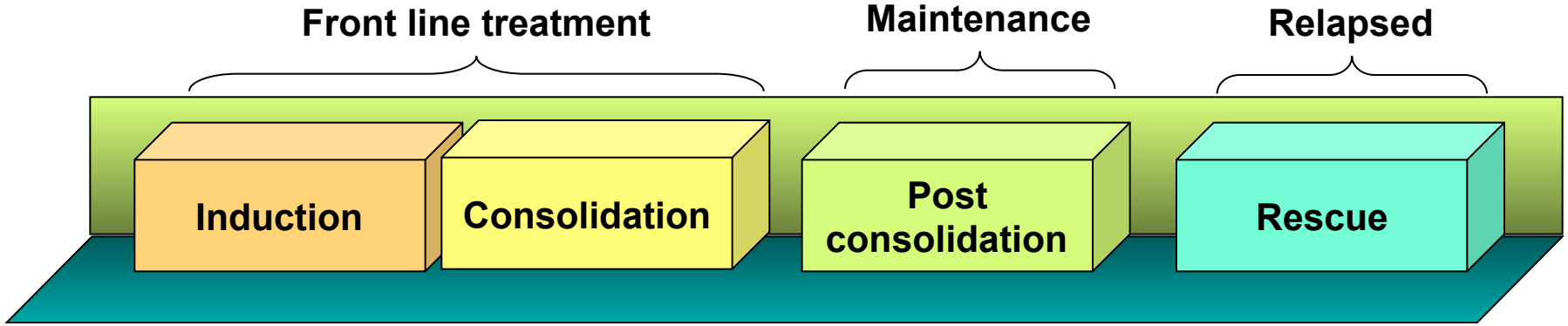
**NEW**

Thal/Dex
VD
Rev/Dex
CyBorD
VTD
VRD
CDR

SCT
VD/VRD

Nothing
Thalidomide?
Bortezomib?
Lenalidomide?

Bortezomib
Lenalidomide
Thalidomide
Carfilzomib
Pomalidomide
Monoclonal Ab (CD38)
*Elotuzumab*
*HDAC*
*Bendamustine*




**OLD**

VAD
DEX

SCT

Nothing
Prednisone
Thalidomide

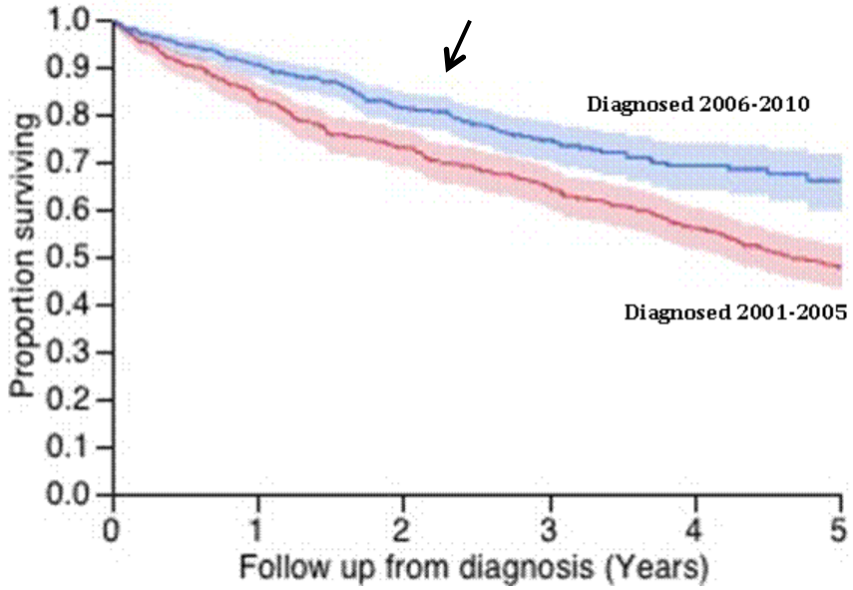
Few options

# Induction Regimens

- Several new classes of drugs are being used in the management of multiple myeloma patients:
  - Proteasome inhibitors
  - Immune modulatory drugs.
  - Monoclonal Antibodies
- The choice of initial induction therapy can be influenced by the underlying medical conditions of the patients and their prognostic features.

# IMPACT OF NOVEL THERAPY 2012/2013

Median 7.3 years




## 5 YEAR SURVIVAL BY AGE

| | AGE ≤ 65 YRS | AGE > 65 YRS |
|---|---|---|
| 2006-2010 | 73% | 56% |
| 2001-2005 | 63% | 31% |

# What to Expect with Novel Combinations Prior to HD Therapy?

| Author (n) | Regimen | CR/VGPR | PFS | OS |
|---|---|---|---|---|
| Cavo (236) | VTD+2HD | 38%/79% | 68% (3 years) | 86% (3 years) |
| Moreau (100) | vTD+HD | 30%/73% | | |
| Palumbo (102) | PAD+2HD+C/M | 66%/86% | 69% (2 year) | 86% (2 year)* |
| Rajkumar (90) | R (D or d)+HD | | | 92% (3 years) |
| Harousseau (223) | VD+HD | 40%’68% | 36 months | 81% (3 years) |
| Richardson (27) | RVD+ HD | 29%/67% | 75% (18 mon) | 97% (18 mon) |

N= number of subjects, Mon= month
VTD Bortezomib, thalidomide and dexamethasone
vTD Modified bortezomib, thalidomide and dexamethasone
PAD Bortezomibe, doxirubicin and dexamethasone * age 65-75
RD or Rd Lenalidomide with high dose dexamethasone (D) or low dose (d)
RVD Lenalidomide Bortezomib and Dexamethasone.
HD high dose chemotherapy.

# 3-Year Overall Survival Rates

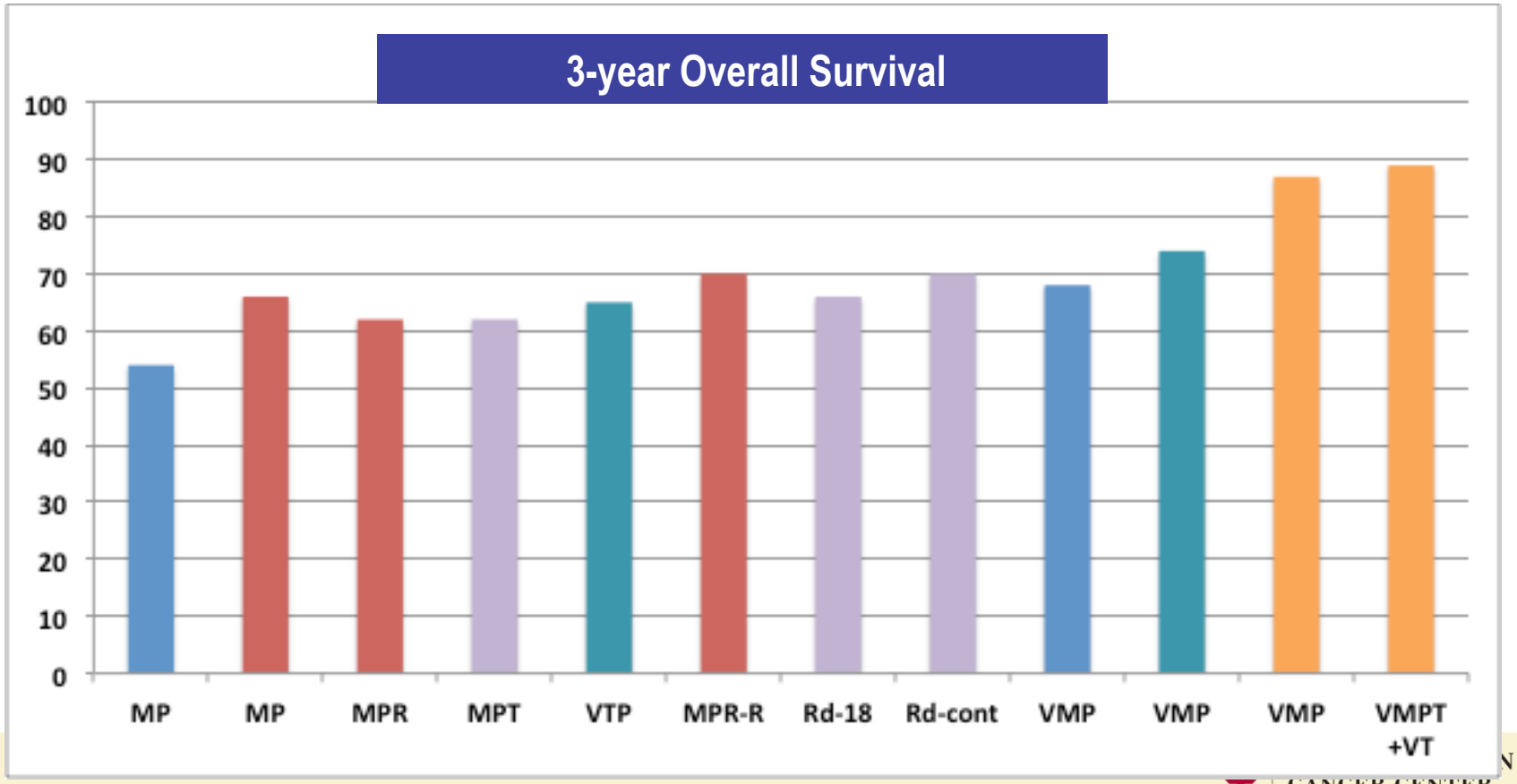
VISTA Trial

MM-015 Trial

FIRST Trial

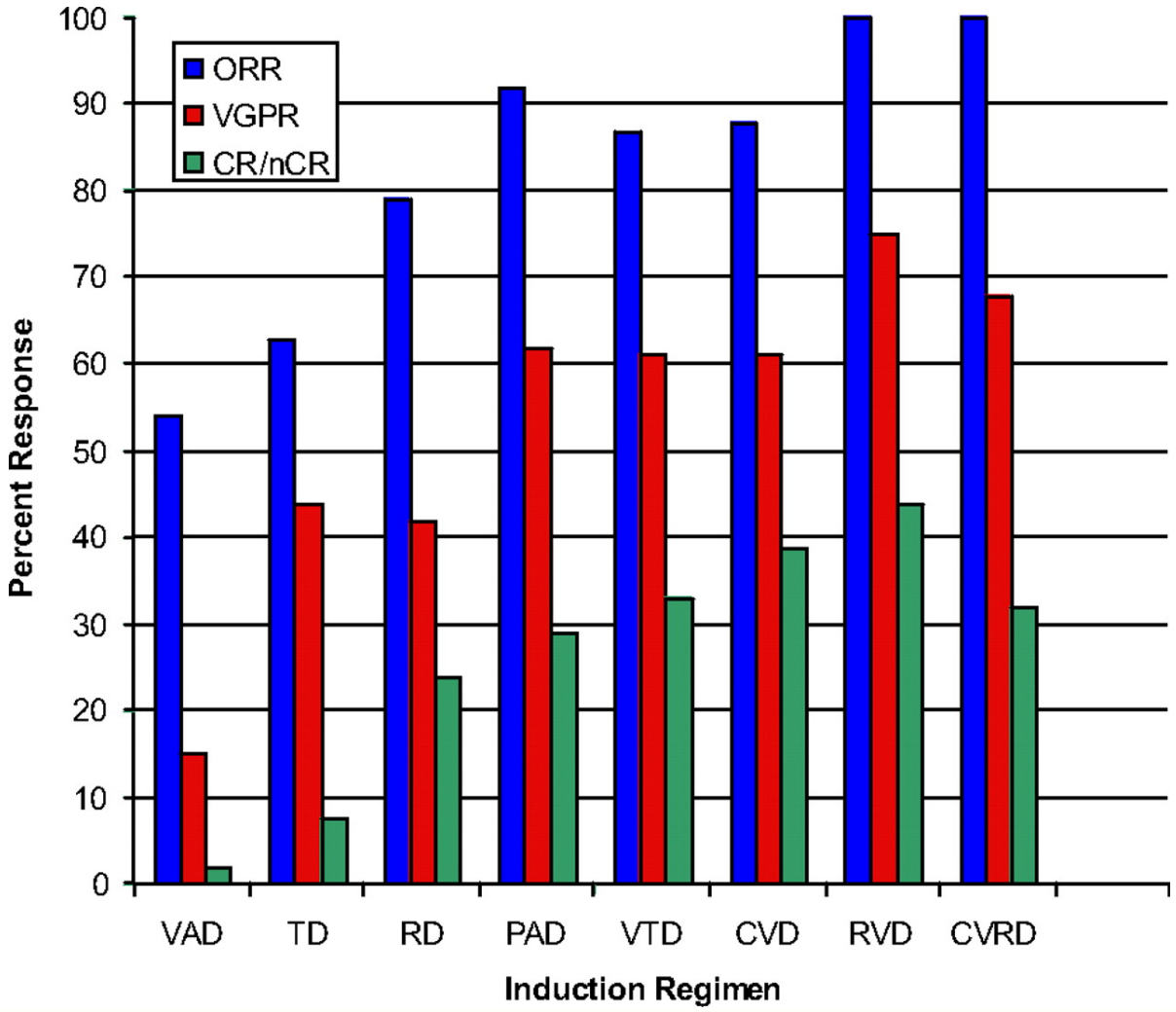
PETHEMA/GEM Trial

VMPT vs VMP Trial



# The Overall, ≥ VGPR, and nCR/CR Rates for a Selection of Phase 2 and Phase 3 Trials

Do we pick the therapy with the biggest green bar and call it a day?




blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Stewart A K et al. Blood 2009;114:5436-5443



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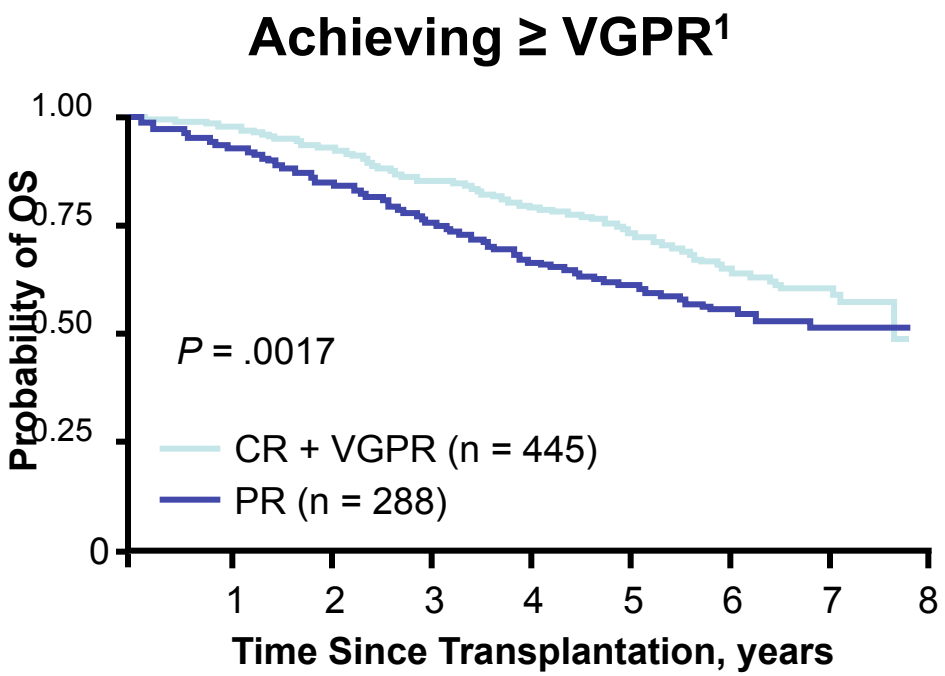
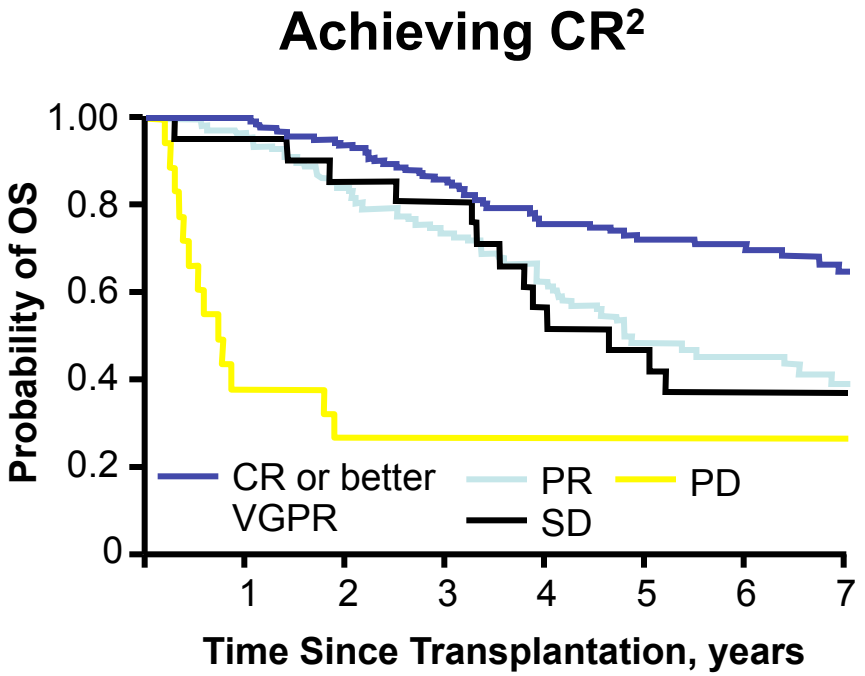
# Achieving Great cytoreduction (≥ VGPR/CR) = Better Outcomes

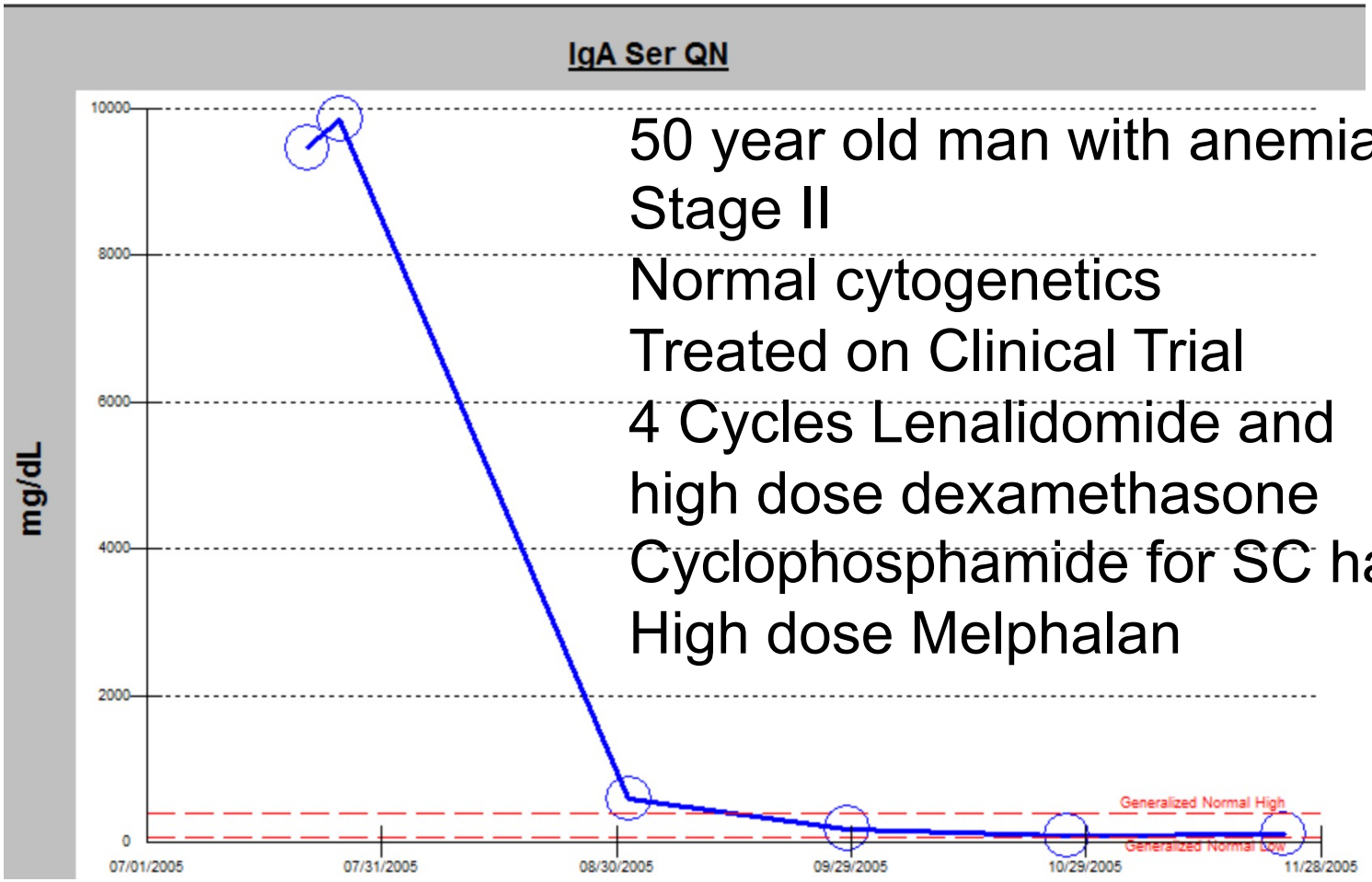




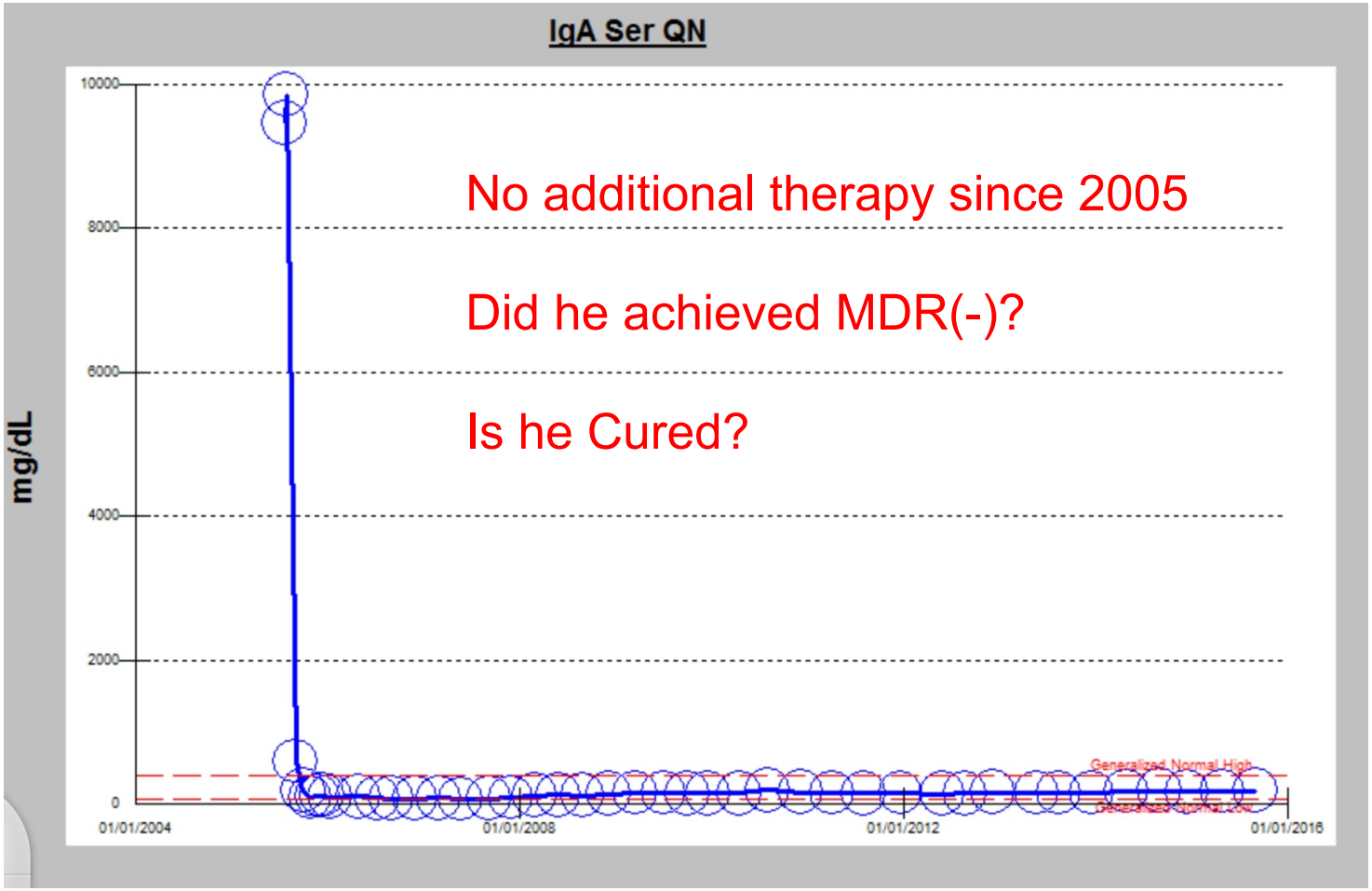

1. Harousseau JL, et al. J Clin Oncol. 2009;27:5720. 2. Kapoor P, et al. J Clin Oncol. 2013;31:4529-4535.

# Patient 1- ECOG Len/ HD vs LD

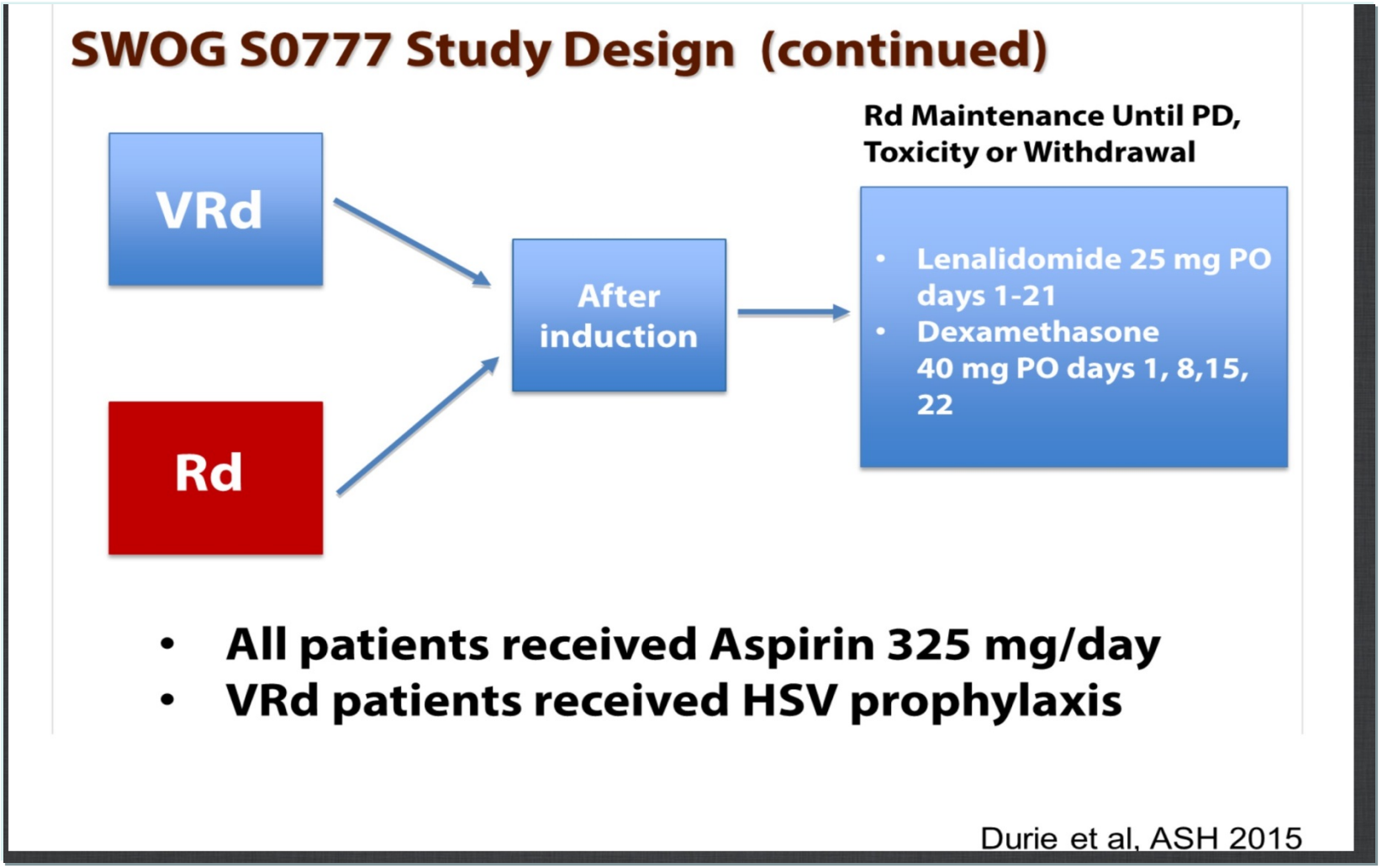



50 year old man with anemia
Stage II
Normal cytogenetics
Treated on Clinical Trial
4 Cycles Lenalidomide and high dose dexamethasone
Cyclophosphamide for SC harvest
High dose Melphalan

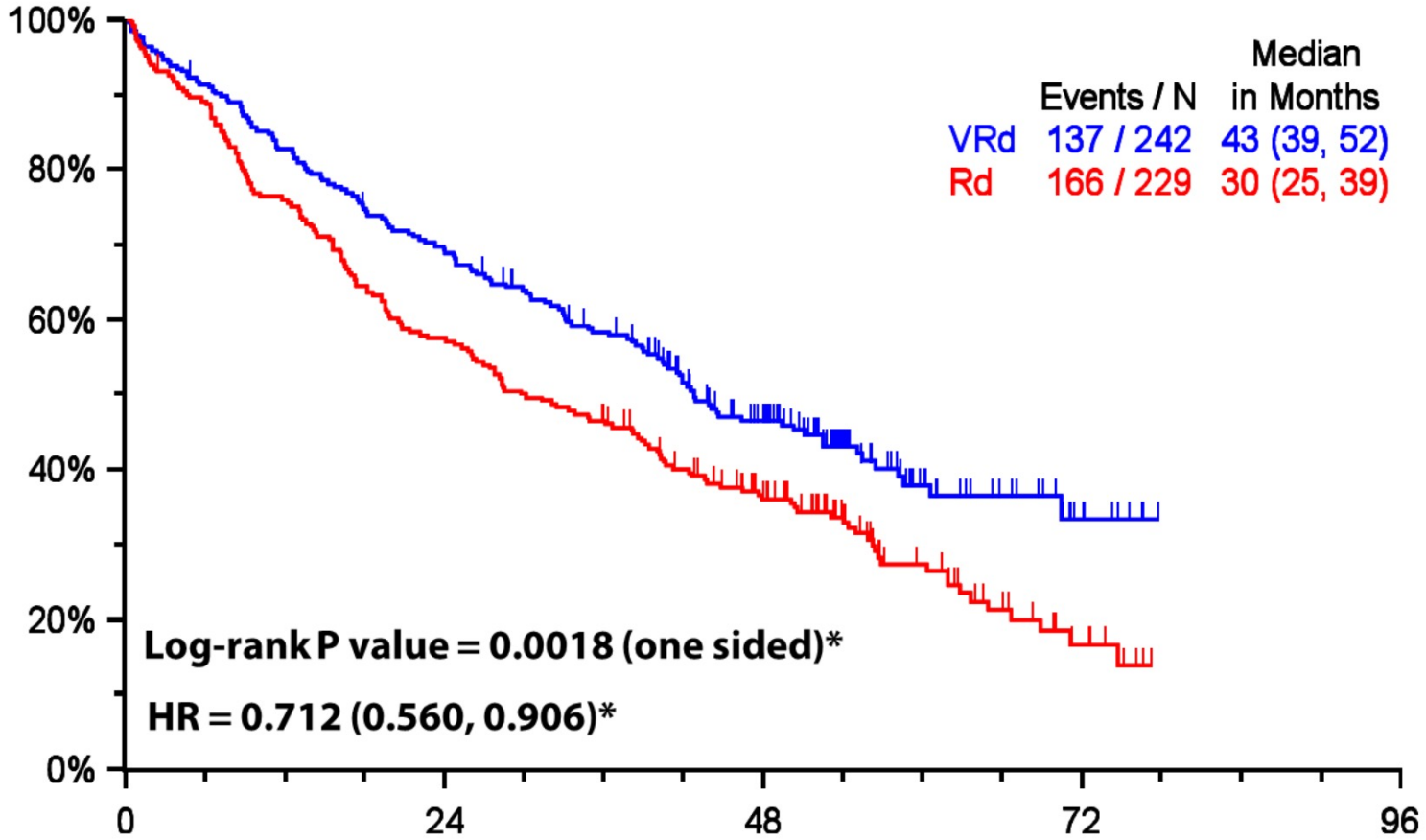
# Patient 1- ECOG Len/ HD vs LD



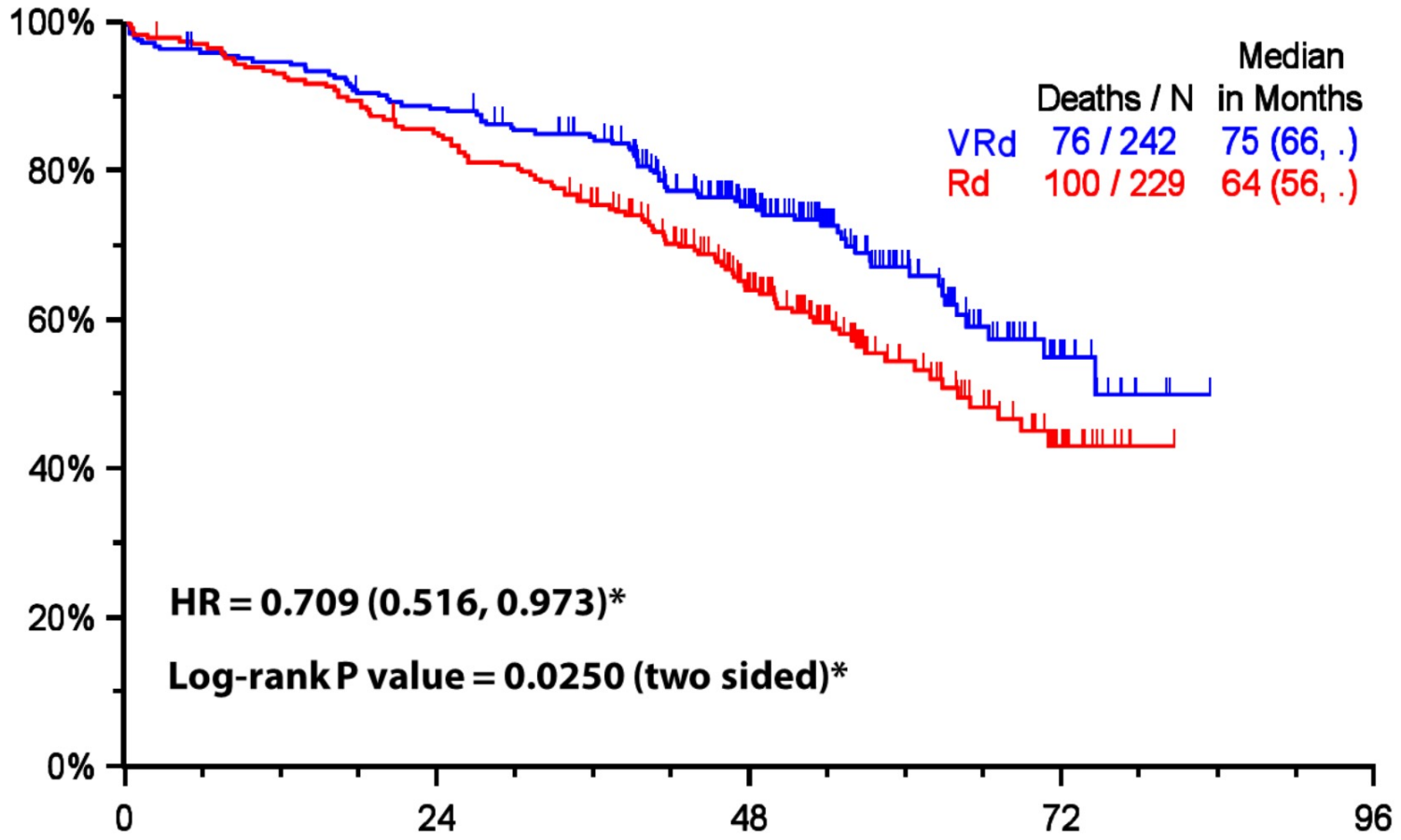
# Is three better than two?



# Progression-Free Survival By Assigned Treatment Arm



# Overall Survival By Assigned Treatment Arm



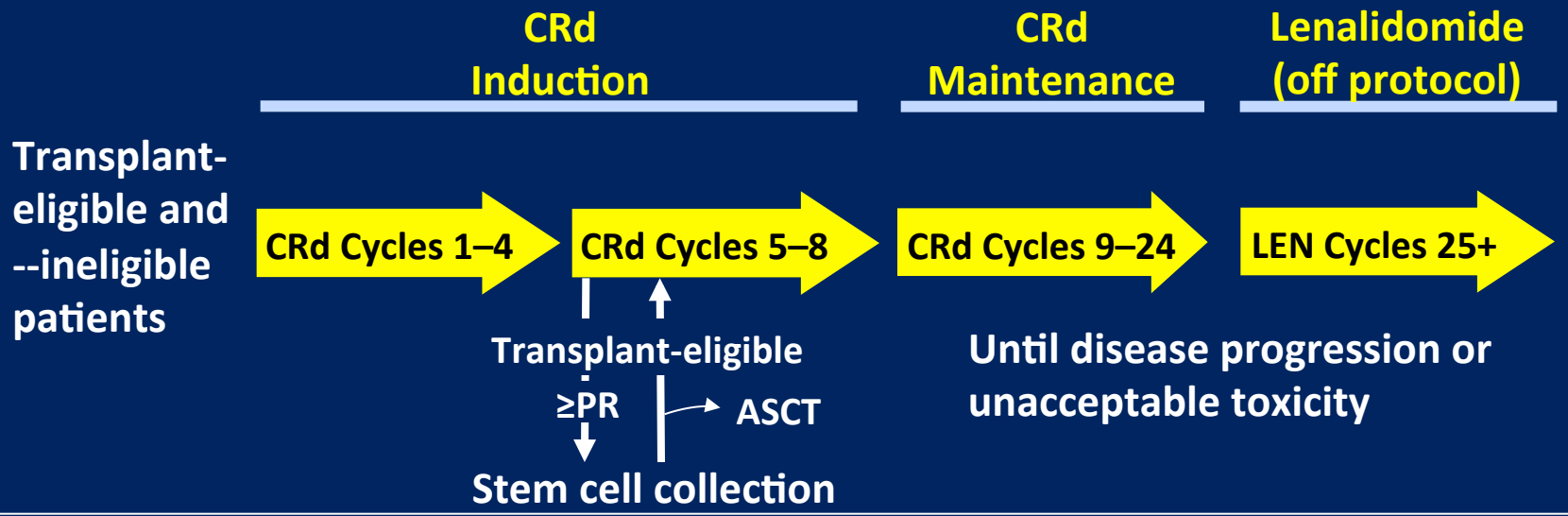

Durie et al, ASH 2015

# The New Kid on the Block :Carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX)

AJ Jakubowiak,[1] K Griffith,[2] D Dytfeld,[3] DH Vesole,[4] S Jagannath,[5] T Anderson,[2] B Nordgren,[2] K Detweiler-Short,[2] D Lebovic,[2] K Stockerl-Goldstein,[6] T Jobkar,[2] S Wear,[7] A Al-Zoubi,[2] A Ahmed,[2] M Mietzel,[2] D Couriel,[2] M Kaminski,[2] M Hussein,[8] H Yeganegi,[9] R Vij[6]

[1]University of Chicago, Chicago, IL; [2]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; [3]Poznan University of Medical Sciences, Poznan, Poland; [4]John Theurer Cancer Center, Hackensack, NJ; [5]Mount Sinai Medical Center, New York, NY; [6]Washington University School of Medicine, St. Louis, MO; [7]Multiple Myeloma Research Consortium, Norwalk, CT; [8]Celgene, Inc, Summit, NJ; [9]Onyx Pharmaceuticals, South San Francisco, CA

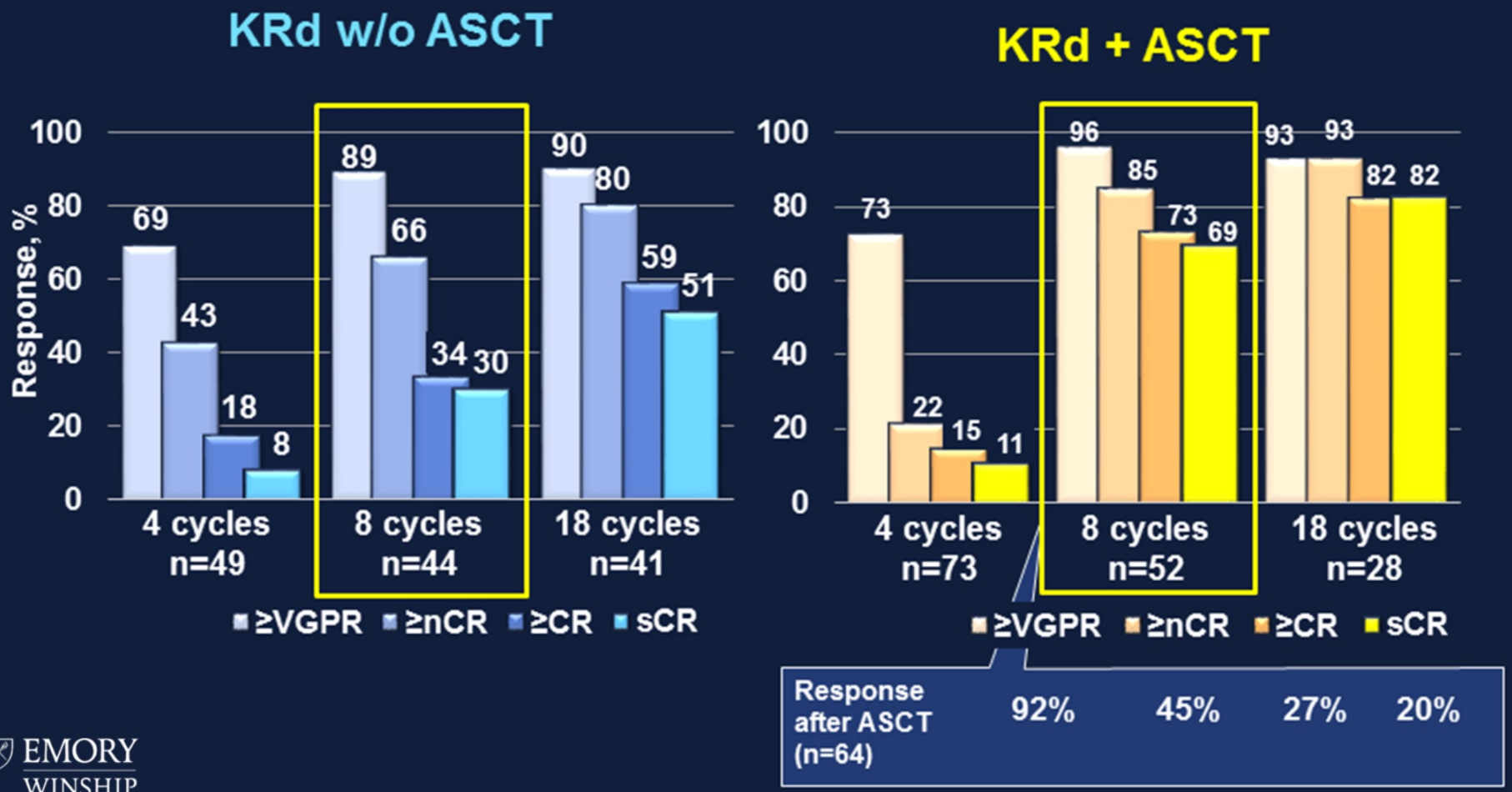
# Treatment Roadmap




- Assessments on D1 and 15 of C1 and D1 thereafter using modified IMWG Criteria with nCR
- Cycles 1–8
  - CFZ Days 1–2, 8–9, 15–16 at assigned doses[1]
  - LEN 25 mg Days 1–21
  - DEX 40 mg weekly Cycles 1-4, 20 mg weekly Cycles 5–8
- Cycles 9–24
  - CFZ on Days 1–2 and 15–16 only
  - CFZ, LEN, DEX at last best tolerated doses
  - After Cycle 4, pts could undergo stem cell collection and then continue CRd with the option to proceed to ASCT

1. Jakubowiak AJ, et al. *Blood*. 2011;118: abstract 631.

# KRD for newly diagnosed Myeloma

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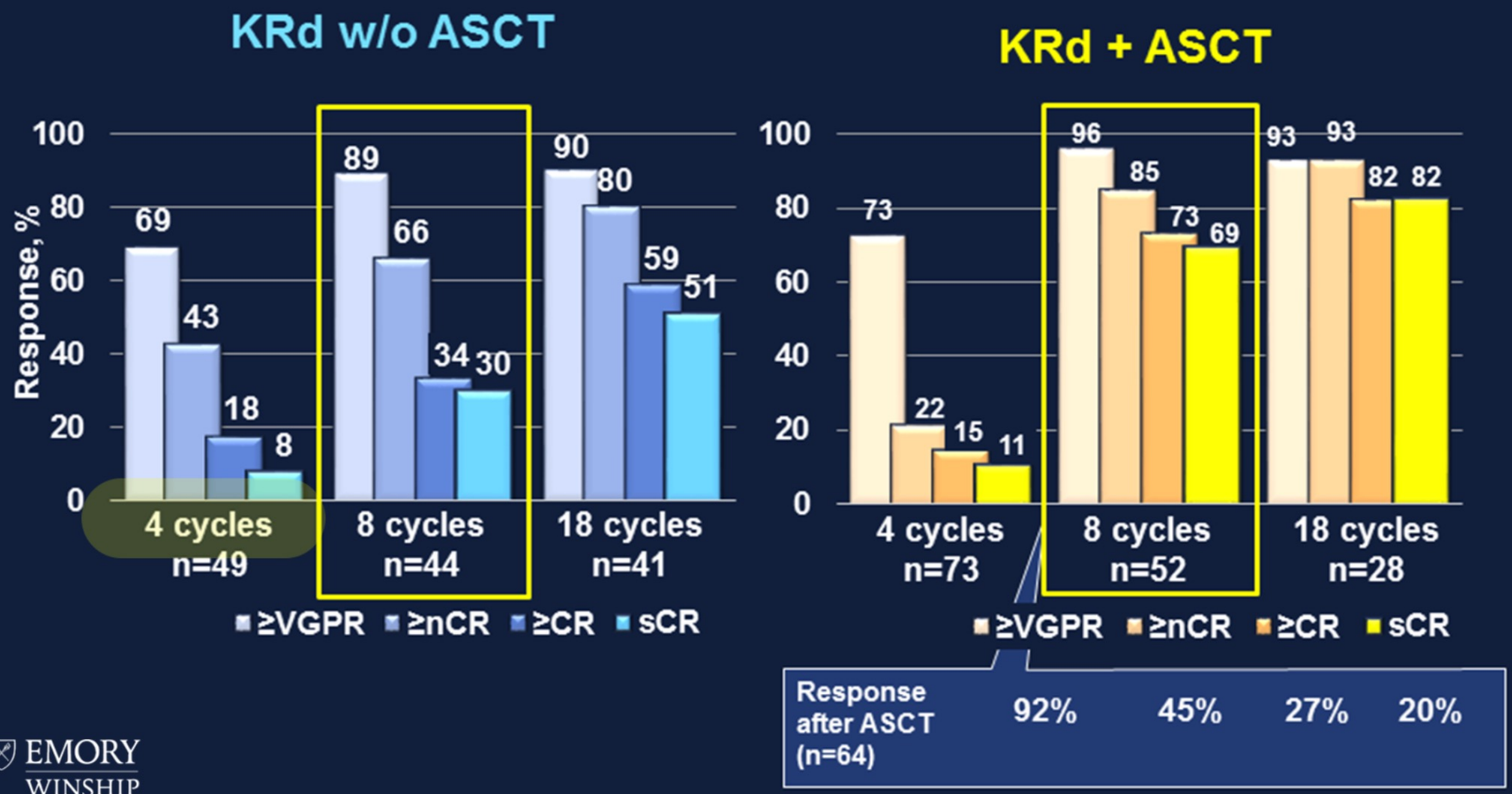
nCR, near complete response; VGPR, very good partial response

# KRD for newly diagnosed Myeloma

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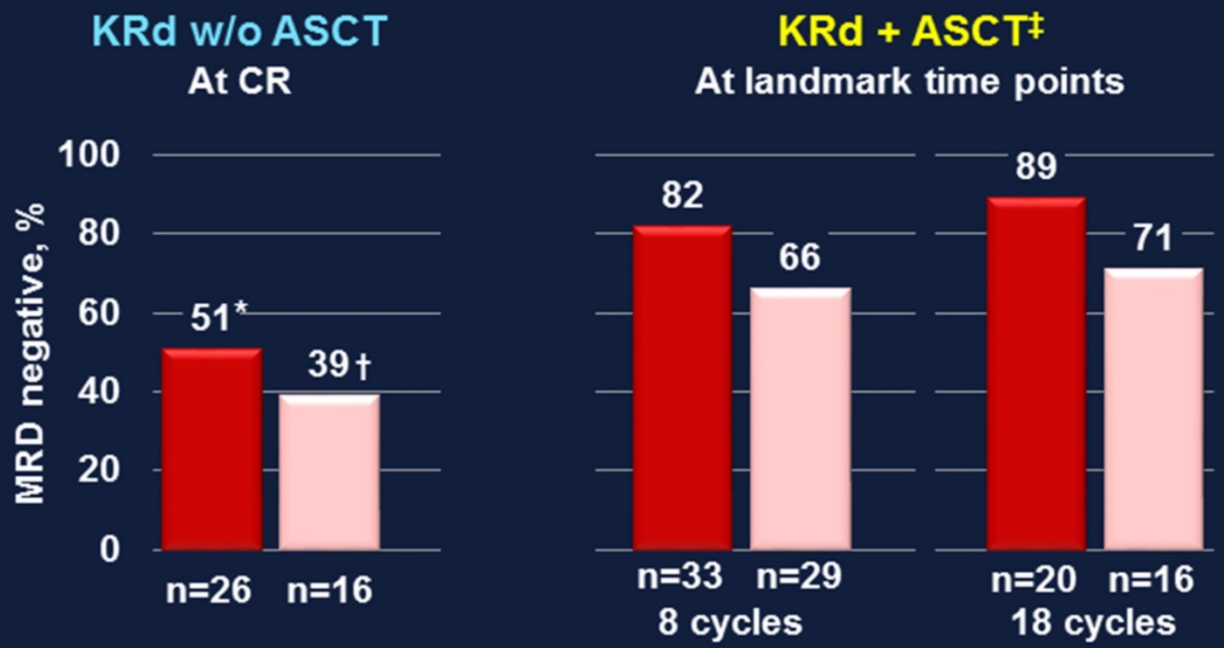
# MRD Evaluation

- **Multiparameter Flow Cytometry (MFC)**
  10 color
  Sensitivity: $10^{-4}$ – $10^{-5}$
- **Next generation sequencing (NGS)**
  Adaptive Biotechnologies
  Sensitivity: $10^{-6}$




*Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR

†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS

‡Actual MRD rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles as per new IMWG MRD criteria (pts were considered MRD – negative only if in CR/sCR)

# First Oral PI: IXAZOMIB TOURMALINE-MM1 Study Design

*28-day cycles*

**Randomization**
**N=722**

**Stratification:**
- Number of prior therapies
- PI exposure
- ISS stage

**IRd**
Ixazomib 4 mg *Days 1, 8, 15*
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

**Rd**
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

**LEN NAÏVE OR LEN SENSITIVE**

**Moreau P et al.** N Engl J Med. 2016 Apr 28;374(17):1621-34. doi: 10.1056/NEJM

# TOURMALINE-MM1 Results

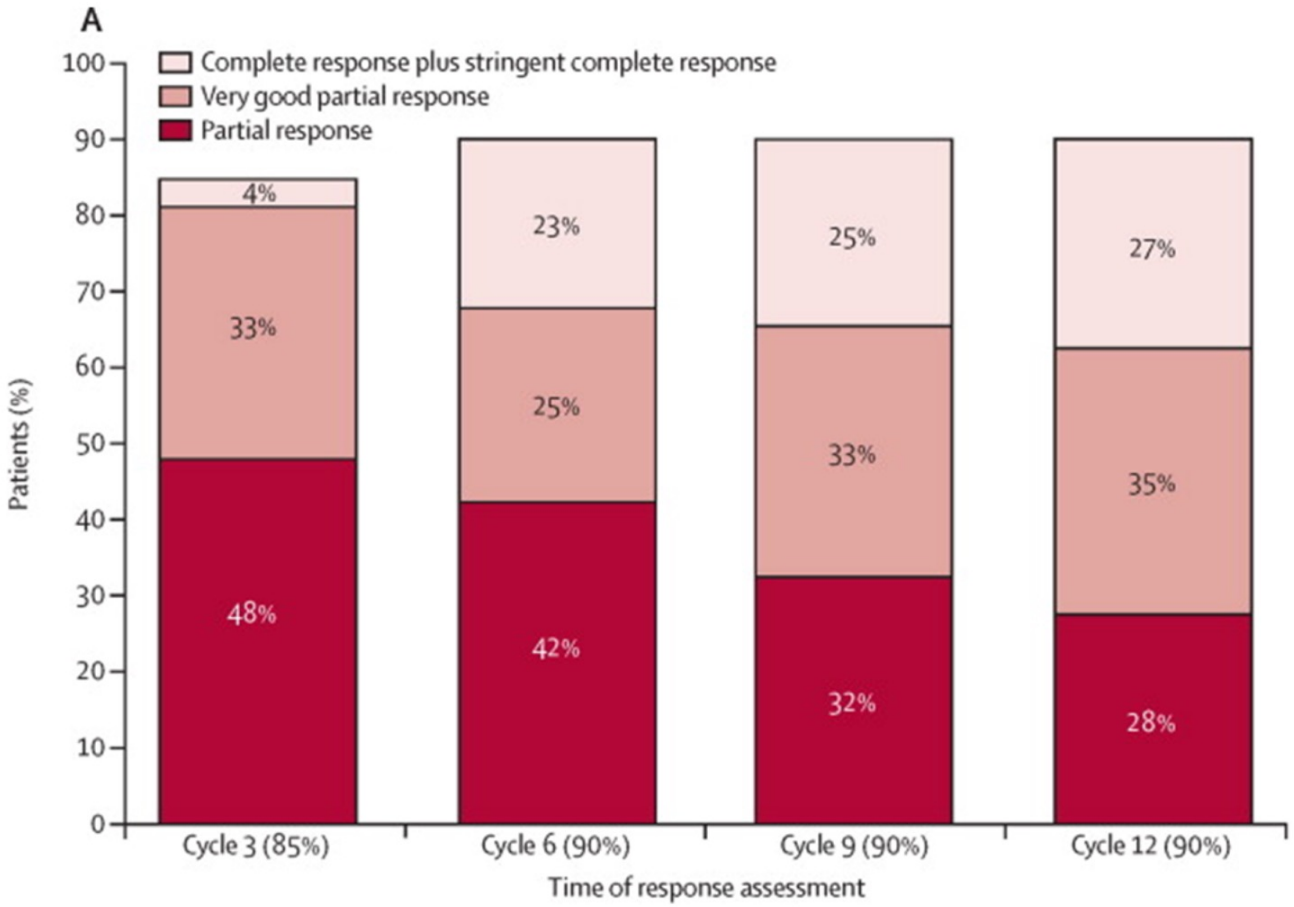
| | I-Rd (n=360) | Rd (n=362) | HR | *P* Value |
|---|---|---|---|---|
| Median PFS, mos | 20.6 | 14.7 | 0.742 | 0.012 |
| ORR, % | 78.3 | 71.5 | — | 0.035 |
| ≥VGPR, % | 48.1 | 39.0 | — | 0.014 |
| AEs, % | | | | |
| ≥G3 Diarrhea | 6 | 2 | — | — |
| ≥G3 PN | 2 | 2 | — | — |

$11 k a month

**Benefit with IRd was also noted in pts with high-risk cytogenetics.**

**Moreau P et al.** N Engl J Med. 2016 Apr 28;374(17):1621-34. doi: 10.1056/NEJM.

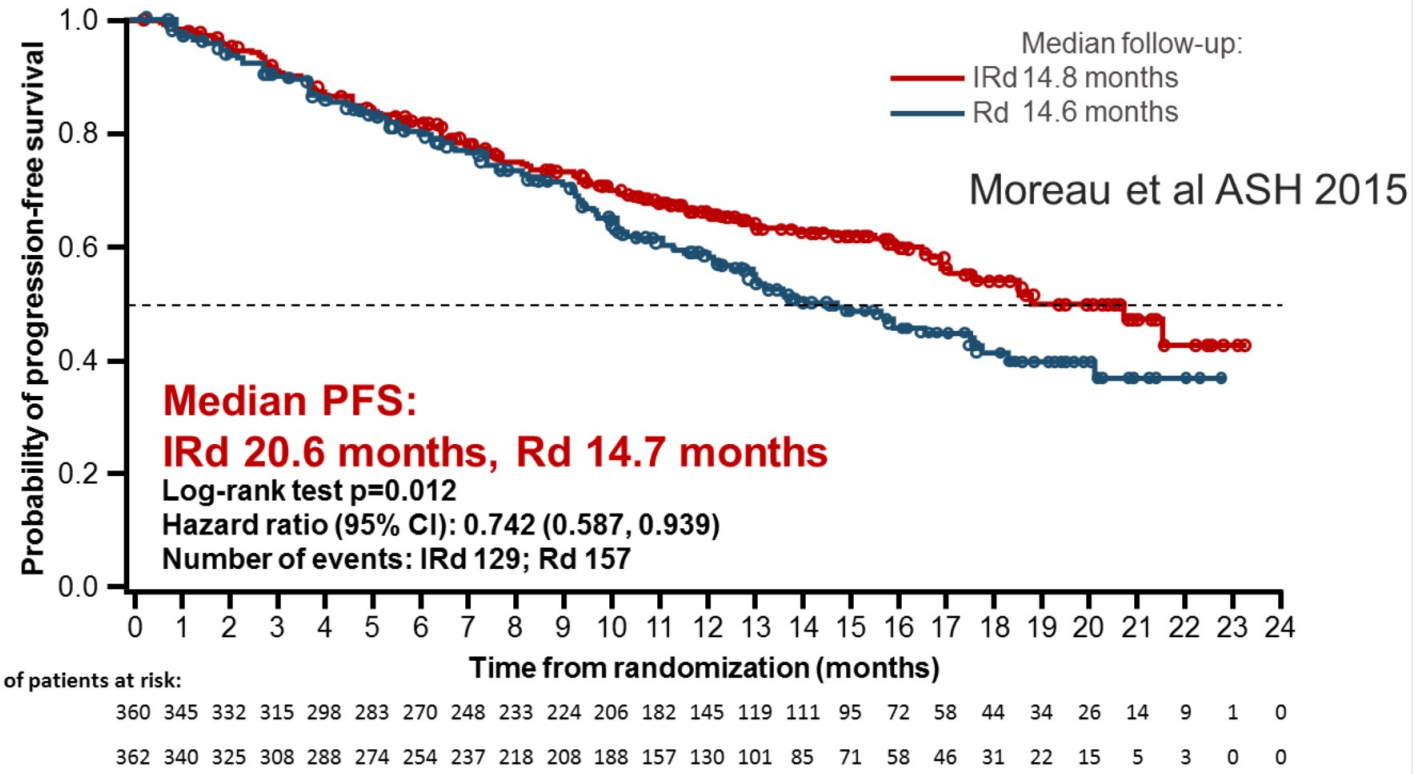
# IRD Response Rates




Kumar SK, et al. *Lancet Oncol*. 2014;15(13):1503–1512.

# Phase 3 study of weekly oral ixazomib plus lenalidomide-dex: final PFS analysis

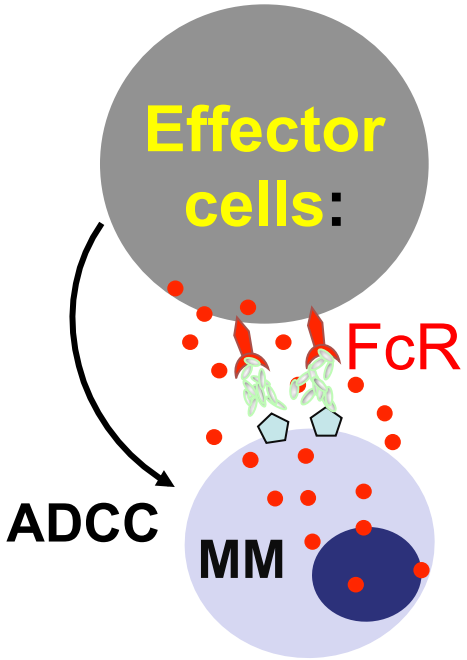
- **35% improvement in PFS with IRd vs Rd** (data cut-off 30 October 2014)




- A subsequent exploratory analysis of PFS was conducted (median follow-up 23.3 and 22.9 months in the IRd and Rd arms); median PFS 20 vs 15.9 months

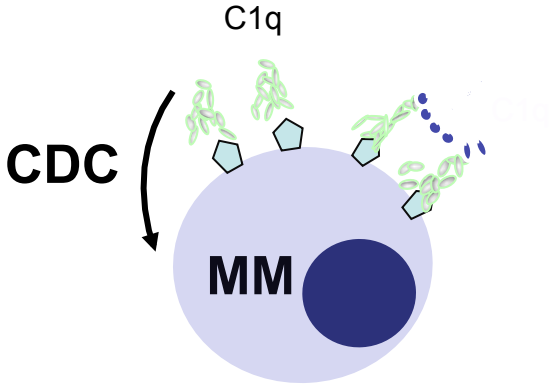
# MAb-Based Targeting of Myeloma

**Antibody-dependent cellular cytotoxicity (ADCC)**



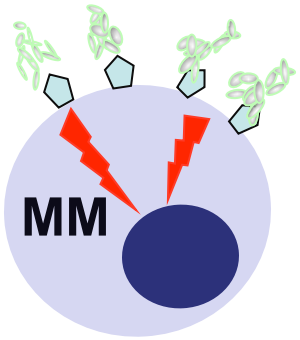

Lucatumumab or dacetuzumab (CD40)
Elotuzumab (SLAM 7)
Daratumumab (CD38)
MOR208 (HM1.24)

**Complement-dependent cytotoxicity (CDC)**




Daratumumab (CD38)

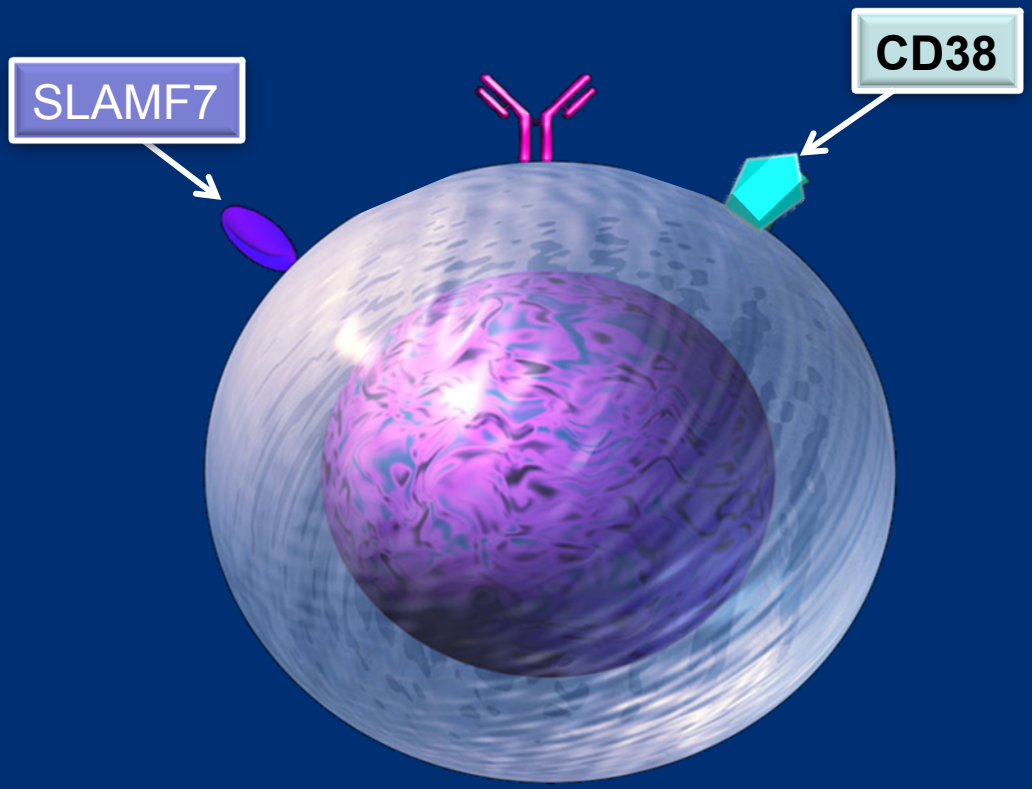
**Apoptosis/growth arrest via targeting signaling pathways**



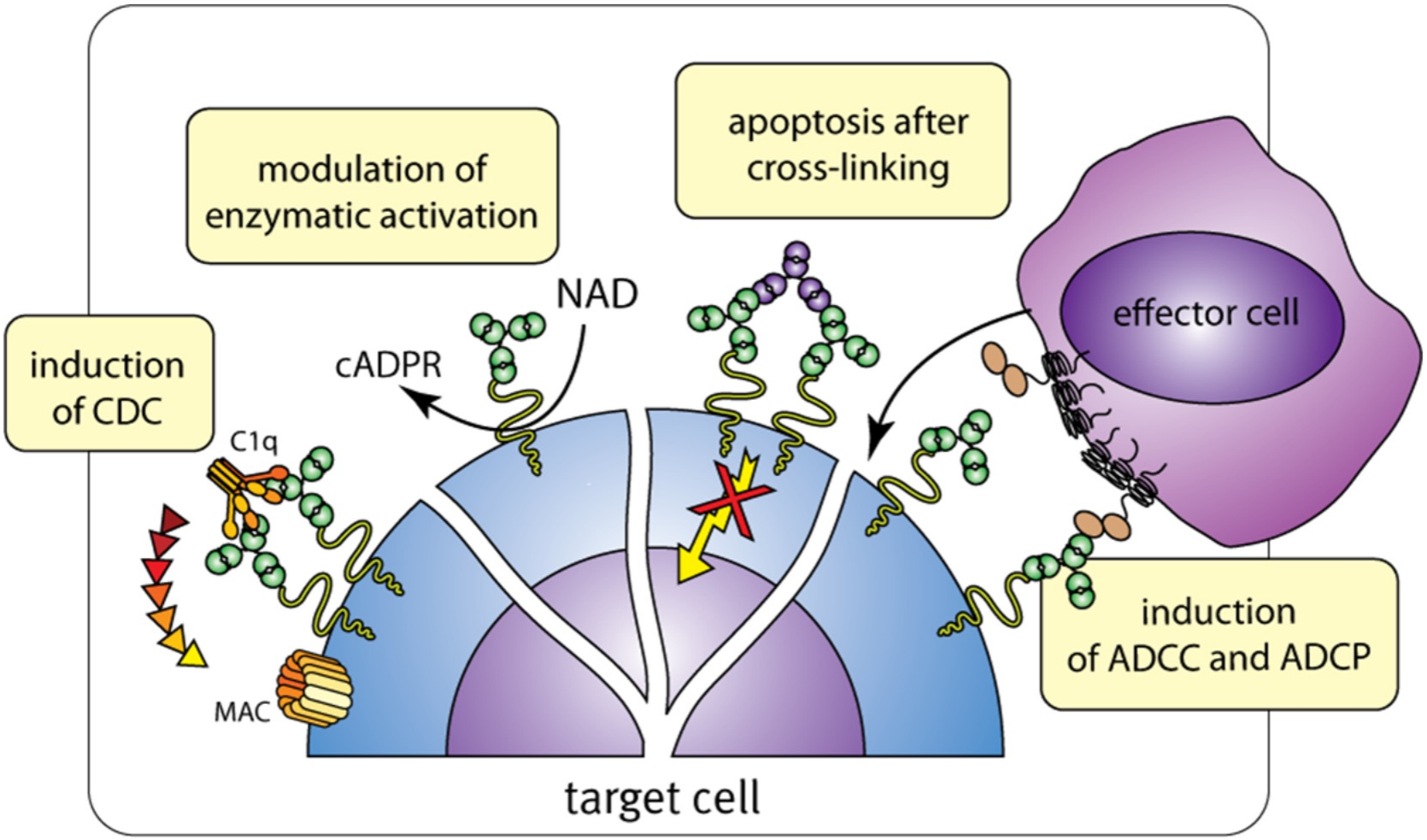

Lorvotuzumab mertansine (CD56)
nBT062-maytansinoid (CD138)
1339 (IL-6)
BHQ880 (DKK1)
RAP-011 (activin A)
Daratumumab (CD38)

Tai YT, et al. Bone Marrow Res. 2011;2011:924058.

# Targets on the Myeloma Cell Surface



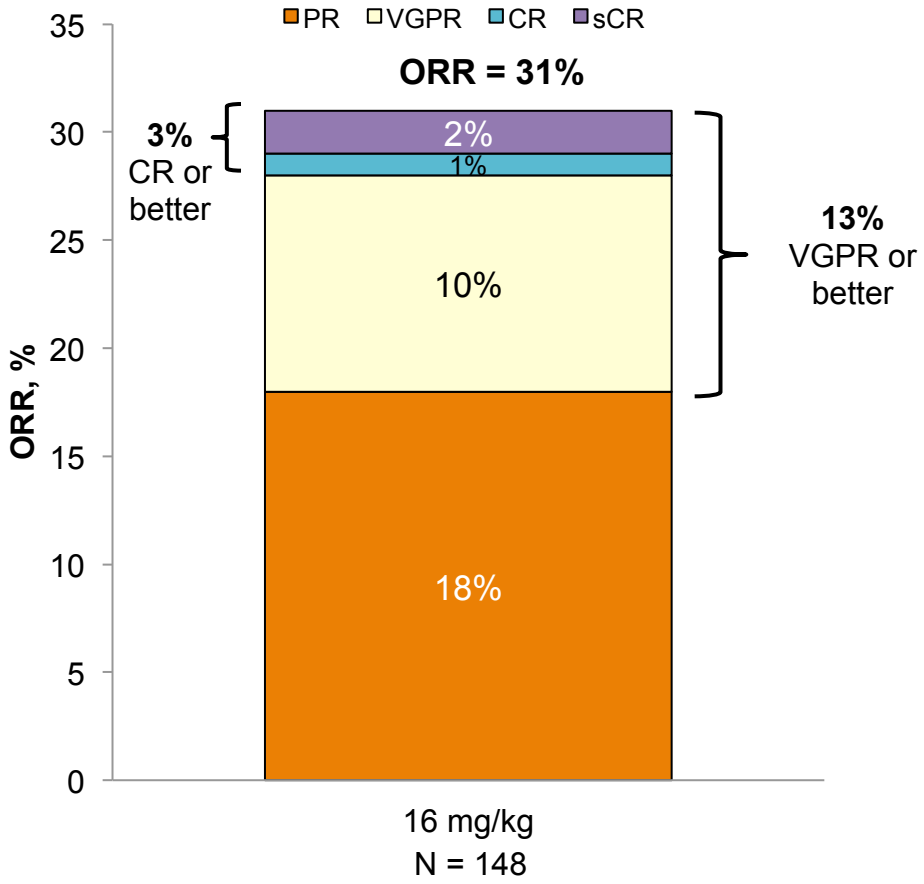
# Daratumumab Anti-CD 38 MoAb




18 of 29 patients in phase I benefit (5PR,4MR,9SD)

DeWeers et al, J Immunol 2011; 186: 1840 Laubach et al 2014;23:445.

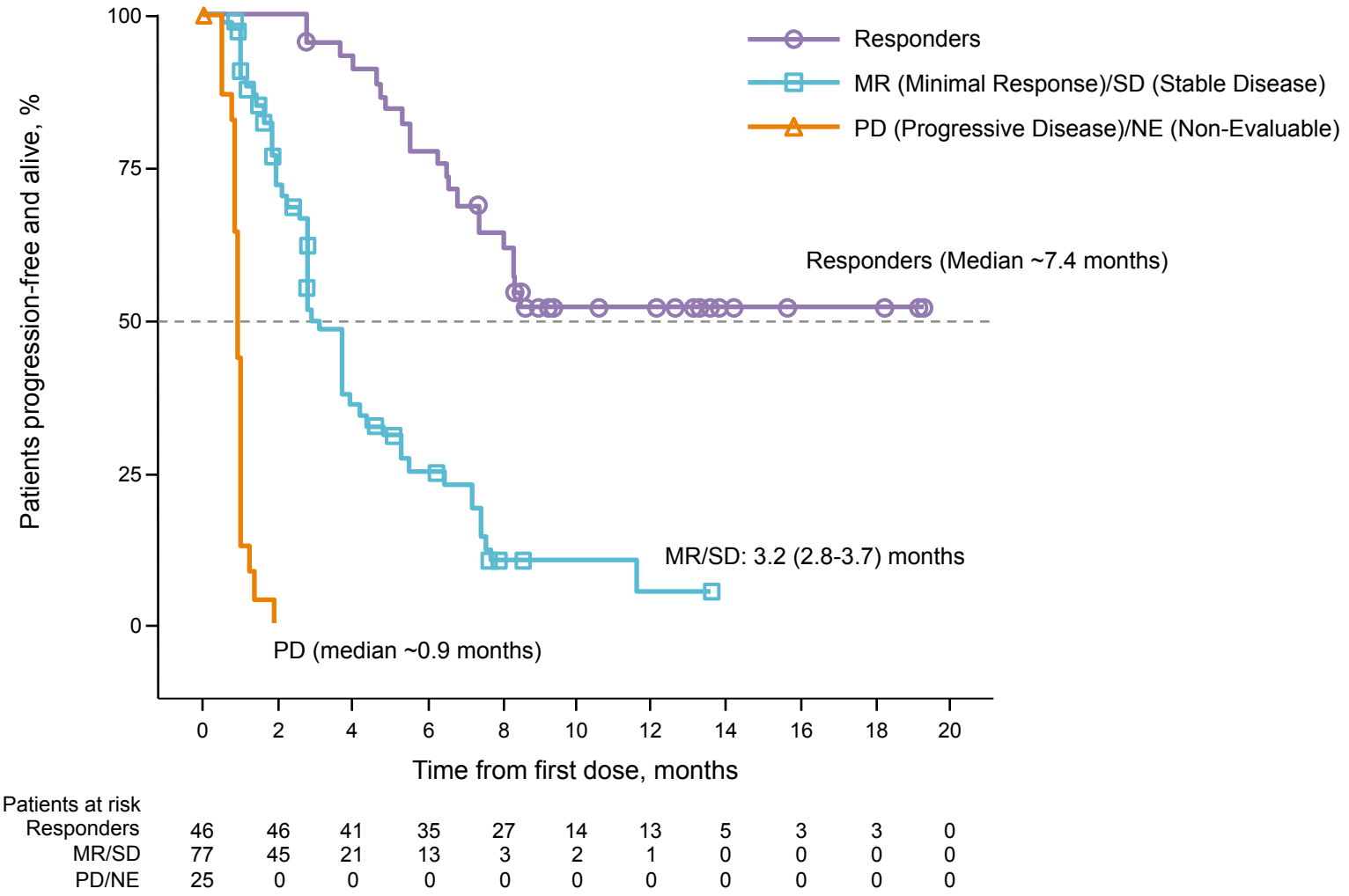
# Daratumumab
# Efficacy in Combined Analysis



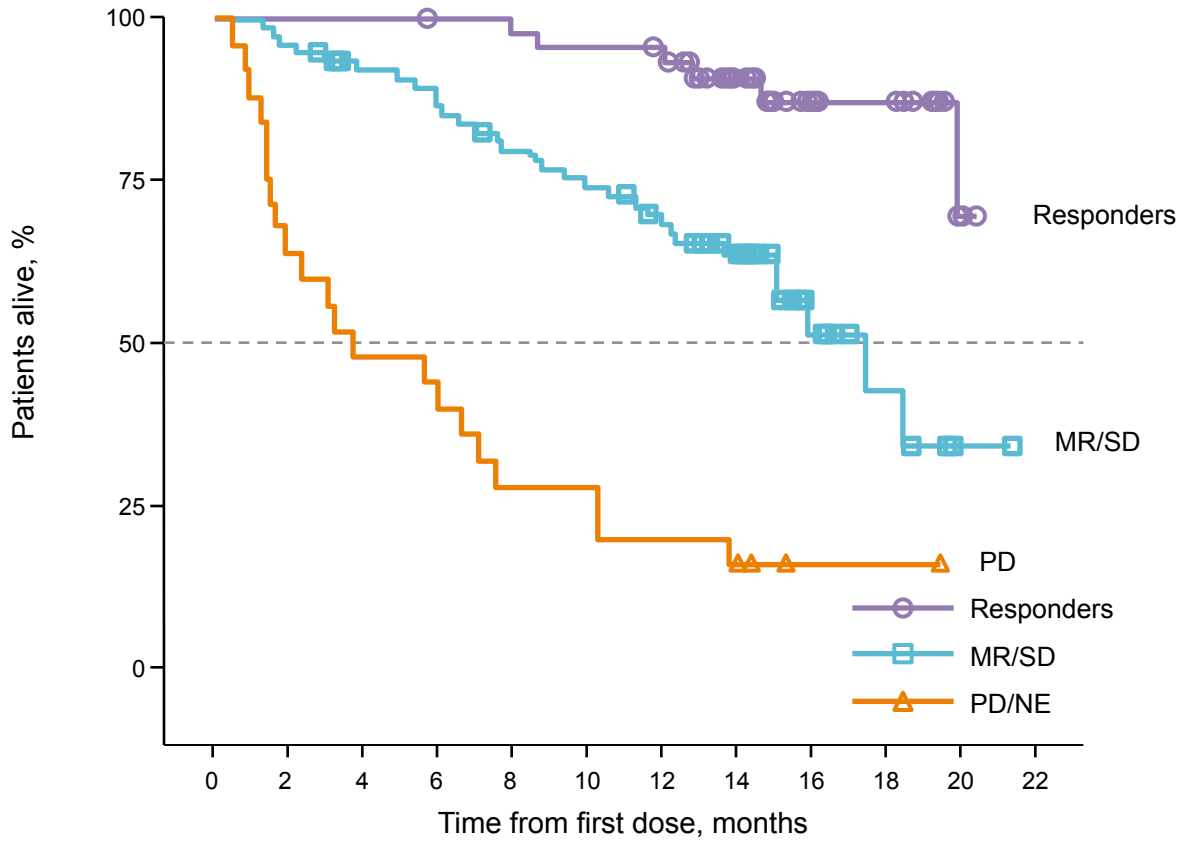

$32 k
cycle1,2
$15 k cycle
2-6

- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

# Progression-free Survival



# Overall Survival



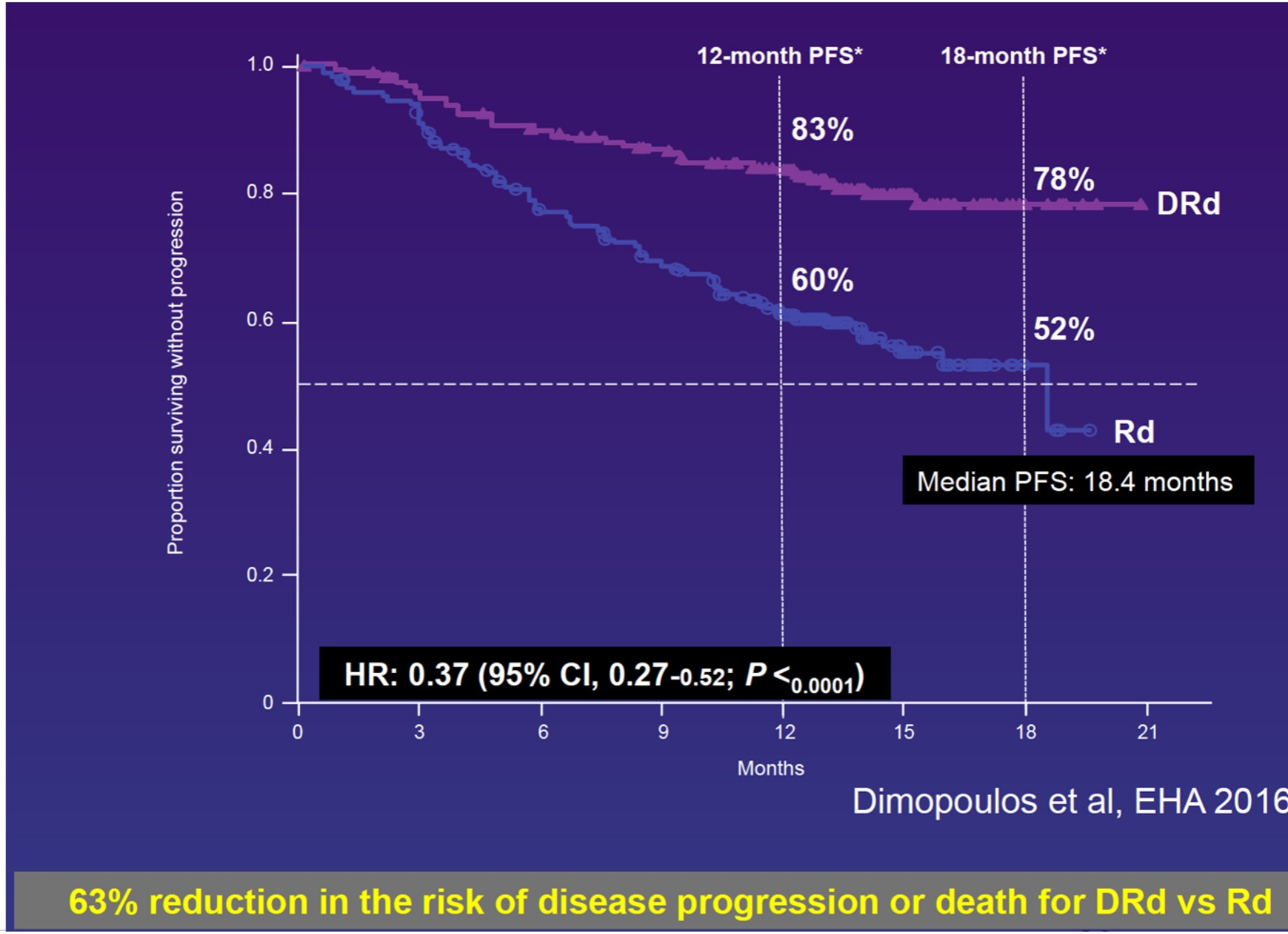

Patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Responders | 46 | 46 | 46 | 45 | 44 | 43 | 42 | 29 | 15 | 13 | 3 | 0 |
| MR/SD | 77 | 74 | 67 | 63 | 57 | 53 | 47 | 37 | 10 | 5 | 1 | 0 |
| PD/NE | 25 | 16 | 12 | 11 | 7 | 7 | 5 | 4 | 1 | 1 | 0 | 0 |

For the combined analysis, median OS = 19.9 months

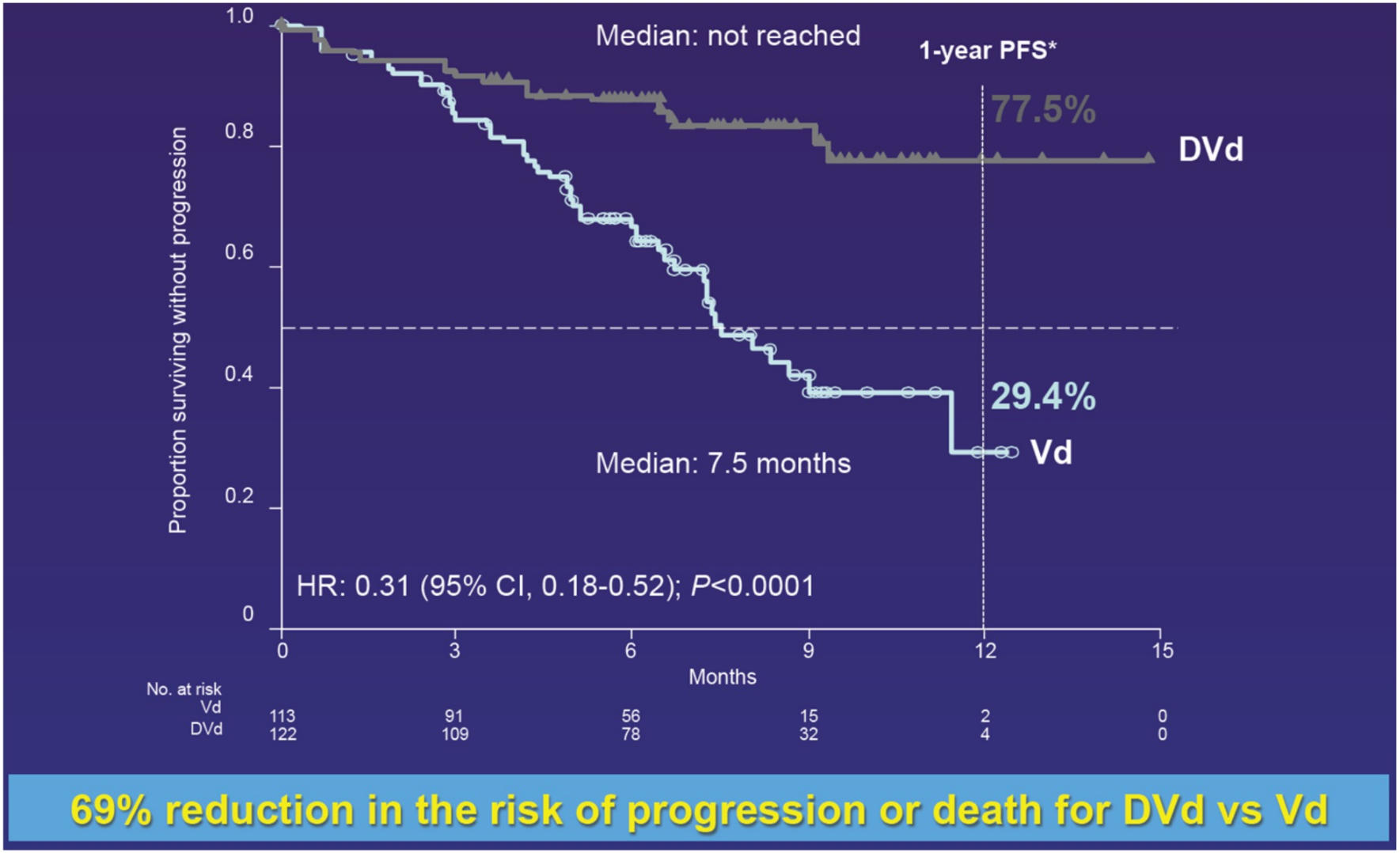
1-year overall survival rate = 69% (95% CI, 60.4-75.6)

# Progression-free Survival : Dara Len Dex vs Len Dex




**63% reduction in the risk of disease progression or death for DRd vs Rd**

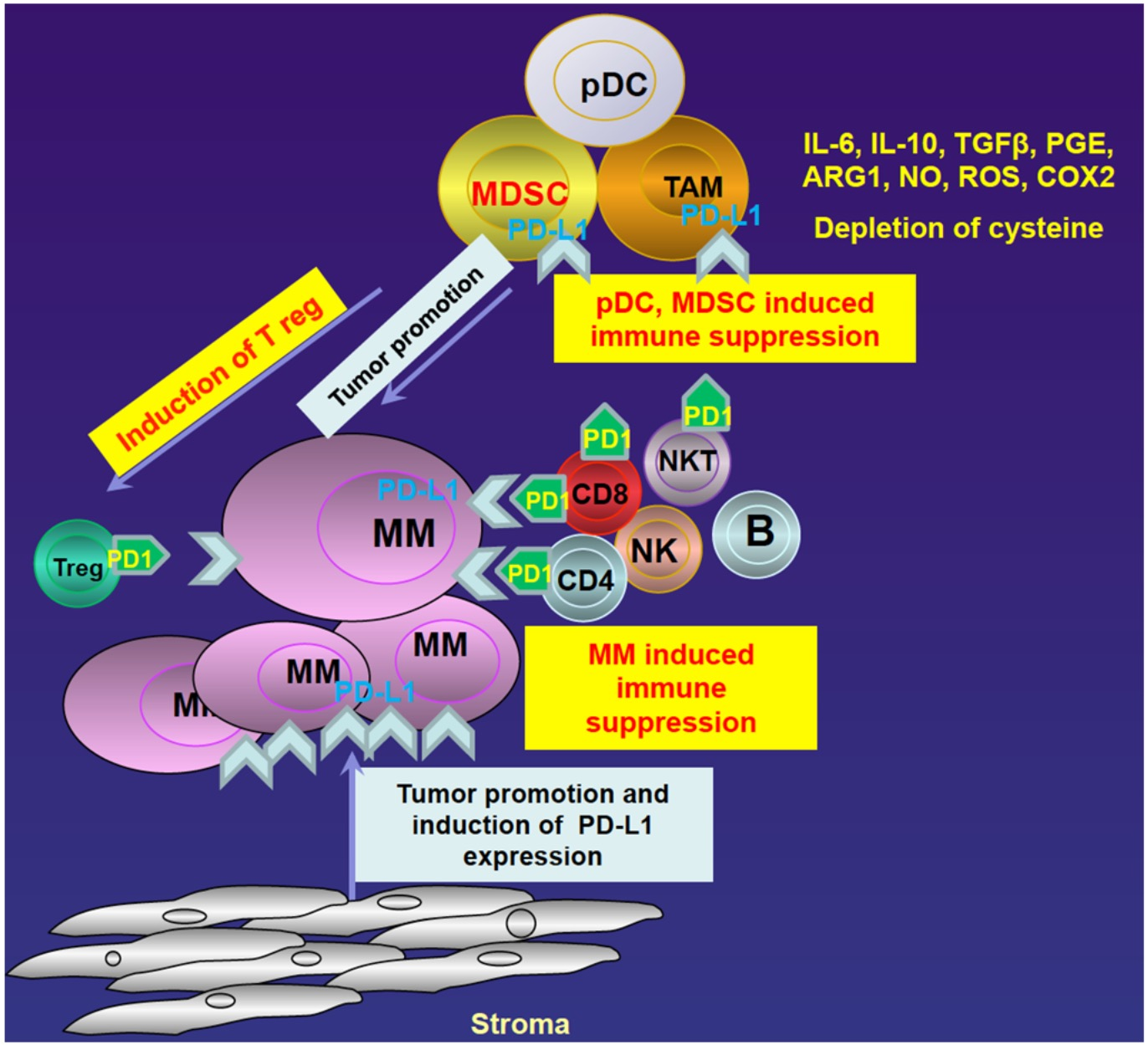
# PFS: 1 Prior Line Treatment




**69% reduction in the risk of progression or death for DVd vs Vd**

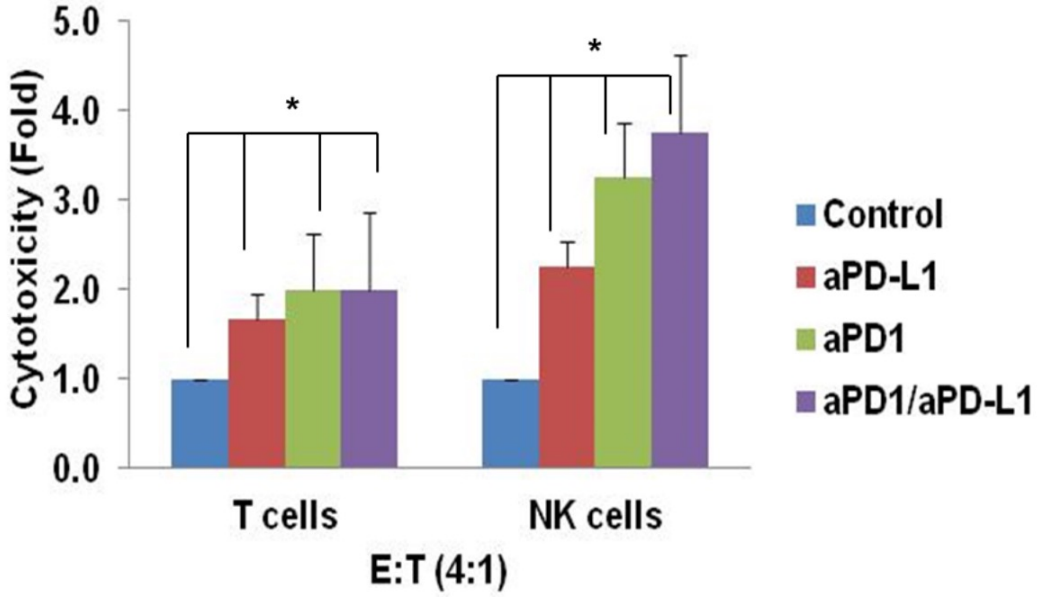
Palumbo et al ASCO 2016

# Immune Suppressive Microenvironment in MM




Görgün GT, et al. Blood 2013;121:2975-8

# Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity




**Effector: Autologous effector cells (CD3T cells, NK cells)**

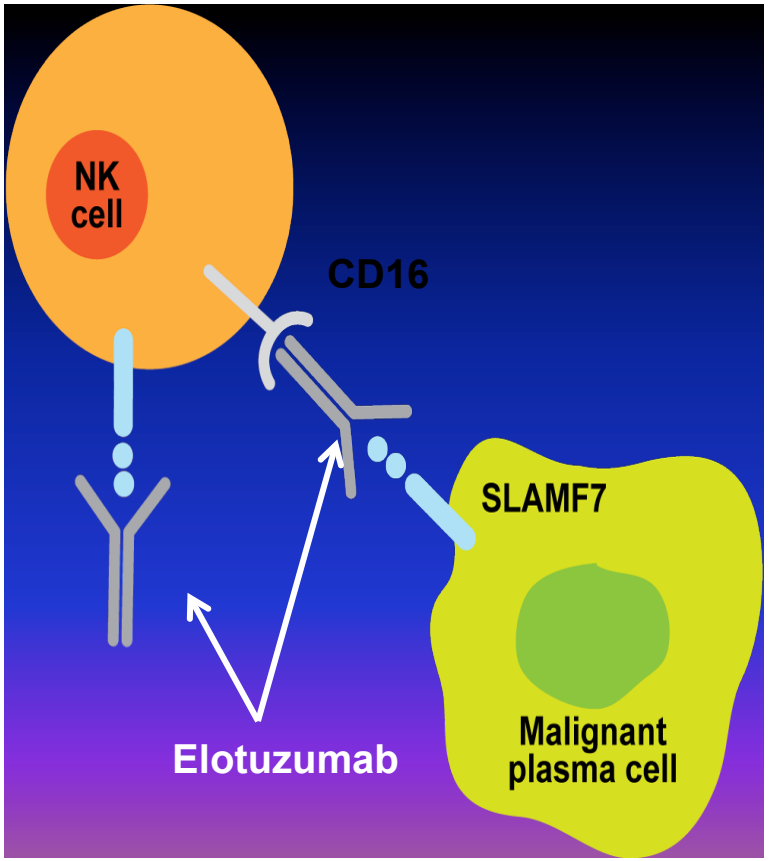
**Target: CD138$^{+}$ MM cells from Rel/Ref MM-BM**

Görgün G. et al. Clin Cancer Res, 2015

# Elotuzumab

Elotuzumab (HuLuc63) is an IV humanized monoclonal antibody targeting human SLAMF7, a cell surface glycoprotein.

$22 k cycle 1,2
$11k cycle 3 and beyond



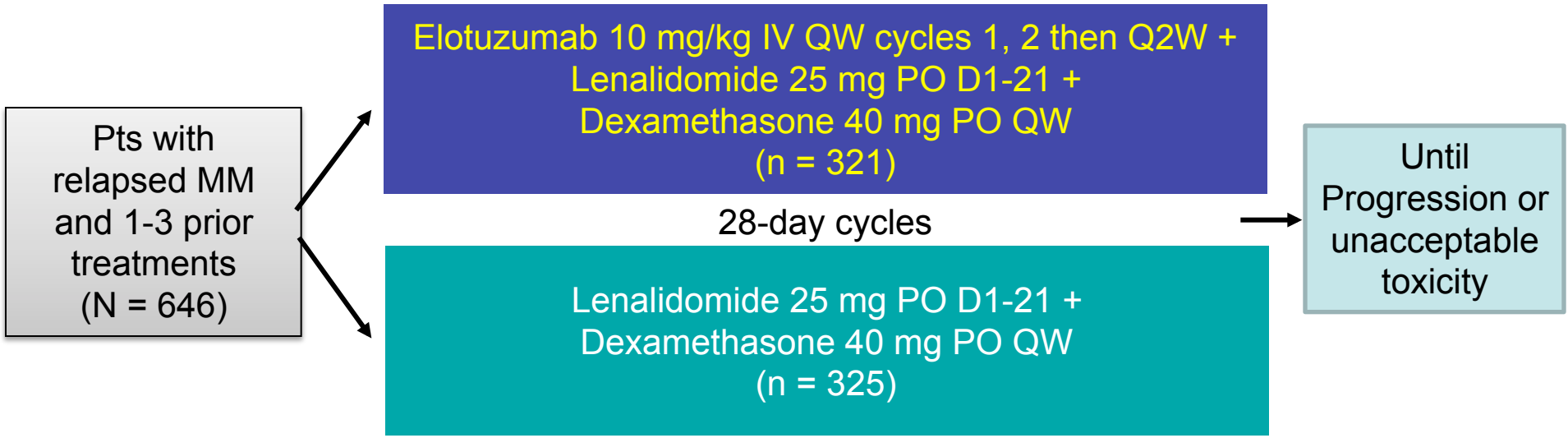

Hsi ED et al. Clin Cancer Res. 2008;14:2775-2784. Tai YT et al. Blood. 2008;112:1329-1337.
van Rhee F et al. Mol Cancer Ther. 2009;8:2616-2624. Lonial S et al. Blood. 2009;114:432. Richardson PG, et al. ASH 2014. Abstract 302

# Elotuzumab is an IV humanized monoclonal antibody targeting human SLAMF7

- Elotuzumab: Low single agent activity
- Original study with elo only in 35 pts, doses ranging from 0.5-20 mg/kg every two weeks demonstrated no responses but stable disease in 27% of pts
- However when combined with lenalidomide and dex in relapsed pts, response rate was 82% (expected would be about 60%)

# ELOQUENT-2: Elotuzumab With Lenalidomide/Dexamethasone R/R MM

- Randomized, open-label, multicenter phase III trial




- Primary endpoints: Progression Free time (PFS), Overall Response
- Secondary endpoints: Overall Survival, safety, health-related Quality of Life

Dimopoulos MA, et al. ASH 2015. Abstract 28.

# ELOQUENT-2 Results

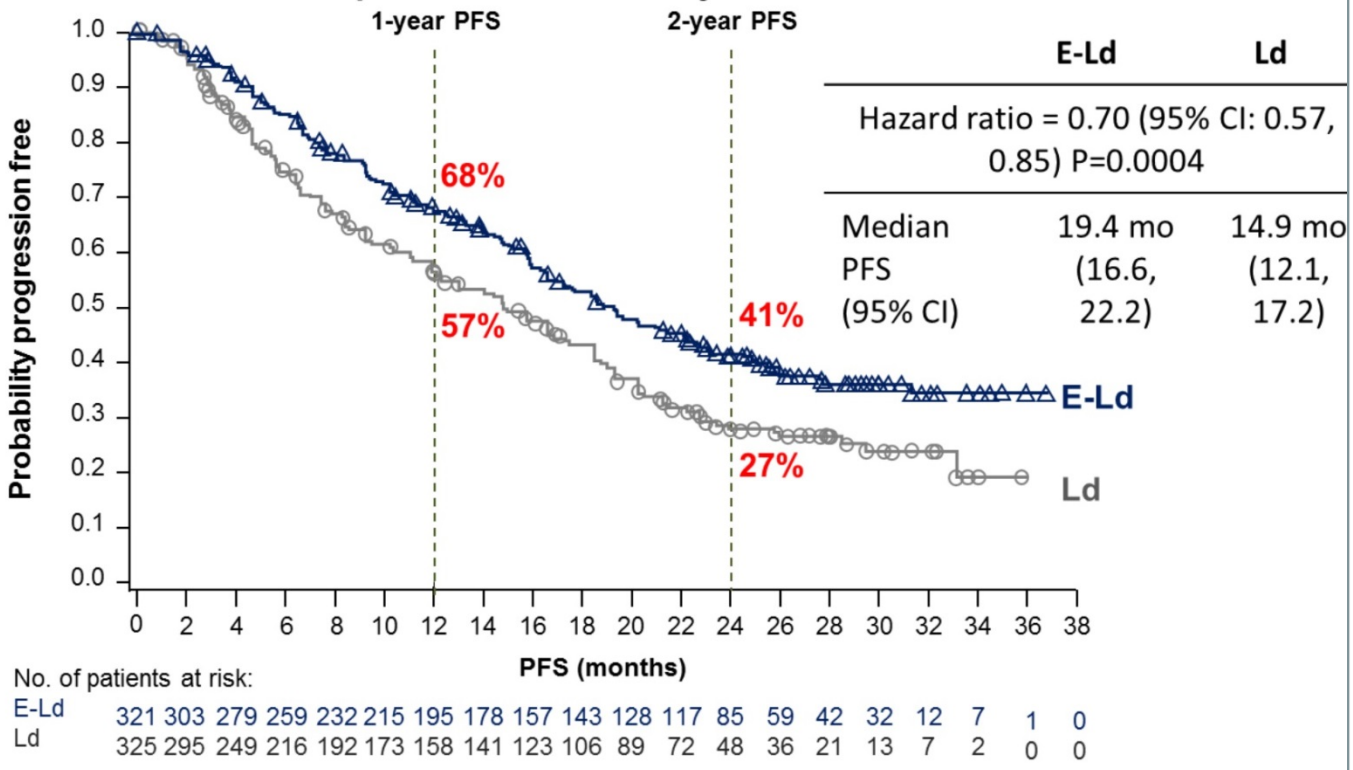
| | E-Rd (n=321) | Rd (n=325) | HR | *P* Value |
|---|---|---|---|---|
| Median PFS, mos | 19.4 | 14.9 | 0.70 | <0.001 |
| ORR, % | 79 | 66 | — | <0.001 |
| ≥VGPR, % | 33 | 28 | — | — |
| AEs, % | | | | |
| ≥G3 cardiac failure | 4 | 6 | — | — |
| ≥G3 acute renal failure | 4 | 4 | — | — |

**No benefit observed in patients who were previously exposed to immunomodulatory agent.**

**Patients with Del17p, 1q21 amplifications and t(4;14) faired as well as standard risk.**

Lonial S et al. *N Engl J Med*. 2015;373:621.

# Phase 3 Study of Lenalidomide/Dex with or without Elotuzumab in Relapsed/Refractory MM: PFS




| | E-Ld | Ld |
|---|---|---|
| Hazard ratio = 0.70 (95% CI: 0.57, 0.85) P=0.0004 | | |
| Median PFS (95% CI) | 19.4 mo (16.6, 22.2) | 14.9 mo (12.1, 17.2) |

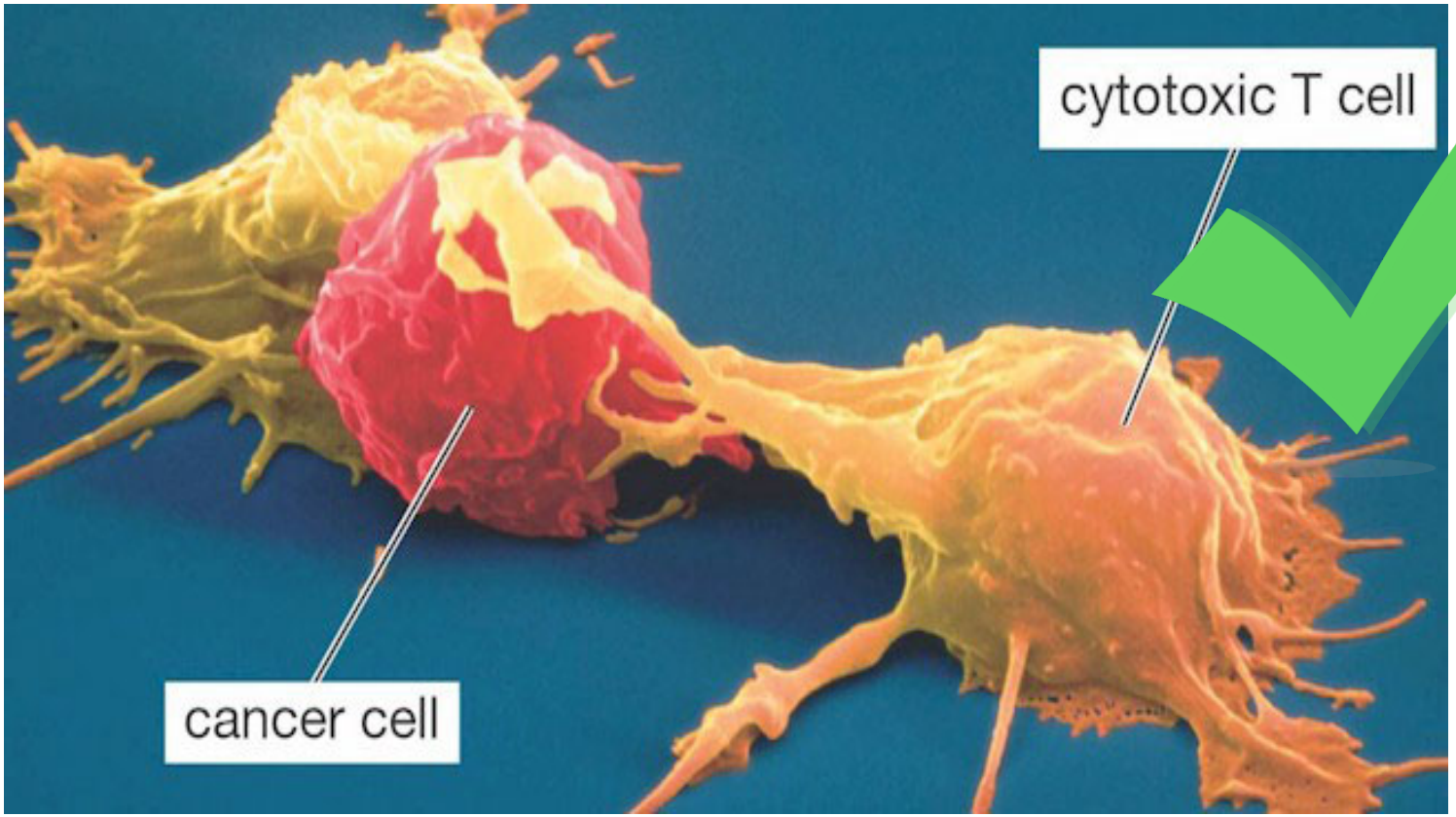


**E-Ld-treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively**

FDA approved November 2015

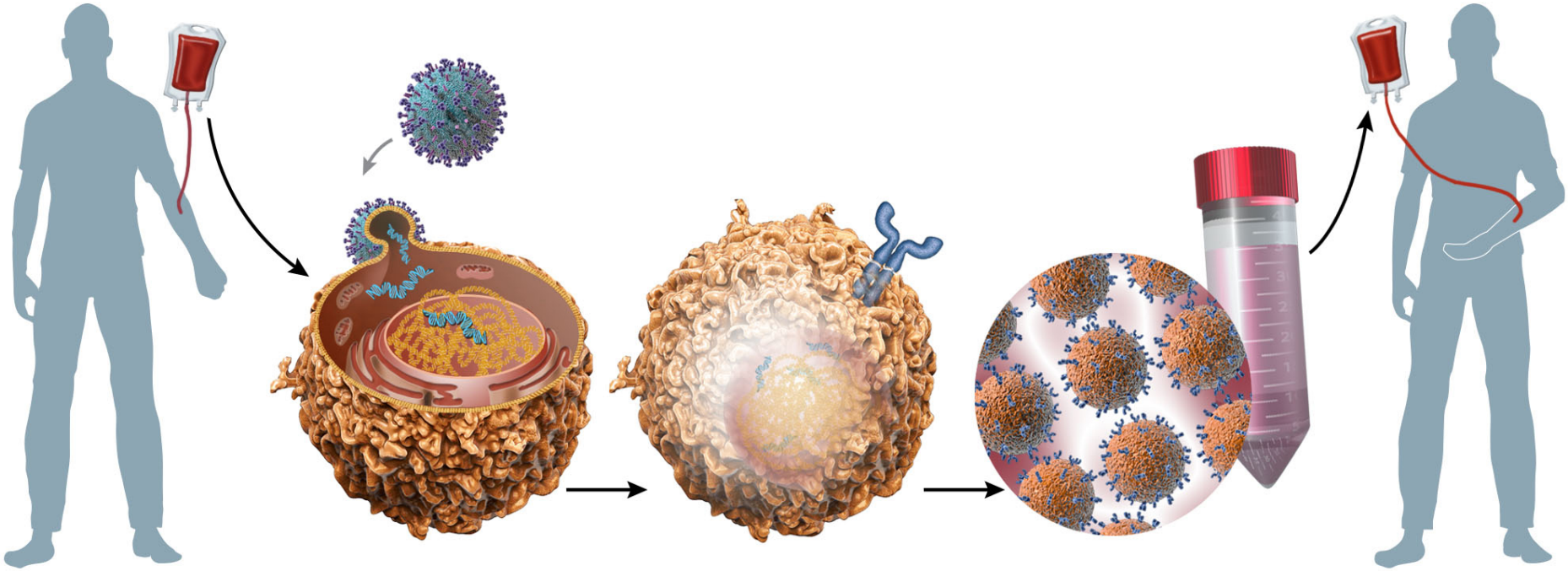
Lonial et al, NEnglJMed 2015: 373:621-31

# CAR –T Immune Therapy



# T cells are white blood cells that attack and kill viruses and cancer cells

## Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells



1. T cells are collected from the patient. A machine removes the desired cells from the blood, then returns the rest back to the patient.

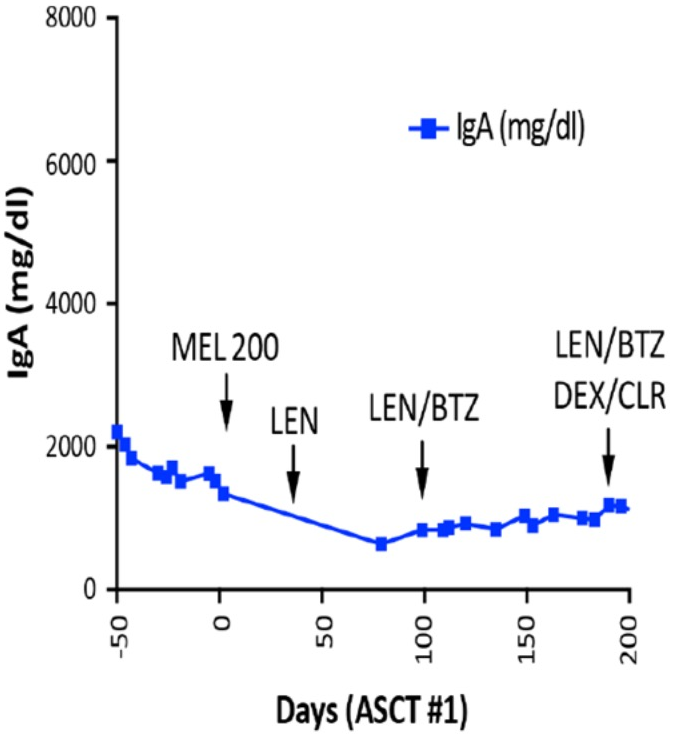
2. A modified virus (blue) is used to transfer DNA to the patient's T cells so they will produce CAR proteins.

3. CARs have two ends: a binding site (blue) specific to the tumor cells, and a signaling engine that activates the T cell to kill the tumor it binds to.

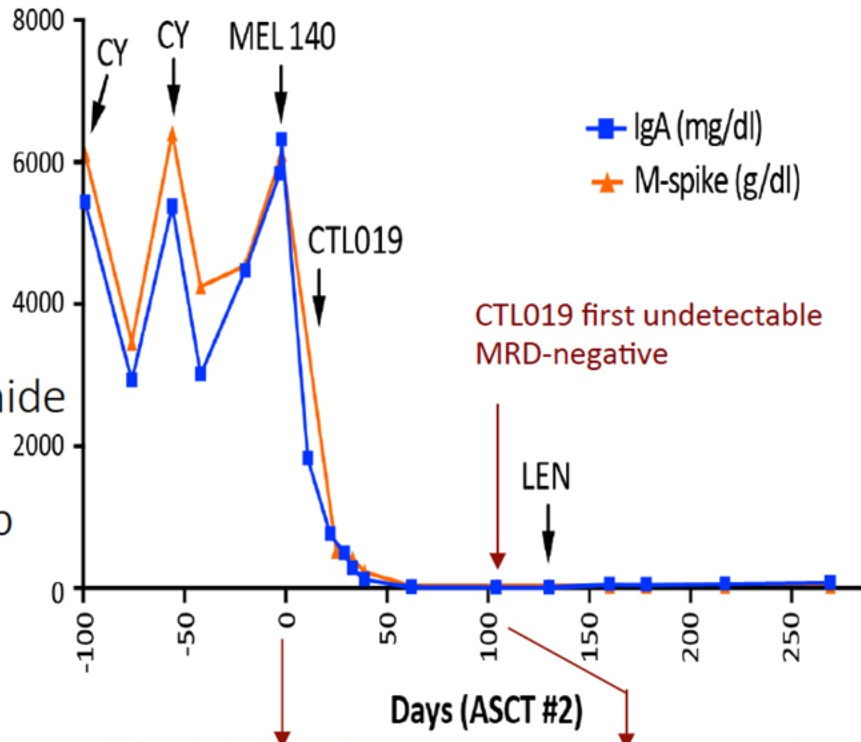
4. Once designed, millions of engineered CAR T cells are grown in the laboratory.

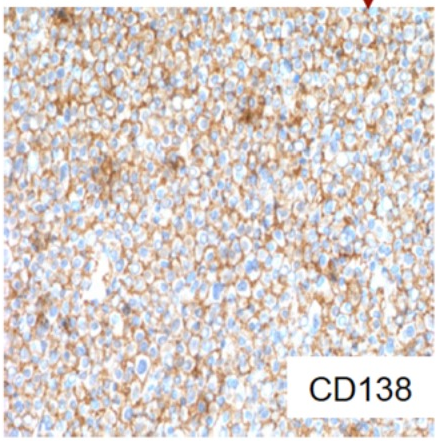
5. The expanded population of CAR T cells is infused into the patient through a standard blood transfusion

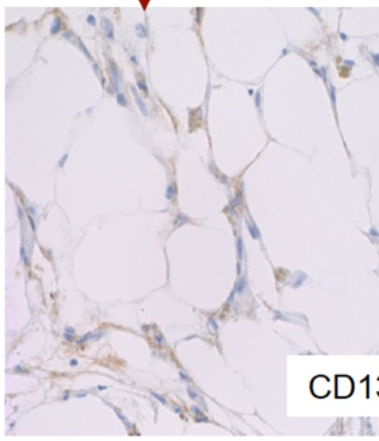
# MM Patient #1: Response to CD19 CAR Thera




Additional regimens including…
- carfilzomib
- pomalidomide
- vorinostat
- elotuzomab



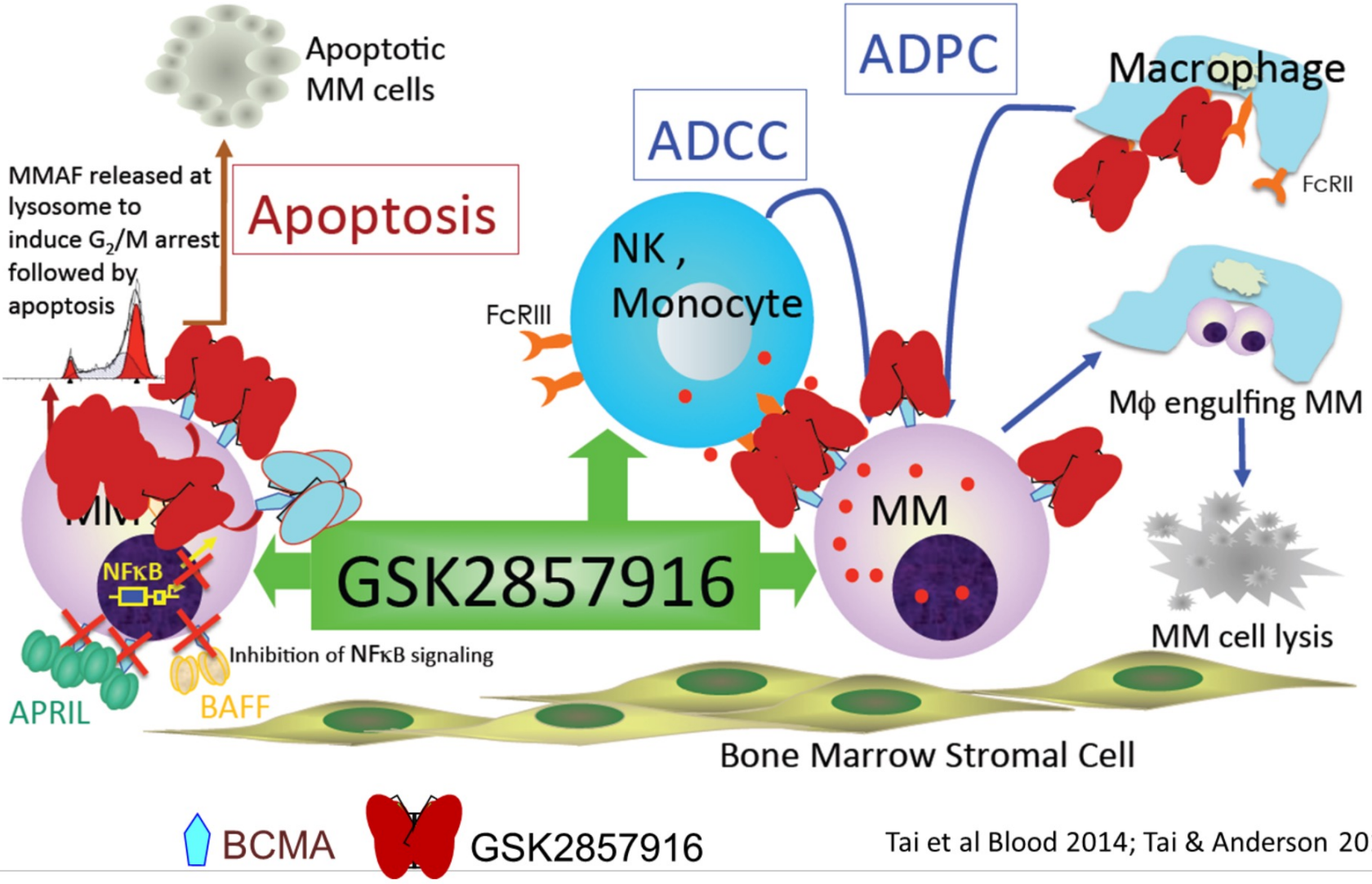




sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

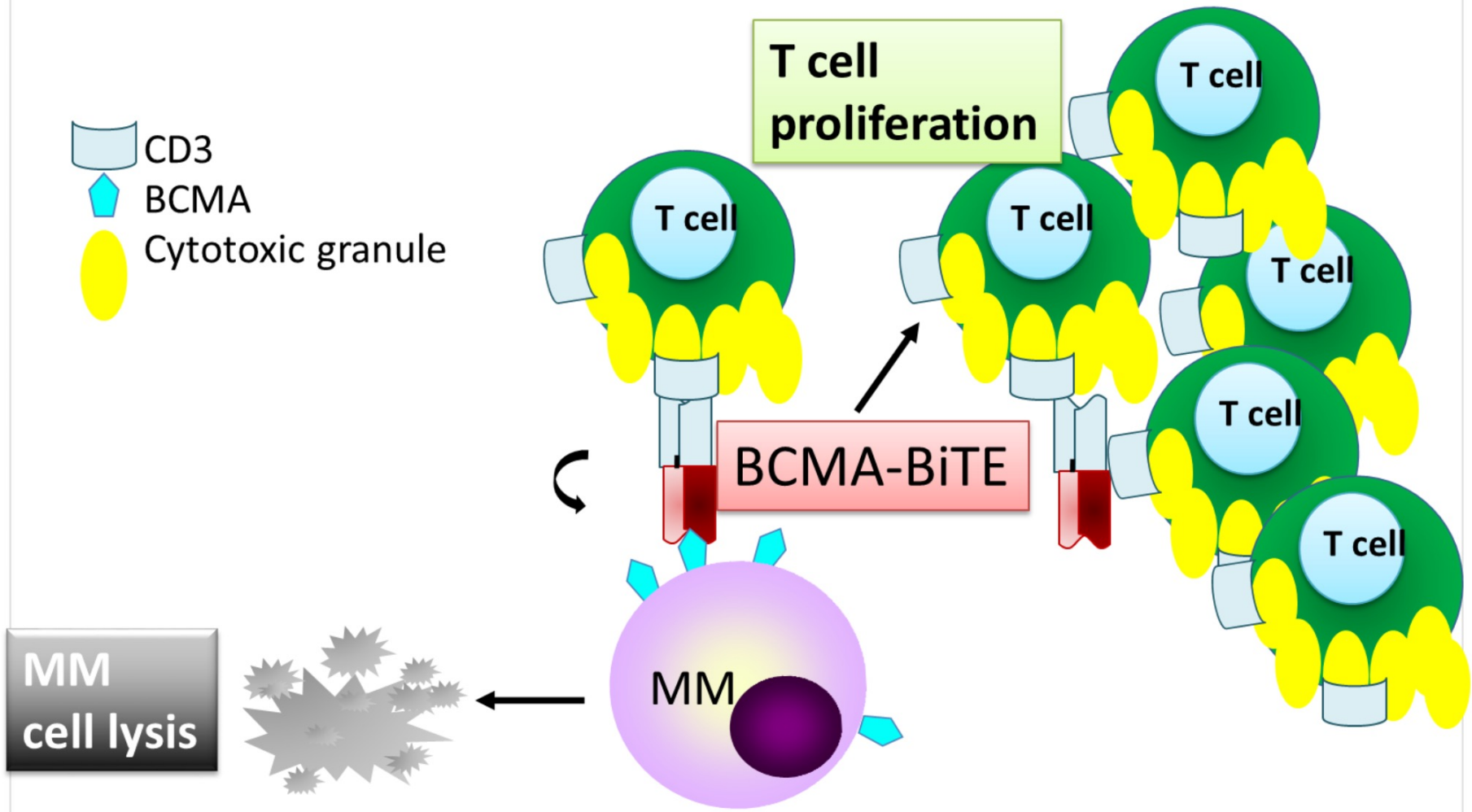
Garfall et al, NEJM 2015; 373: 1040-7

# A BCMA Auristatin Immunotoxin Induces Strong Anti-MM Effects




Tai et al Blood 2014; Tai & Anderson 2015

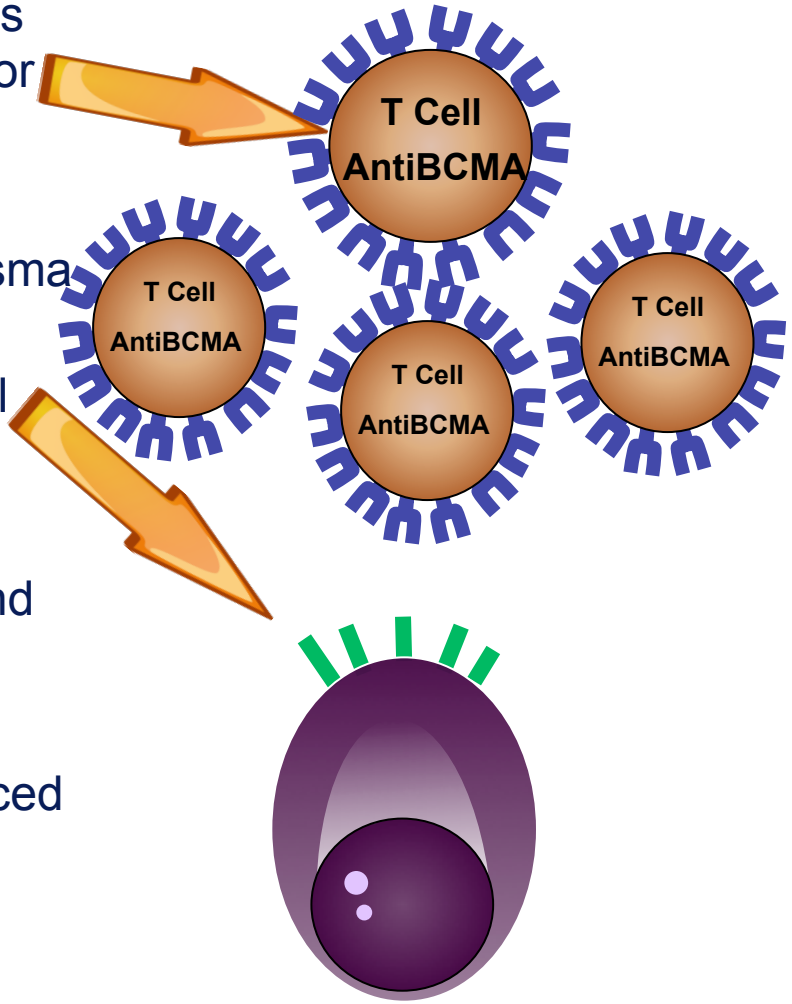
# BCMA-BiTE-based Immunotherpaies




Tai et al 2016

# CAR-BCMA T Cells in Myeloma: Background

- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for malignancy-associated antigens
- B-cell maturation antigen (BCMA) is expressed by normal and malignant plasma cells.
  - BCMA is a potential target for CAR T-cell therapy for MM
- The patient's own T-cells were stimulated, transduced with CAR-BCMA retroviruses, and cultured for 9 days before infusion.
- Study presented ASH 2015 evaluated CAR-BCMA T cell infusion for treatment of advanced MM




1. Carpenter RO, et al. Clin Cancer Res. 2013;19:2048-2060. Ali SA, et al. ASH 2015. Abstract LBA-1.

# CAR-BCMA T Cells in Myeloma: Study Design

- First-in-human phase I trial

- Pts with advanced relapsed/ refractory MM
- More than 3 prior lines of therapy;
  - BCMA expression on myeloma cells
- 12 patients enrolled

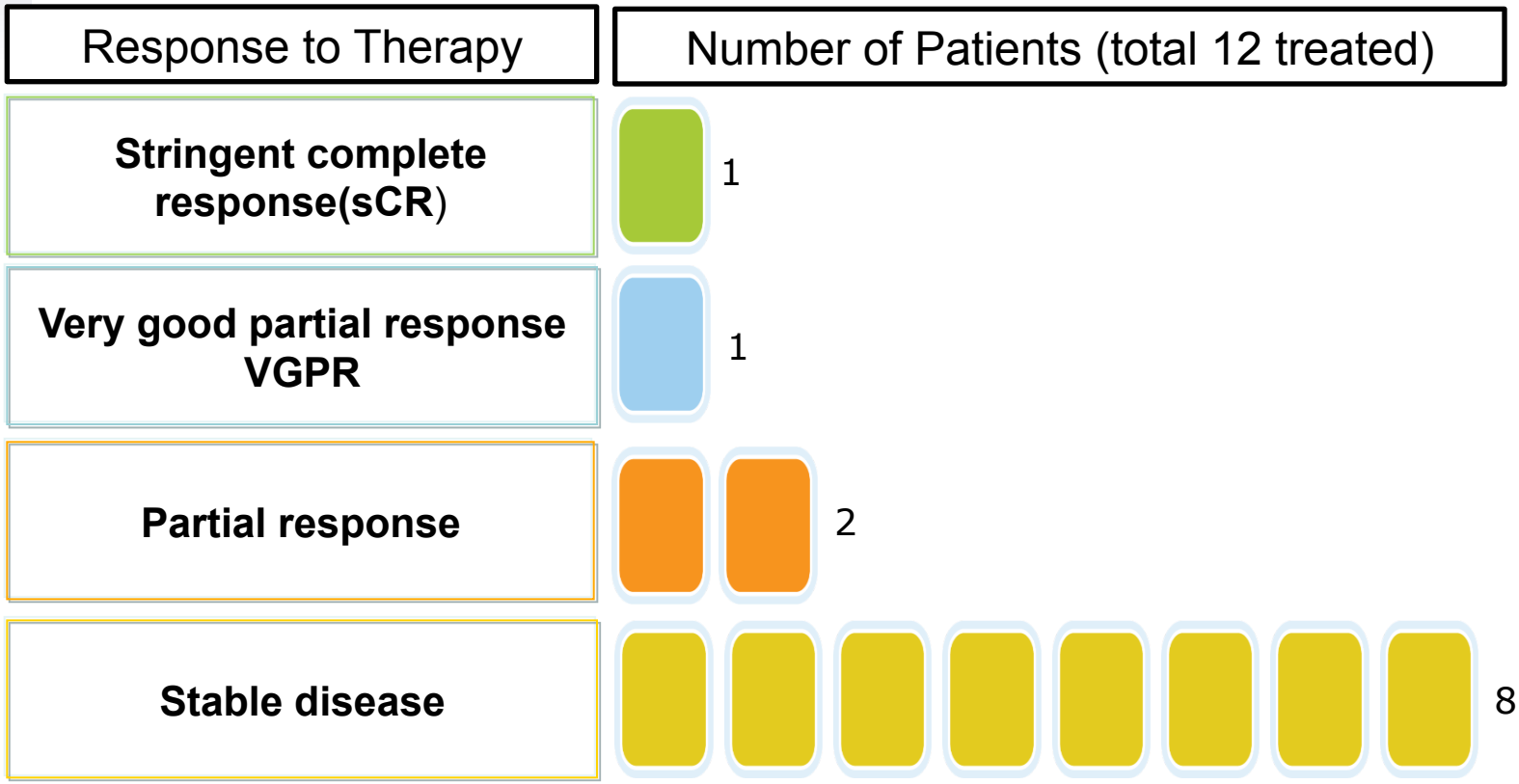
→ Cyclophosphamide 300 mg/m$^2$
Fludarabine 30 mg/m$^2$
QD for 3 days

→ CAR-BCMA T cells*
Single infusion

*Dose escalation of CAR+ T cells/kg
$0.3 \times 10^6$
$1.0 \times 10^6$
$3.0 \times 10^6$
$9.0 \times 10^6$

Ali SA, et al. ASH 2015. Abstract LBA-1.

# CAR-BCMA T Cells in Myeloma: Response to therapy




Ali SA et al. *Proc ASH* 2015;Abstract LBA1.

# The Path to Cure

- Require validated minimal residual disease assessment tools and their inclusion in response criteria.
- Clonal heterogeneity and epigenetics need to be addressed at time of treatment selection. This may explain clonal dominance at different stages of the disease.

# The Path to Cure

- We need to build a treatment program that can eradicate clonal heterogeneity and produce a negative minimal disease status.
- Improving immune surveillance to eradicate residual disease.


Thanks to the patients, their
family, and the care givers
we will find a cure