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CANCER INSTITUTE

Myeloma Therapies: New Options & Understanding the Role of Sequencing & Transplantation

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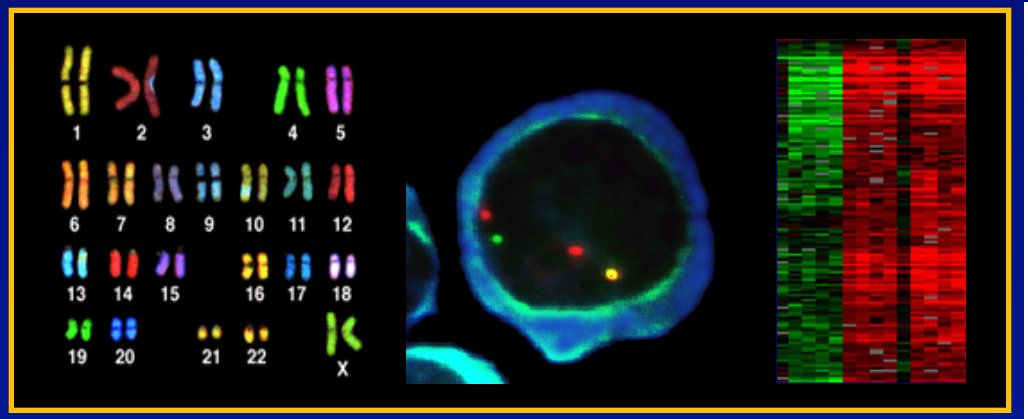
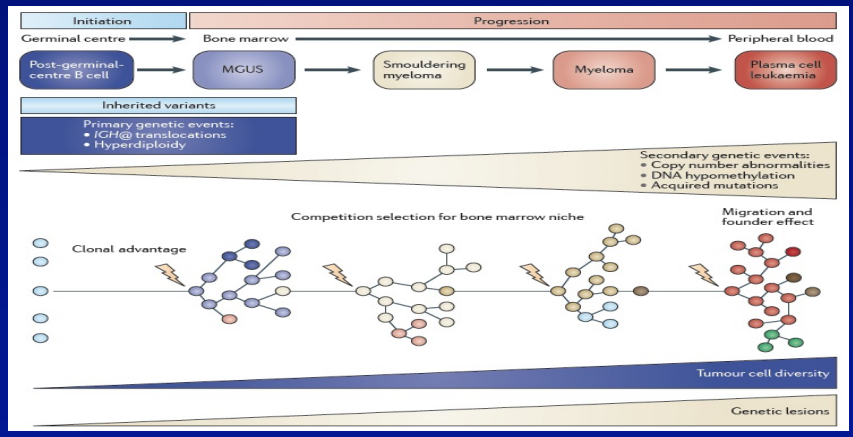
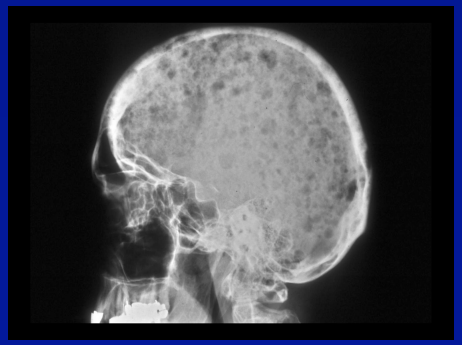
MULTIPLE MYELOMA
…not just one disease!

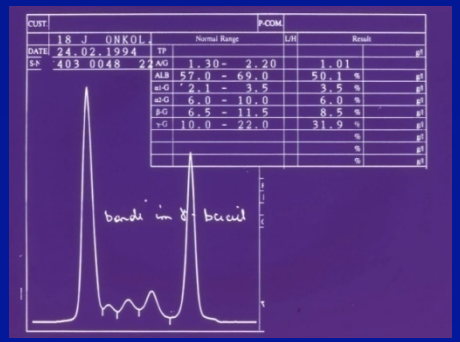
- Risk stratification, recognition of clonal heterogeneity
- Individualization of treatment, advent of novel therapies

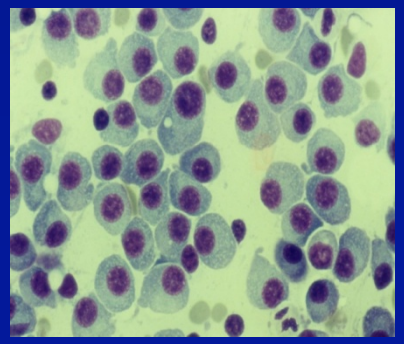
3 decades







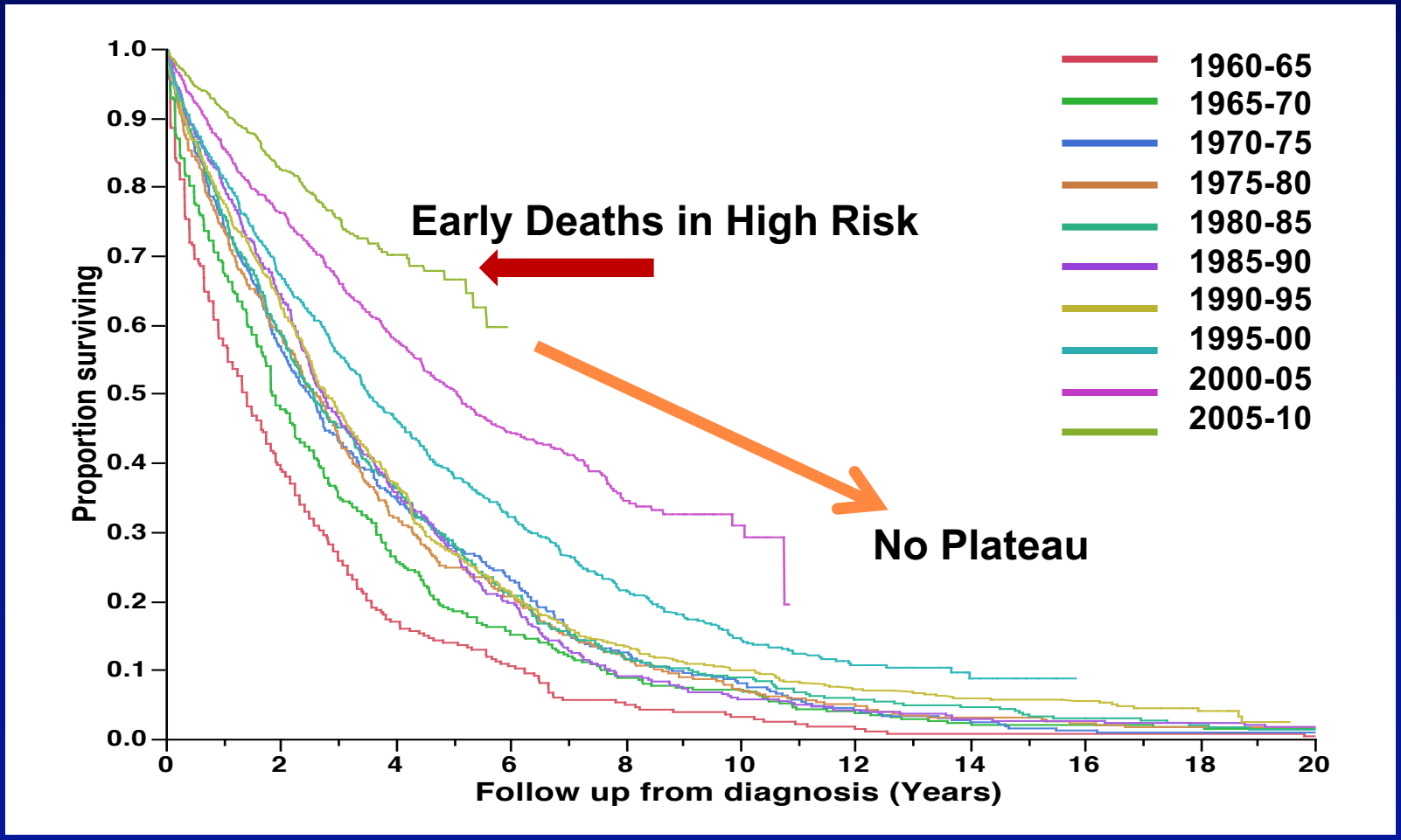




Drach J, ASH 2012

Morgan et al. *Nat Rev Cancer* 2012;12:335-348

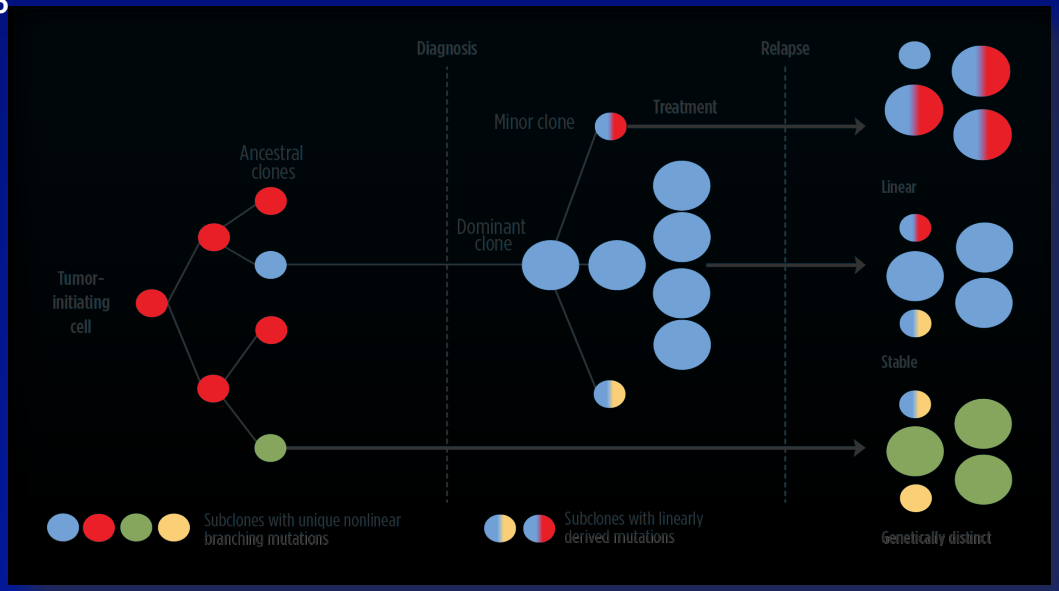
Multiple Myeloma survival improving with new drugs: but all patients still relapse after IMiD and PI failure



Adapted from Kumar et al *Leukemia* 2014

Multiple genetically distinct subclones can occur in multiple myeloma

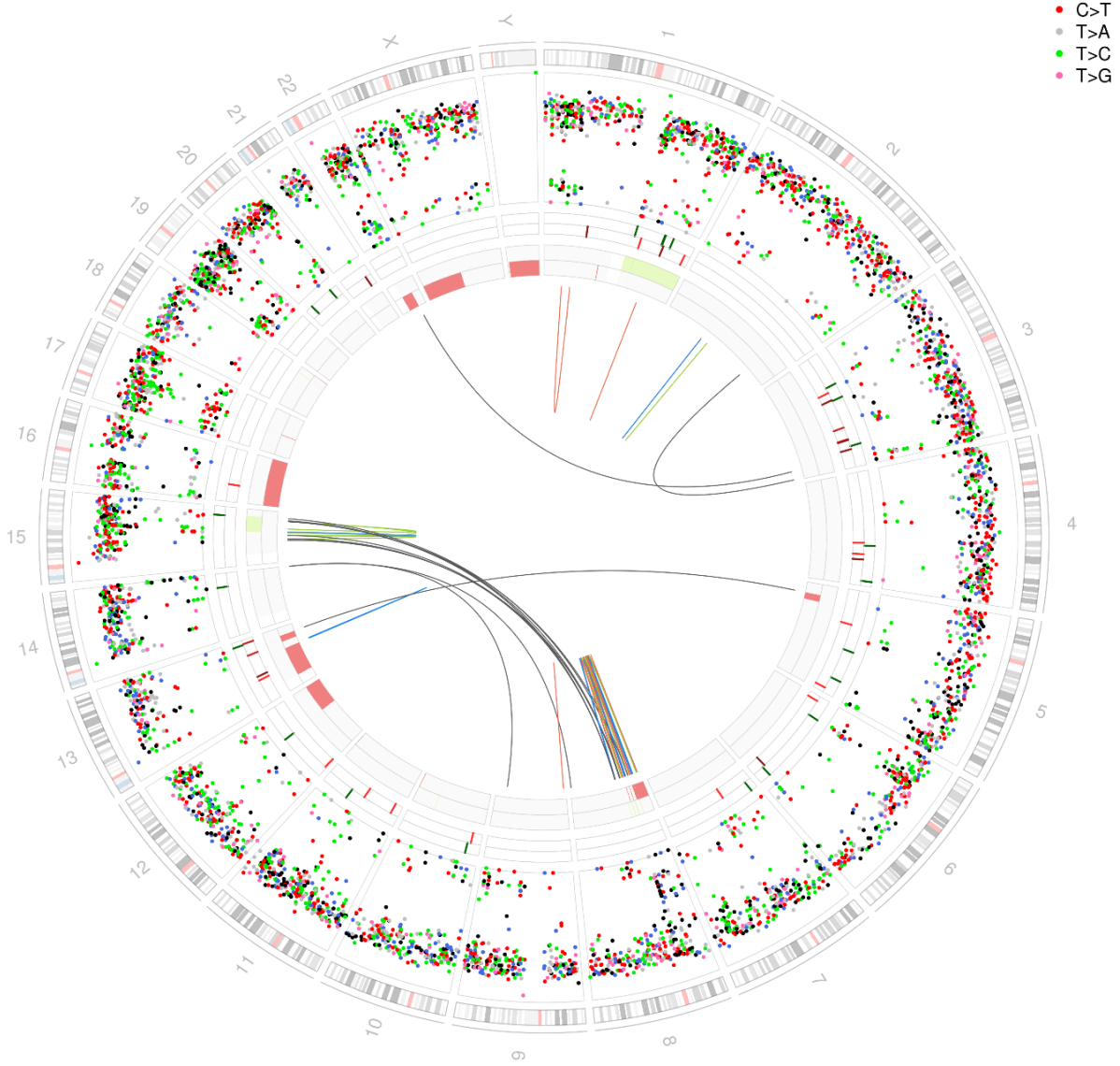
- **Multiple genetically distinct subclones are present at diagnosis[1–4]**
  - These evolve over time due to selective pressures from treatment and factors in the microenvironment[1,4]
  - This clonal evolution can result in disease progression and treatment resistance[5]

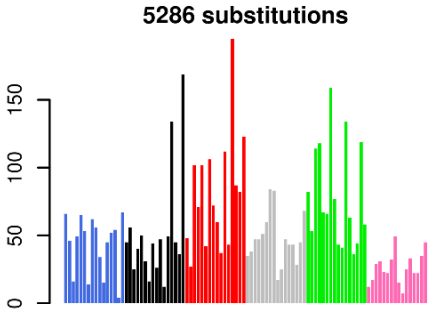


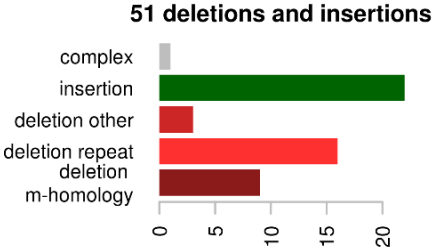
1. Bahlis N et al. *Blood* 2012;120:927–28
2. Keats JJ et al. *Blood* 2012;120:1067–76
3. Bianchi G, Ghobrial IM. *Curr Cancer Ther Rev* 2014;10:70–9
4. Bolli N et al. *Nat Commun* 2014;5:2997
5. Brioli A et al. *Br J Haematol* 2014;165:441–54.

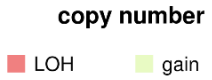
WGS at diagnosis

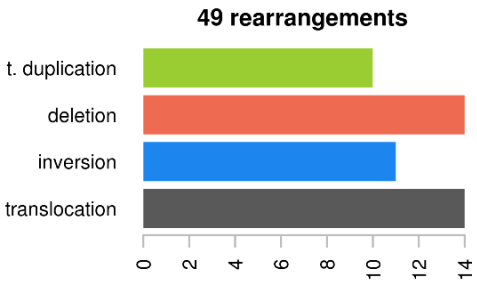
PD26419c







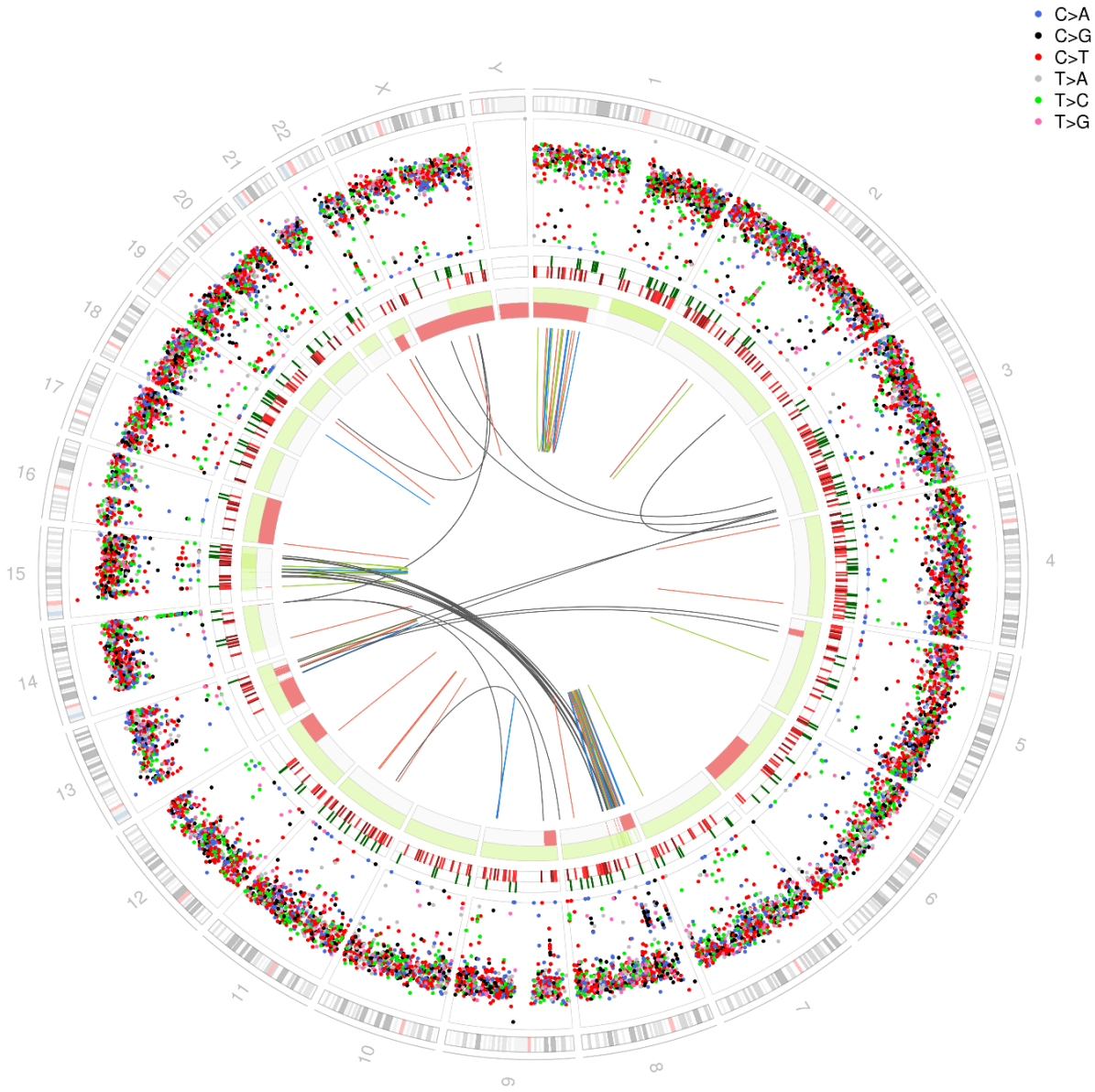


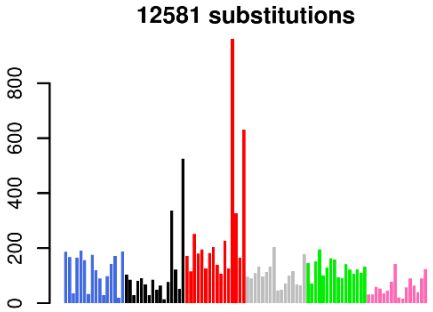


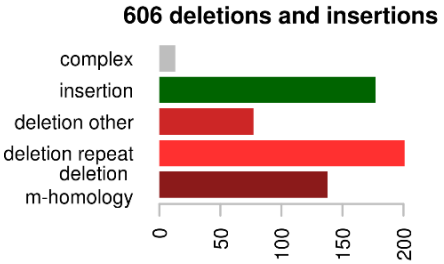
Courtesy of Nikhil Munshi MD, DFCI

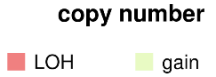
WGS at relapse

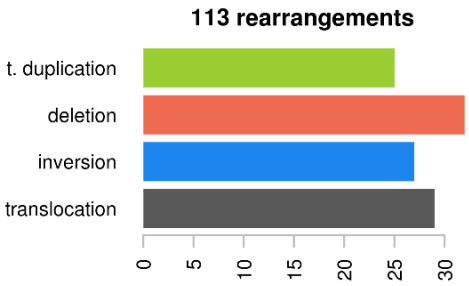
PD26419d











Courtesy of Nikhil Munshi MD, DFCI

Key Targets in MM 2017

Excess Protein Production:

- Target Protein degradation

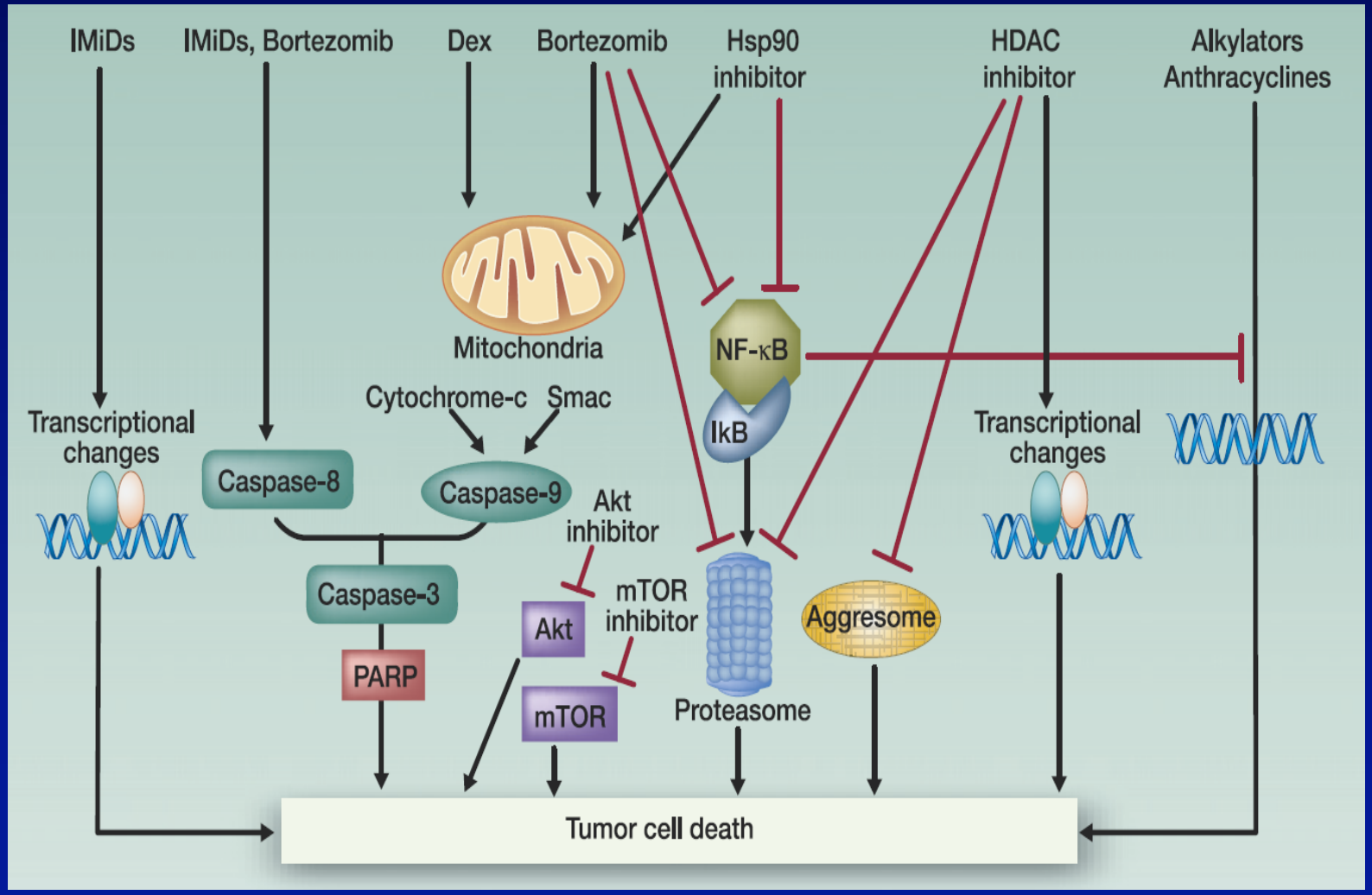
Genomic abnormalities:

- Target and overcome mutations
- Critical Role of Combination Therapy

Immune Suppression:

- Restore anti-MM immunity

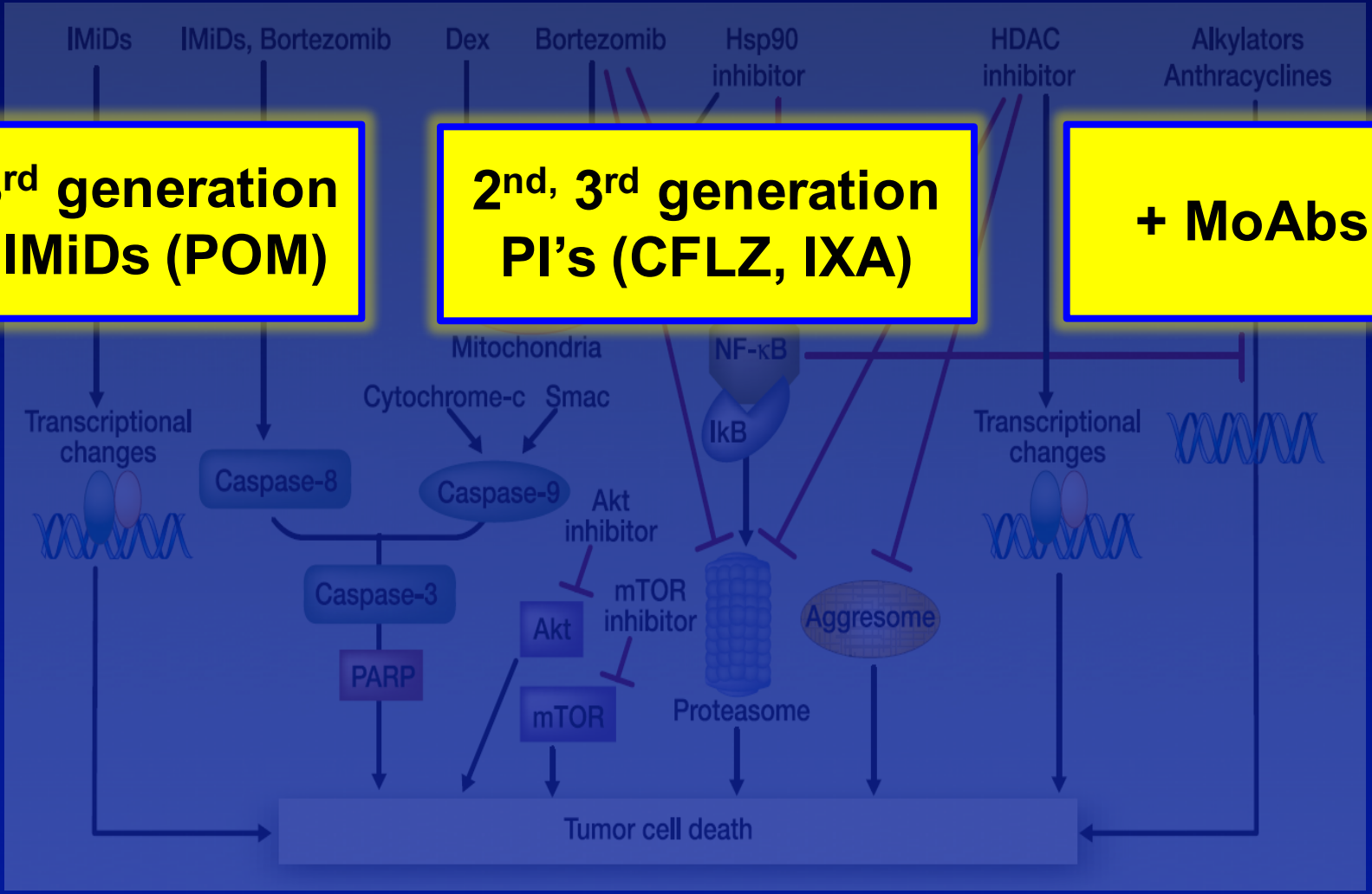
Rational combination strategies in MM



Clinical Cancer Research

Adapted from Lonial S, Mitsiades CS, Richardson PG. *Clin Cancer Res* 2011;17:1264-77.

Rational combination strategies in MM



Clinical Cancer Research

Adapted from Lonial S, Mitsiades CS, Richardson PG. *Clin Cancer Res* 2011;17:1264-77.

Immunomodulatory Agents
IMiDs: Mechanism of Action

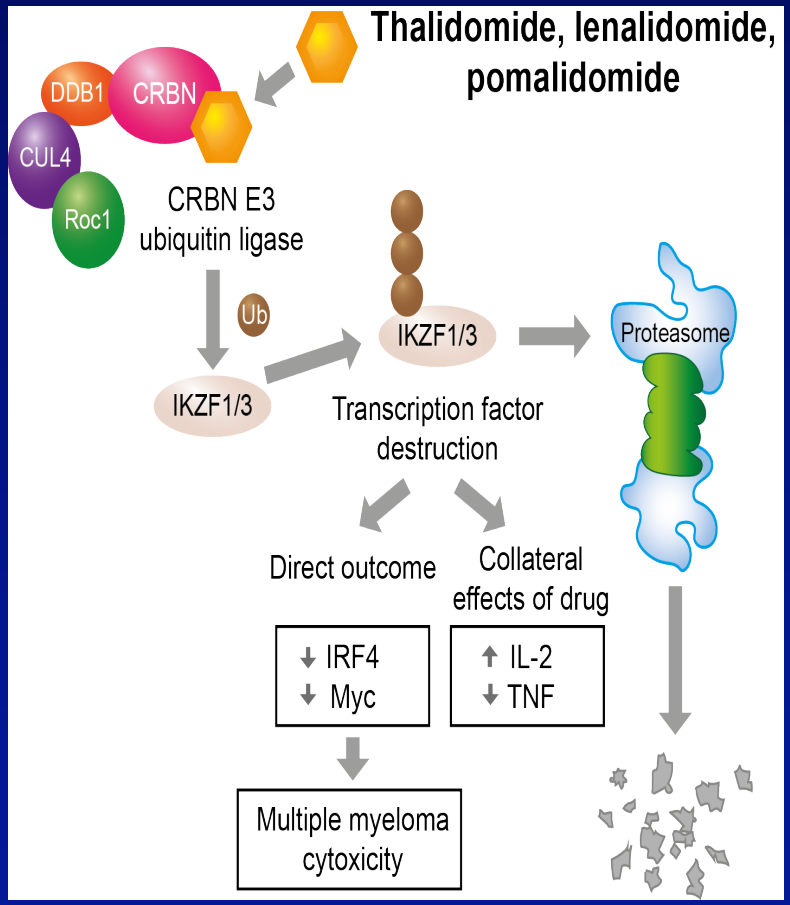
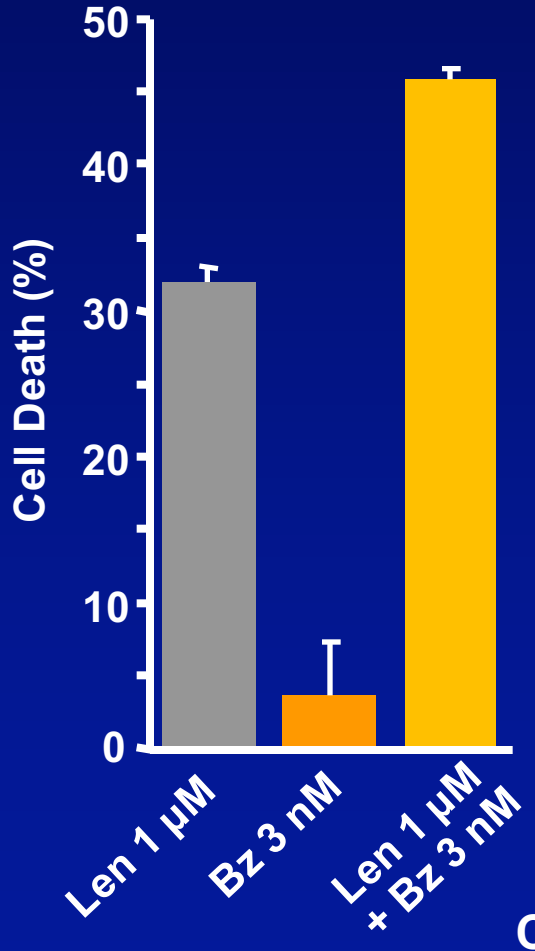
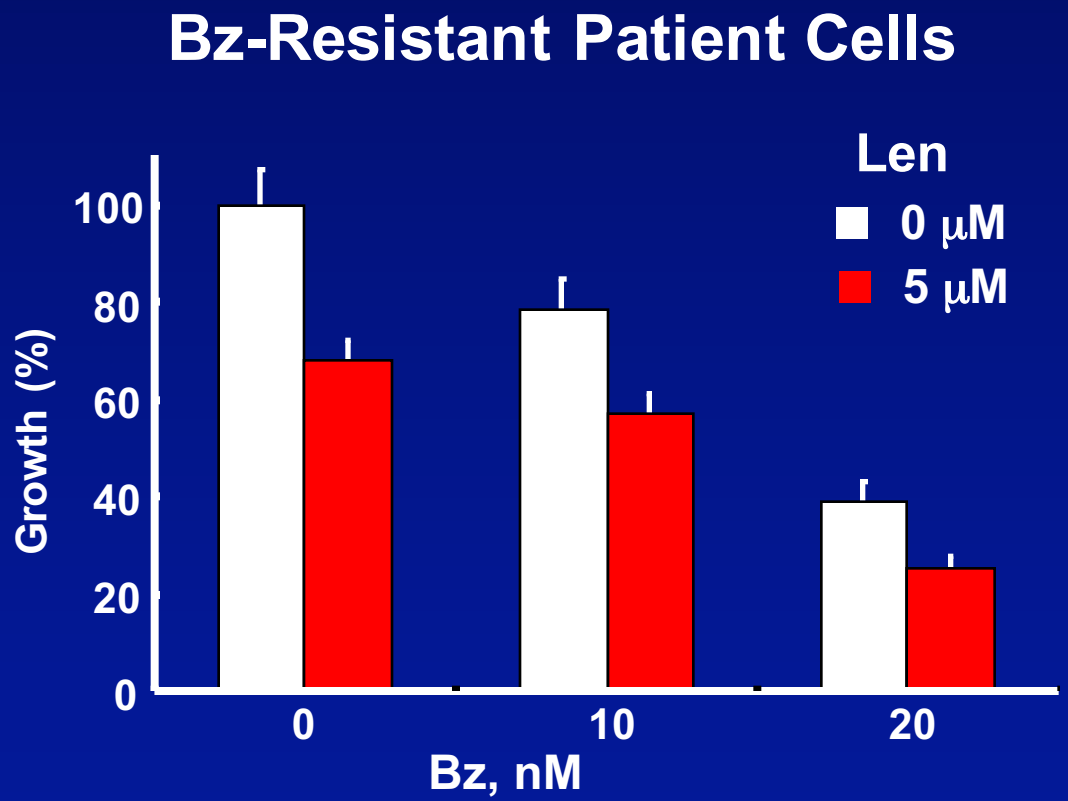


Figure adapted from Stewart KA. *Science* 2014; 343: 256-257.0
Kronke et al, *Science*, 2014
Lu et al, *Science*, 2014

Rationale: Preclinical Combination of Lenalidomide (Len) + Bortezomib (Bz)





Combination therapy now standard of care

Mitsiades N, et al. *Blood.* 2002;99(12):4525-4530
Hideshima T, et al. 2003

VOLUME 27 · NUMBER 34 · DECEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter, Phase I, Dose-Escalation Trial of Lenalidomide Plus Bortezomib for Relapsed and Relapsed/Refractory Multiple Myeloma

Paul G. Richardson, Edie Weller, Sundar Jagannath, David E. Avigan, Melissa Alsina, Robert L. Schlossman, Amitabha Mazumder, Nikhil C. Munshi, Irene M. Ghobrial, Deborah Doss, Diane L. Warren, Laura E. Lunde, Mary McKenney, Carol Delaney, Constantine S. Mitsiades, Teru Hideshima, William Dalton, Robert Knight, Dixie-Lee Esseltine, and Kenneth C. Anderson

blood®

2010 116: 679-686
doi:10.1182/blood-2010-02-268862 originally published online April 12, 2010

Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma

Paul G. Richardson, Edie Weller, Sagar Lonial, Andrzej J. Jakubowiak, Sundar Jagannath, Noopur S. Raje, David E. Avigan, Wanling Xie, Irene M. Ghobrial, Robert L. Schlossman, Amitabha Mazumder, Nikhil C. Munshi, David H. Vesole, Robin Joyce, Jonathan L. Kaufman, Deborah Doss, Diane L. Warren, Laura E. Lunde, Sarah Kaster, Carol DeLaney, Teru Hideshima, Constantine S. Mitsiades, Robert Knight, Dixie-Lee Esseltine and Kenneth C. Anderson

blood®

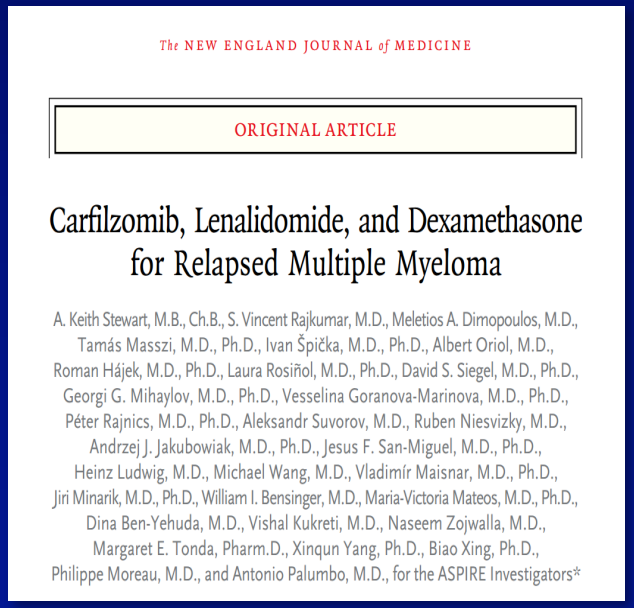
2014 123: 1461-1469
doi:10.1182/blood-2013-07-517276 originally published online January 15, 2014

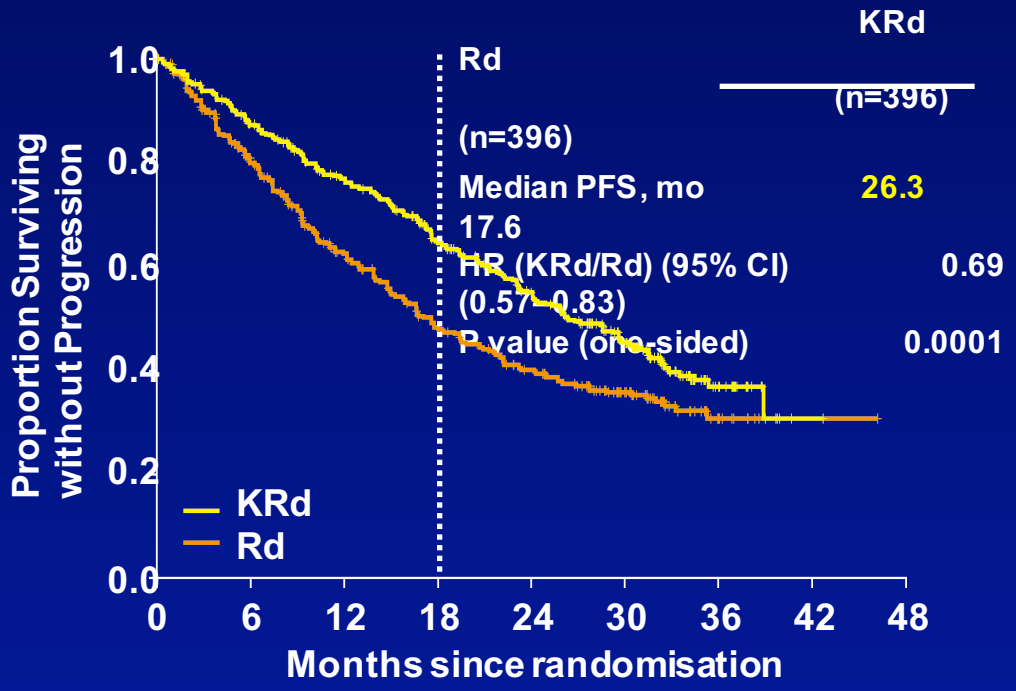
A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma

Paul G. Richardson, Wanling Xie, Sundar Jagannath, Andrzej Jakubowiak, Sagar Lonial, Noopur S. Raje, Melissa Alsina, Irene M. Ghobrial, Robert L. Schlossman, Nikhil C. Munshi, Amitabha Mazumder, David H. Vesole, Jonathan L. Kaufman, Kathleen Colson, Mary McKenney, Laura E. Lunde, John Feather, Michelle E. Maglio, Diane Warren, Dixil Francis, Teru Hideshima, Robert Knight, Dixie-Lee Esseltine, Constantine S. Mitsiades, Edie Weller and Kenneth C. Anderson

Richardson PG, et al. *J Clin Oncol.* 2009; 27:5713-9. *Blood.* 2010; 116:679-86. *Blood.* 2014; 123:1461-9.

ASPIRE Study:
Carfilzomib + lenalidomide + dexamethasone
Primary endpoint – PFS





KRd-treated patients had a 31% reduction in the risk of disease progression or death in comparison with Rd

Intention to treat (ITT) population (N=792)

PFS: progression-free survival; Krd: carfilzomib, lenalidomide and dexamethasone; Rd:

Stewart AK, et al. *N Engl J Med* 2015; 372:142-52.

TOURMALINE-MM1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

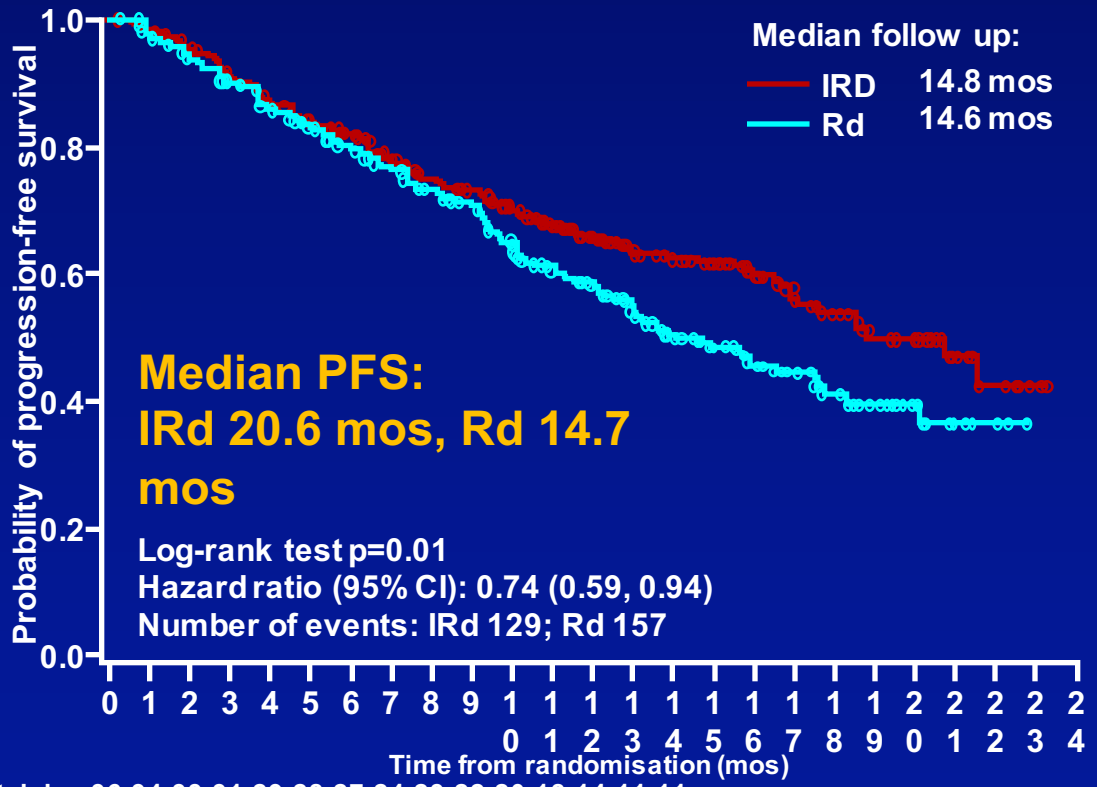
Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

P. Moreau, T. Masszi, N. Grzasko, N.J. Bahlis, M. Hansson, L. Pour, I. Sandhu, P. Ganly, B.W. Baker, S.R. Jackson, A.-M. Stoppa, D.R. Simpson, P. Gimsing, A. Palumbo, L. Garderet, M. Cavo, S. Kumar, C. Touzeau, F.K. Buadi, J.P. Laubach, D.T. Berg, J. Lin, A. Di Bacco, A.-M. Hui, H. van de Velde, and P.G. Richardson, for the TOURMALINE-MM1 Study Group*

Moreau P. et al. *N Engl J Med.* 2016; 374:1621-34.

TOURMALINE-MM1:
Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone ~ Significantly improved PFS with IRd *vs* Rd

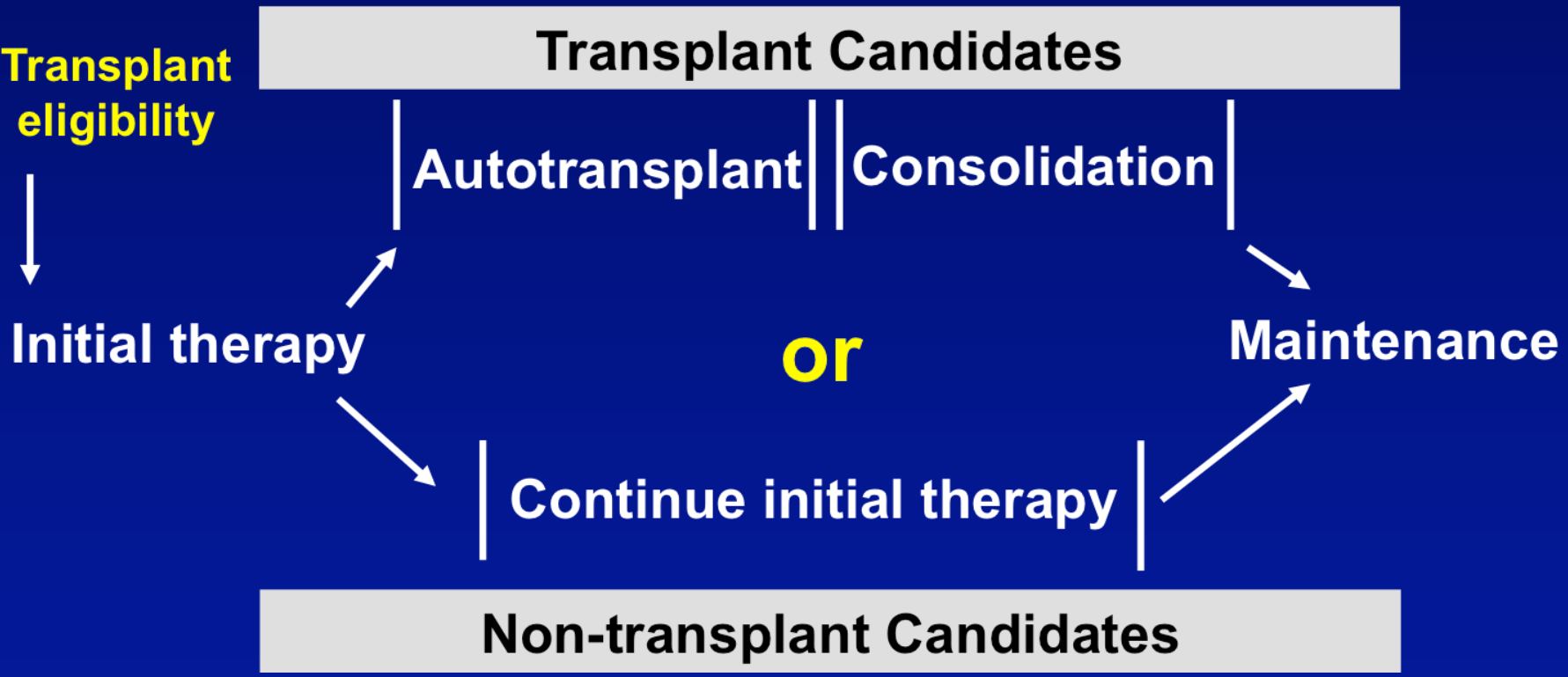
35% longer PFS with IRd *vs* Rd



IRD: Ixazomib, lenalidomide and dexamethasone; RD: lenalidomide and dexamethasone

Moreau P. et al. *N Engl J Med.* 2016; 374:1621-34.

Current Paradigm of Initial Treatment



Adapted from Ludwig H, et al. *Oncologist.* 2012;17:592-606
Richardson PG et al, *BJH* 2011; McCarthy PJ et al, 2016

Lenalidomide/Bortezomib-Based Rx in ND MM

Response	RVD[1] N = 66	RVDD[2] N = 70	VDCR[3] N = 41
CR + nCR	39% (51%)*	33%	32%
≥VGPR	67% (75%)*	59%	59%
≥PR	100%	97%	93%

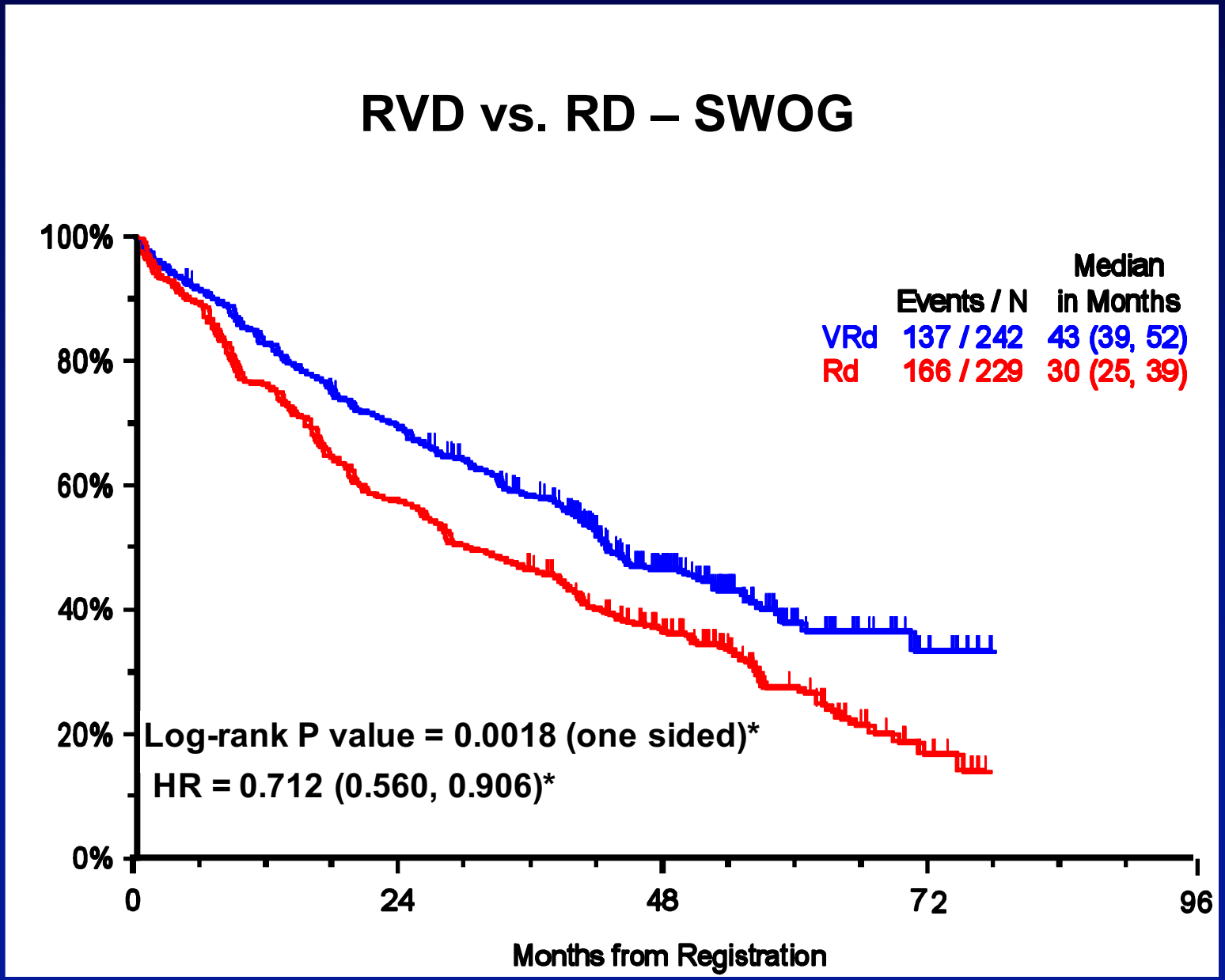
RVD: lenalidomide, bortezomib, dexamethasone; RVDD: RVD with pegylated liposomal doxorubicin; VDCR: VRD plus cyclophosphamide (wkly low dose dex with VRd, vs RVD)

- Active in pts with Adverse Cytogenetics
- Hematologic toxicity is more severe with addition of Chemo (Cy or Doxil)
- Risk of DVT does not appear to be increased over Lenalidomide/dex alone
- Risk of PN moderately increased over Bortezomib alone
- Generally otherwise well tolerated, although TRM seen with VDCR

[1] Richardson PG, et al. *Blood.* 2010; [2]Jakubowiak AJ, et al. *Blood.* 2011.
[3] Kumar S, et al. *Blood.* 2009:114(22) (abstr 127), *Leukemia* 2010. *Blood.* 2012.

* Phase 2 Cohort

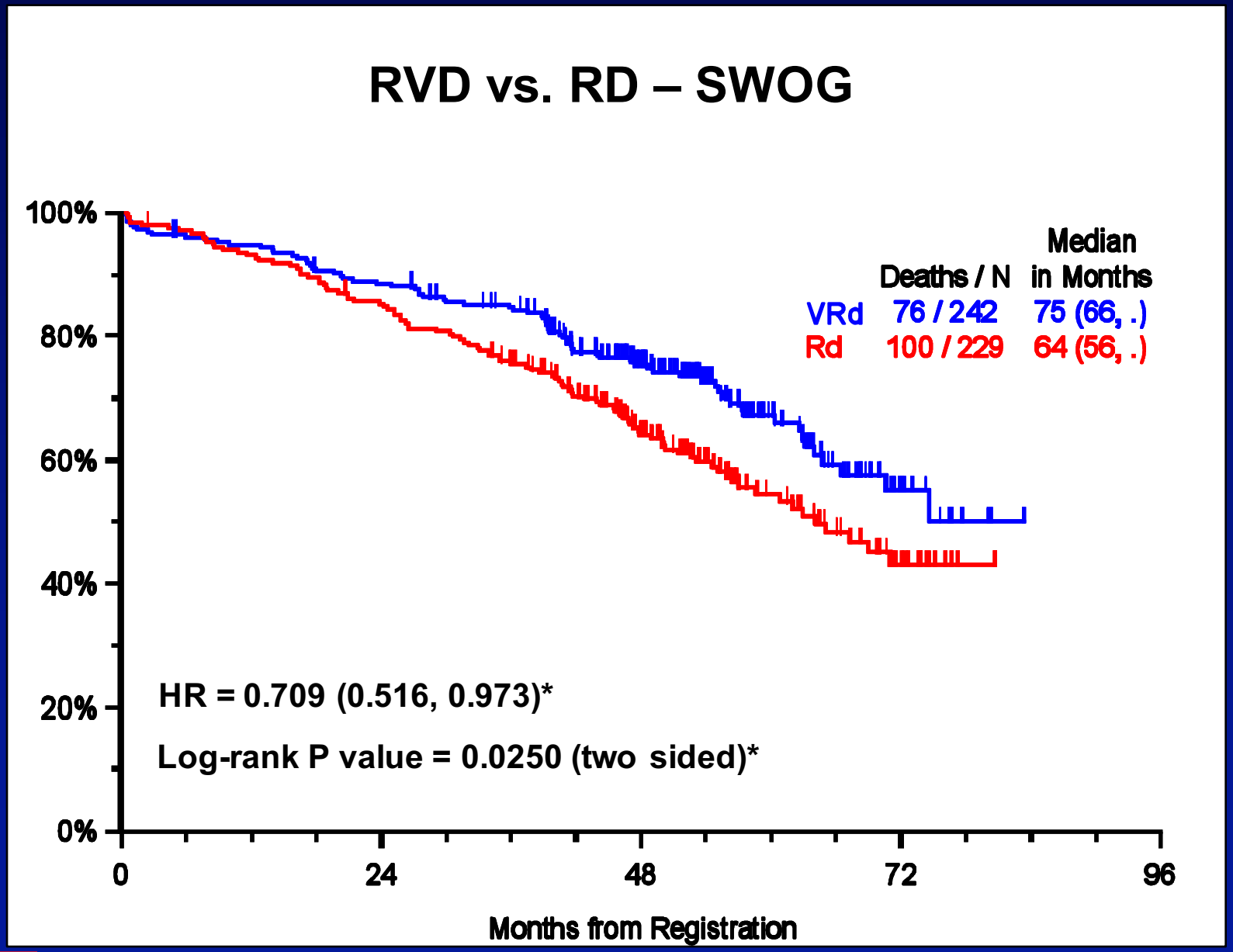
ASH 2015: Progression-Free Survival By Assigned Treatment Arm



*Assessable patients

Durie et al, *Lancet*, 2016

ASH 2015: Overall Survival By Assigned Treatment Arm



*Stratified

Durie et al, *Lancet*, 2016

Novel Agent-based Induction Therapies ASH 2016

	Thal-based	Len-based	Bort-Based	Bort+IMiD-based	New agents
2-drug combinations	TD	RD Rd	VD		
3-drug combinations	TAD CTD	RAD RCD BiRD	PAD VCD	VTD RVD	*CfzTD CfzRd **RId
4-drug combinations				VTDC RVDC RVDD	***R2V2 PanRVD MoAbs

Thal = Thalidomide, Len = Lenalidomide, Bortz = Bortezomib
Cfz: carfilzomib, MoAbs – monoclonal antibodies, Pan: panobinostat
***R2V2: RVD + vorinostat
**RId: lenalidomide, ixazomib (mln 9708), dex

A Phase II Multi-Center Study of Lenalidomide, Subcutaneous Bortezomib and Dexamethasone (RsqVD) in Newly Diagnosed Multiple Myeloma – Ctrial-IE (ICORG) 13-17 Study

ASH 2016

O'Gorman P, O'Dwyer ME, Gilligan O, Quinn J, Cyne M, Krawczyk J, Murphy PT, del Rosario McAlester L, Harraghy O, Cormican O, Lenihan E, Egan K, Perera MR, Crotty G, Hayden PJ, Hennessy B, O'Leary HM, Scott K, Parker I, Cunnane M, Marron J, Connel A,
Coghlan E, Laubach JP, Richardson PG

Results: Response Rates After 4 Induction Cycles

Response according to IMWG Criteria N = 40[a] Response	n	%
ORR	37	93
CR[b]	7	18
VGPR	18	45
PR	12	30
PD	3	7

[a]2/42 patients nonevaluable for response
[b]CR to be confirmed for 2 patients
IMWG, International Myeloma Working Group
O'Gorman P, et al. *Blood.* 2016;128: Abstract 2117.

Conclusions and Future Directions

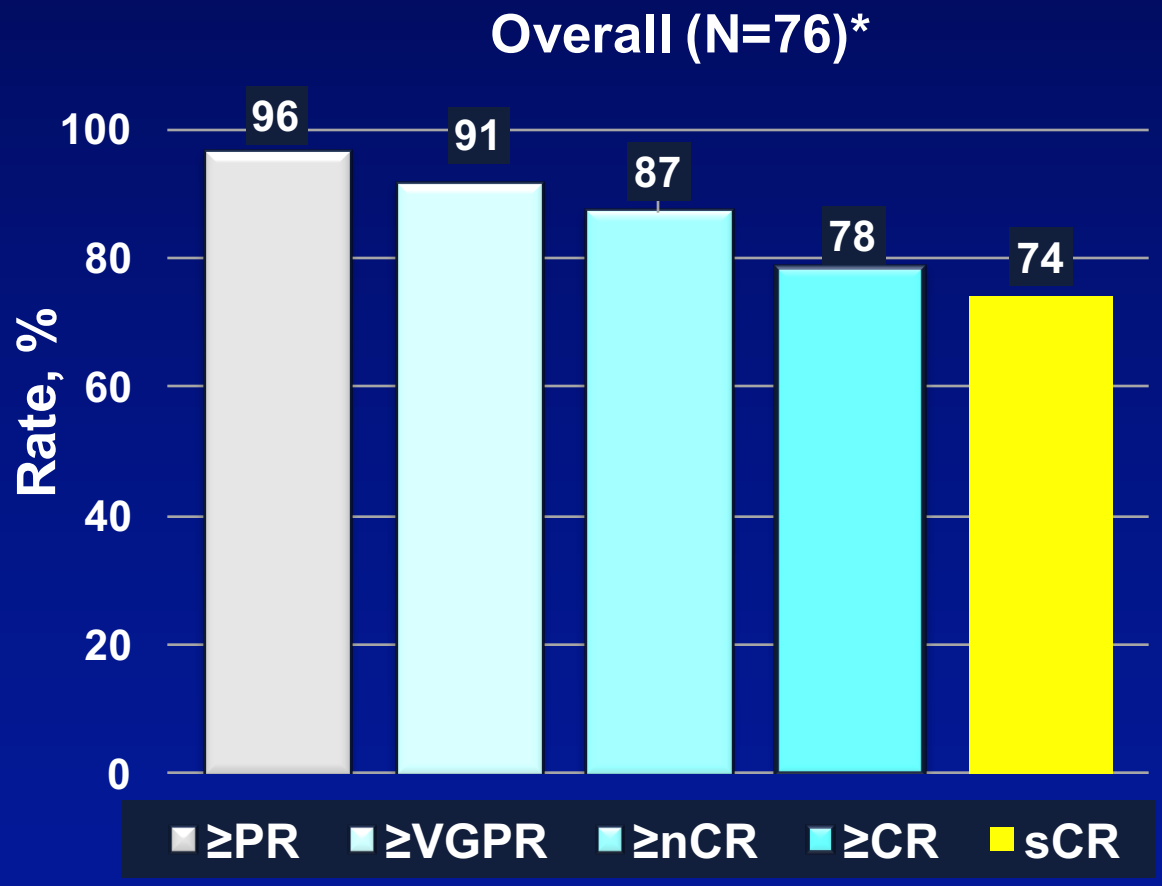
- ORR 93% after 4 cycles of RsqVD
  - CR 18%
  - VGPR 45%
  - PR 30%
- Favorable tolerability (all grade PN 40%, G3 < 5%)
- US/DFCI study underway – 42+ patients enrolled
- Correlatives collected and analyses pending

O'Gorman P, et al. *Blood.* 2016;128: Abstract 2117.

Final Results of a Phase 2 Trial of Extended Treatment With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Plus Autologous Stem Cell Transplant (ASCT) in Newly Diagnosed Multiple Myeloma; ASH 2016

Todd M. Zimmerman, Noopur Raje, Ravi Vij, Donna Reece, Jesus G. Berdeja, Leonor Stephens, Kathryn McDonnell, Cara A. Rosenbaum, Jagoda K. Jasielec, Paul Richardson, Sandeep Gurbuxani, Jennifer Nam, Erica Severson, Brittany Wolfe, Shaun Rosebeck, Andrew Stefka, Dominik Dytfeld, Kent Griffith, Andrzej J. Jakubowiak

Best Response



Median (range) follow-up 26.5 months (2.9-44.1)

*ITT

Conclusions

- KRd+ASCT shows high rates of deep responses in NDMM, with higher rates of sCR compared with KRd w/o ASCT
  - Pre-specified time point of 8 cycles 63% vs 30%
  - Best response 74% vs 55%
- KRd+ASCT treatment results in high rates of MRD (-) disease, up to 97% by MFC and 71% by NGS, which appear higher than with KRd w/o ASCT
- Deep responses with KRd+ASCT are associated with high rates of PFS and OS
  - 3-year PFS: 86% for all pts and 91% for MRD (-) pts
  - 3-year OS: 96% for all pts and 95% for MRD (-) pts
  - PFS trending higher for KRd+ASCT vs KRd w/o ASCT and OS appearing similar
- sCR, MRD (-), and PFS rates with KRd+ASCT are comparable in standard- and high-risk pts
- KRd regimen is generally well tolerated and ASCT does not appear to add significant toxicity
- KRd with and w/o ASCT in NDMM compares favorably with historical studies in NDMM, which requires confirmation in the randomized setting

Frontline Therapy with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Induction Followed By Autologous Stem Cell Transplantation, KRd Consolidation and Lenalidomide Maintenance in Newly Diagnosed Multiple Myeloma (NDMM) Patients:

Primary Results of the Intergroupe Francophone du Myélome (IFM) KRd Phase II Study – ASH 2016

NCT02405364

M. Roussel, V. Lauwers-Cances, N. Robillard, K. Belhadj, T. Facon, L. Garderet, M. Escoffre, B. Pegourie, L. Benboubker, D. Caillot, C. Fohrer, P. Moreau, X. Leleu, H. Avet-Loiseau, and M. Attal for the IFM

RESPONSE RATES at the completion of Consolidation

N=46	n	%
sCR	26	57
MRD - CMF	32	70
MRD - NGS	23/34	68
At least CR	28	61
At least VGPR	39	85
ORR	41	89
PD	1	2

4 patients were not evaluable due to toxicities

MRD CMF $10^{-4}/10^{-5}$
MRD NGS clonoSEQ Adaptive 10^{-6}

CARDIO-VASCULAR + PULMONARY TOXICITIES

all grades

25 CARDIAC AND VASCULAR EVENTS	Total	
	No of events	No of patients (%)
Cardiac Failure	2	2 (4)
Pulmonary Embolism	2	2 (4)
Venous Thrombosis	2	2 (4)
Intra Cardiac Thrombus	1	1 (2)
Superfical Thrombosis	8	8 (17)
Bradycardia	2	2 (4)
Arrhythmia	1	1 (2)
Atrial Fibrillation	1	1 (2)
Tachycardia	1	1 (2)
Hypertension	5	4 (9)
Cough	11	9 (20)
Dyspnea	5	5 (11)

CONCLUSIONS

Intensive program with 8 cycles of KRd as induction and consolidation before lenalidomide maintenance in NDMM pts

- **Highly effective with 61% of sCR+CR at the completion of consolidation**
- **Compared to our standard intensive program with RVD regimen, time to response is fast with 78% pts in VGPR or better at time of transplant (vs 50%)**
- **At the completion of consolidation, 70% pts achieved MRD negativity by Flow that is similar to RVD regimen**
- **In our study, safety was an issue: 4 pts did not receive transplant because of XS toxicities, mechanisms of cardio-vascular events need to be evaluated**

Primary Results from the Randomized Prospective Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network

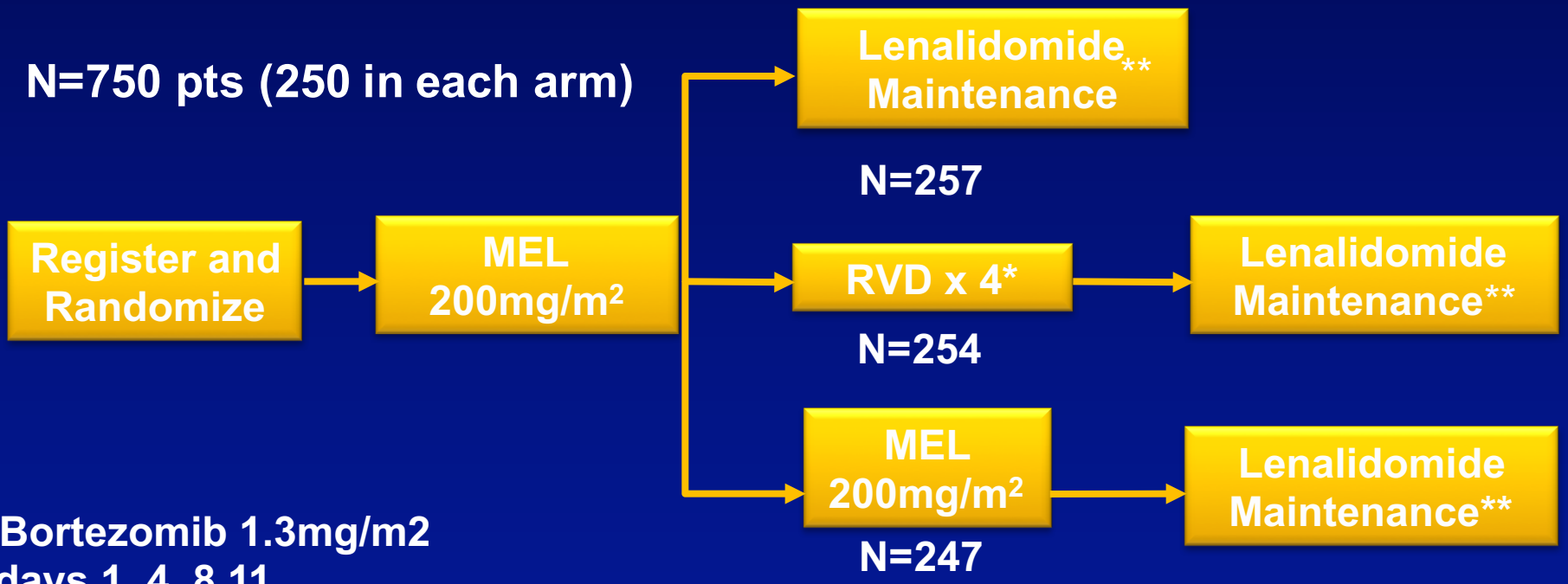
(BMT CTN 0702 – STaMINA Trial)

NCT#01109004

Autologous Hematopoietic Cell Transplant (AHCT), with and without Consolidation (with Bortezomib, Lenalidomide (Len) and Dexamethasone) and Len Maintenance versus Tandem AHCT and Len Maintenance for Up-Front Treatment of Patients with Multiple Myeloma

ASH 2016

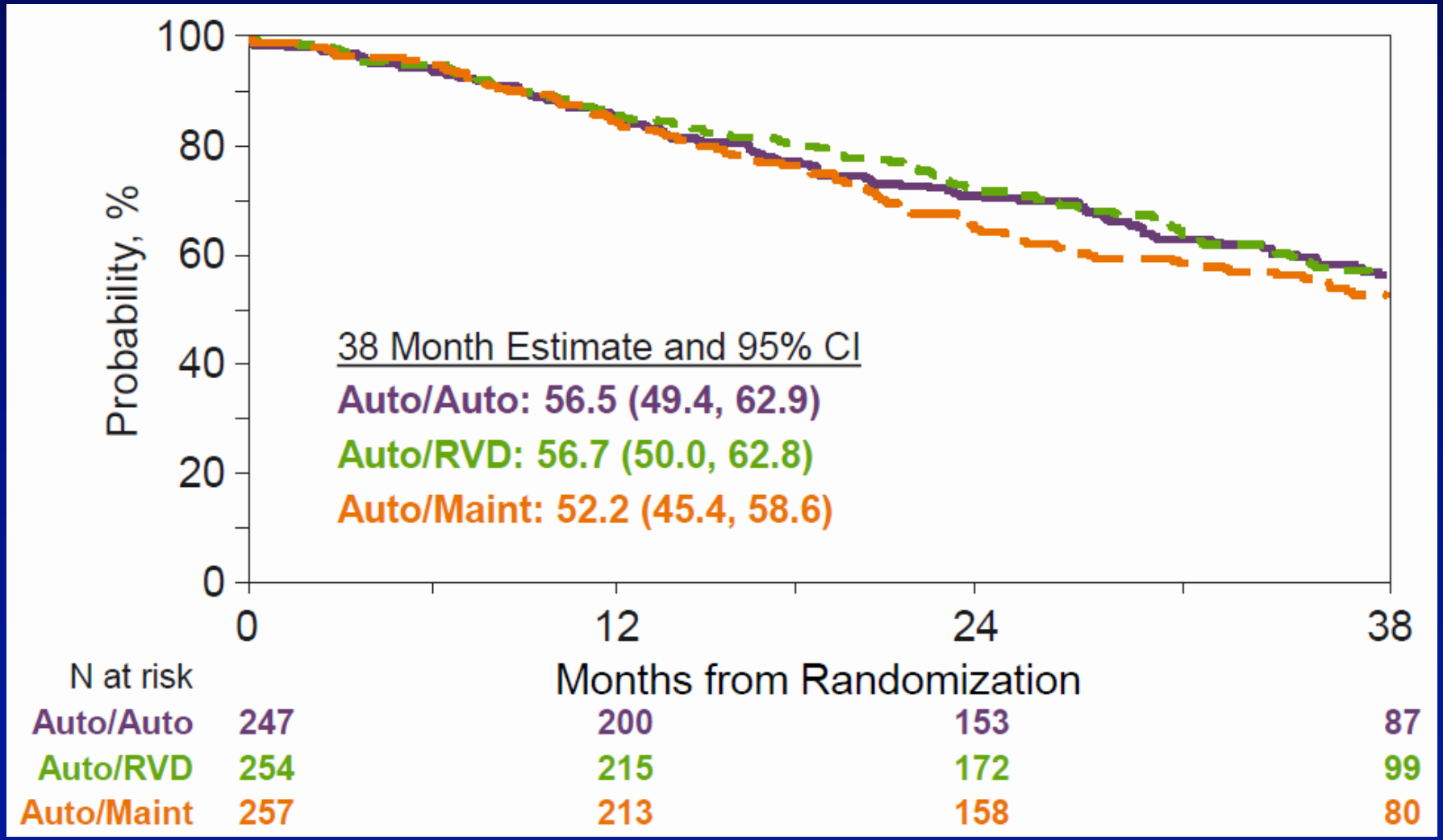
BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA



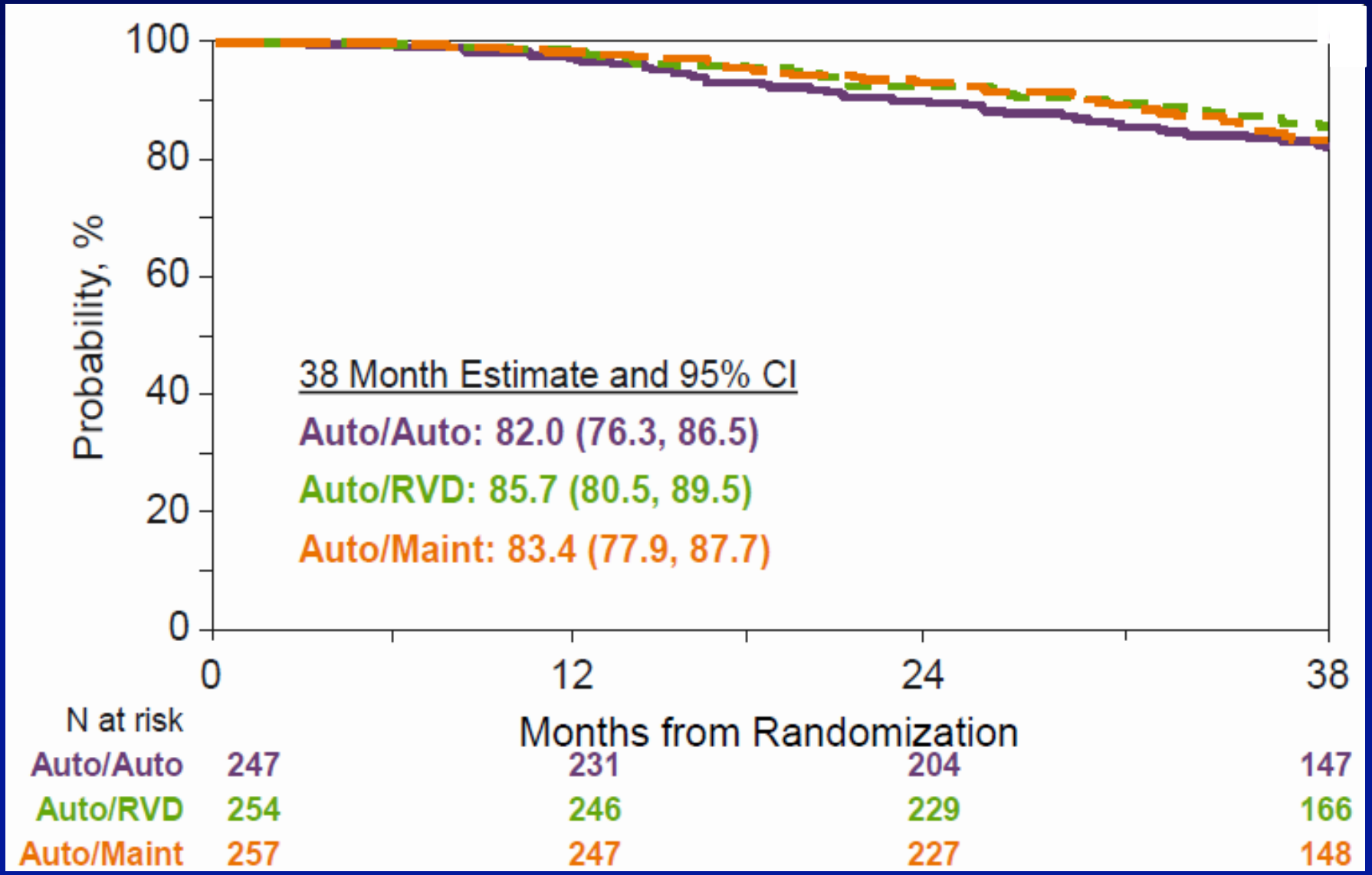
*Bortezomib 1.3mg/m2
days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3 years:
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

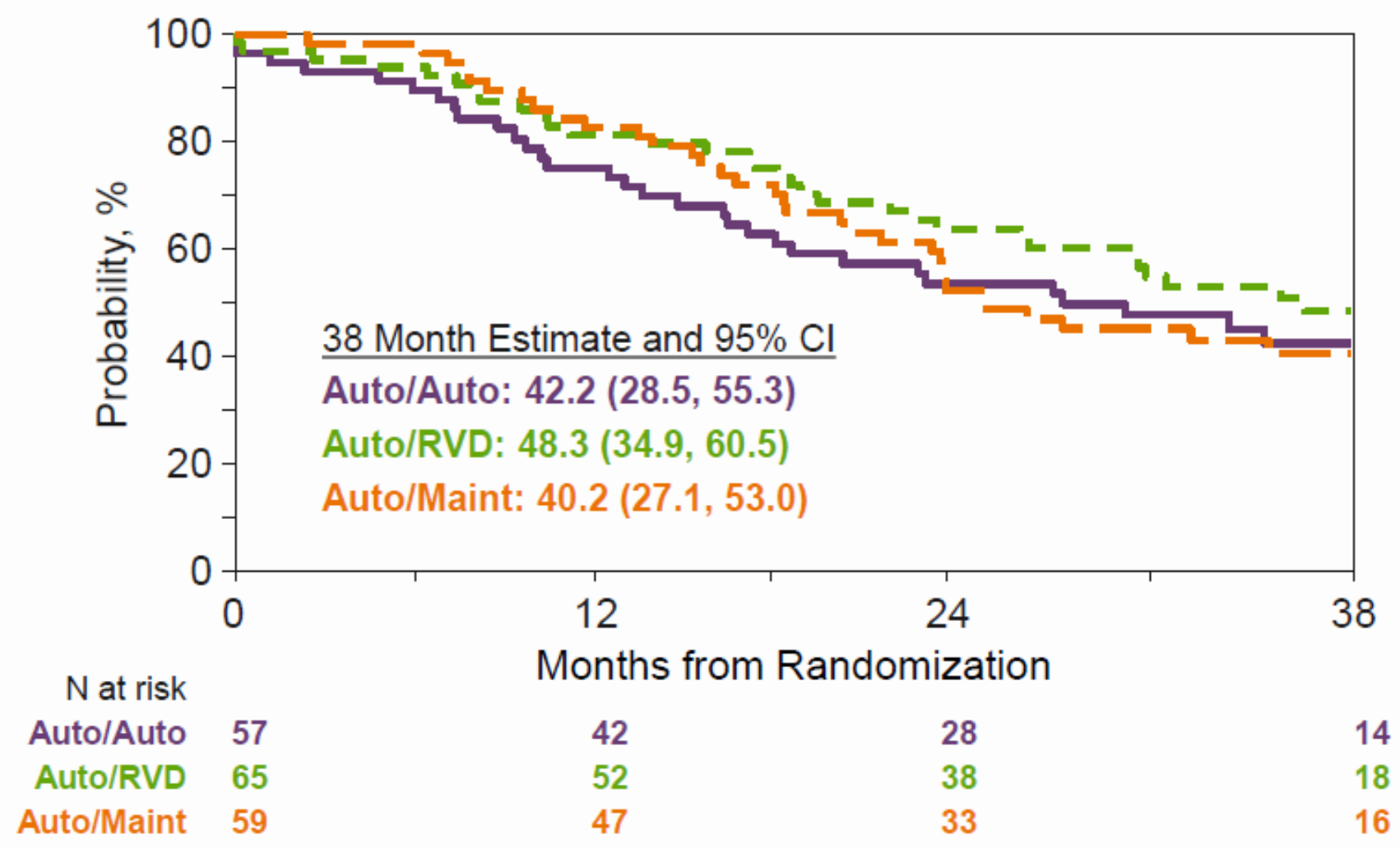
Primary Endpoint: Progression-free Survival



Overall Survival



Progression-free Survival –Patients with High Risk Multiple Myeloma



Preliminary Conclusions

- In the era of IMiD's and PI's used in the initial therapy for myeloma (in this study >90% either, >50% both) and the use of prolonged maintenance therapy with lenalidomide, neither post transplant consolidation nor a second transplant produce significant incremental PFS benefit.
- Longer Follow up needed for OS
- Possible benefit in the High risk group for RVD consolidation
- Compliance with and tolerability of second SCT appears less favorable

The NEW ENGLAND JOURNAL of MEDICINE

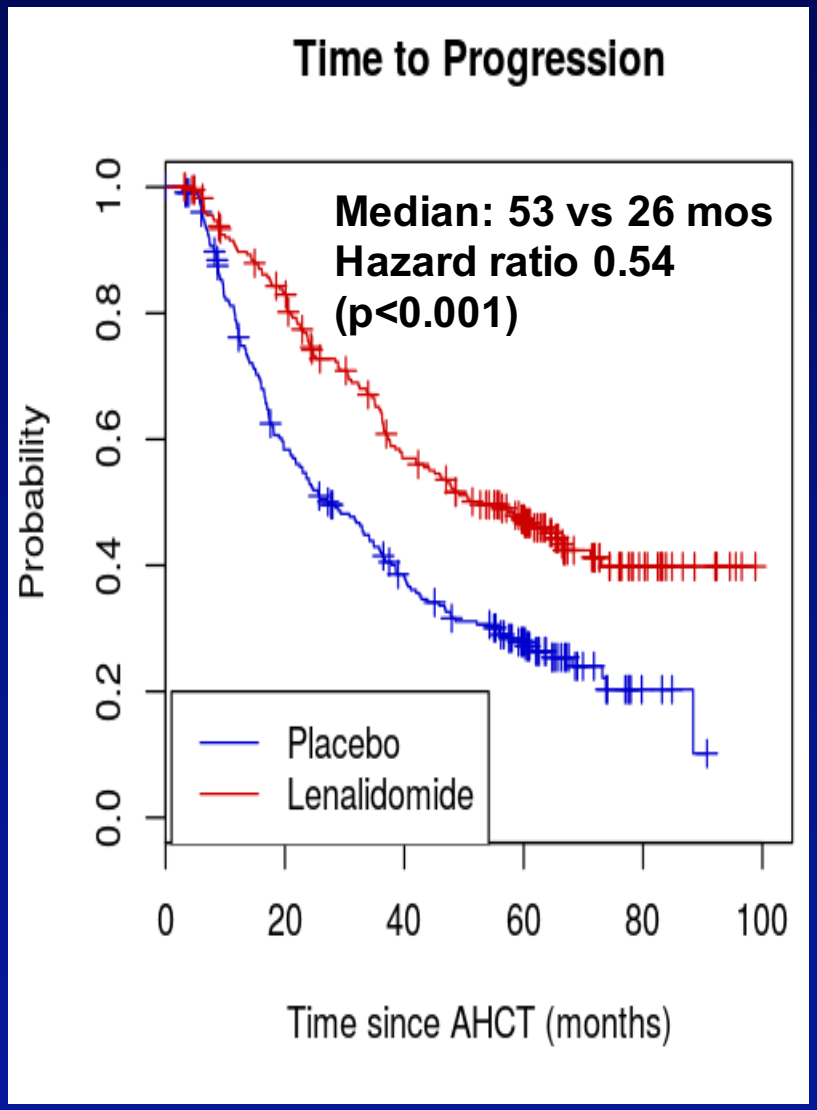
ORIGINAL ARTICLE

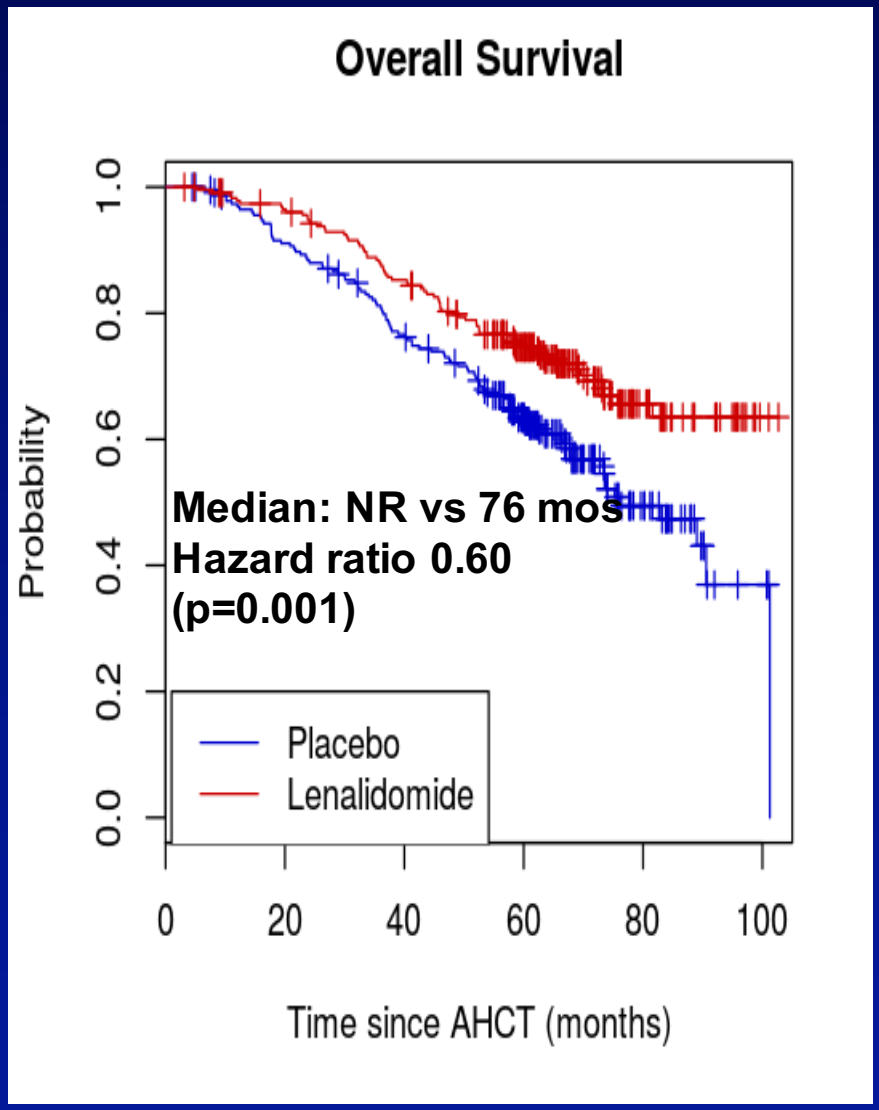
Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma

Philip L. McCarthy, M.D., Kouros Owzar, Ph.D., Craig C. Hofmeister, M.D., David D. Hurd, M.D., Hani Hassoun, M.D., Paul G. Richardson, M.D., Sergio Giralt, M.D., Edward A. Stadtmauer, M.D., Daniel J. Weisdorf, M.D., Ravi Vij, M.D., Jan S. Moreb, M.D., Natalie Scott Callander, M.D., Koen Van Besien, M.D., Teresa Gentile, M.D., Ph.D., Luis Isola, M.D., Richard T. Maziarz, M.D., Don A. Gabriel, M.D., Ph.D., Asad Bashey, M.D., Ph.D., Heather Landau, M.D., Thomas Martin, M.D., Muzaffar H. Qazilbash, M.D., Denise Levitan, M.D., Brian McClune, M.D., Robert Schlossman, M.D., Vera Hars, M.S., John Postiglione, B.A., Chen Jiang, Ph.D., Elizabeth Bennett, B.H.E., Susan Barry, B.A., Linda Bressler, Pharm.D., Michael Kelly, M.A., Michele Seiler, M.S., Cara Rosenbaum, M.D., Parameswaran Hari, M.D., Marcelo C. Pasquini, M.D., Mary M. Horowitz, M.D., Thomas C. Shea, M.D., Steven M. Devine, M.D., Kenneth C. Anderson, M.D., and Charles Linker, M.D.

N Engl J Med. 2012 May 10;366(19):1770-81.

Lenalidomide Improves TTP and OS





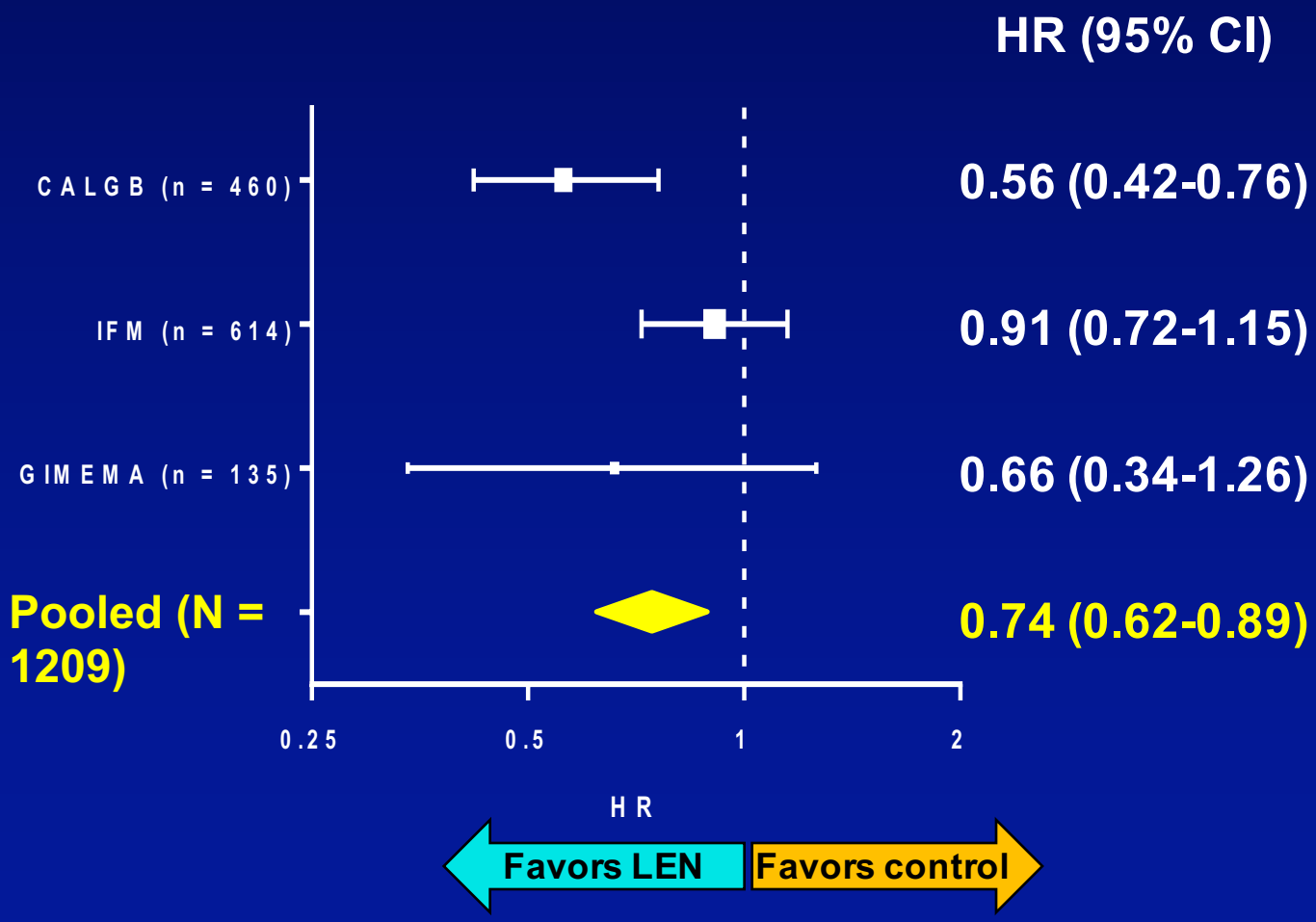
Holstein et al ASCO 2015; Intent-to-treat analysis, data cut-off Nov 2014

Lenalidomide Maintenance After High-Dose Melphalan and Autologous Stem Cell Transplant in Multiple Myeloma: A Meta-Analysis of Overall Survival: ASCO 2016

Michel Attal,[1] Antonio Palumbo,[2] Sarah A. Holstein,[3] Valérie Lauwers-Cances,[1] Maria Teresa Petrucci, [4] Paul Richardson,[5] Cyrille Hulin,[6] Patrizia Tosi,[7] Kenneth C. Anderson,[5] Denis Caillot,[8] Valeria Magarotto,[9] Philippe Moreau,[10] Gerald Marit,[11] Zhinuan Yu,[12] Philip L. McCarthy[13]

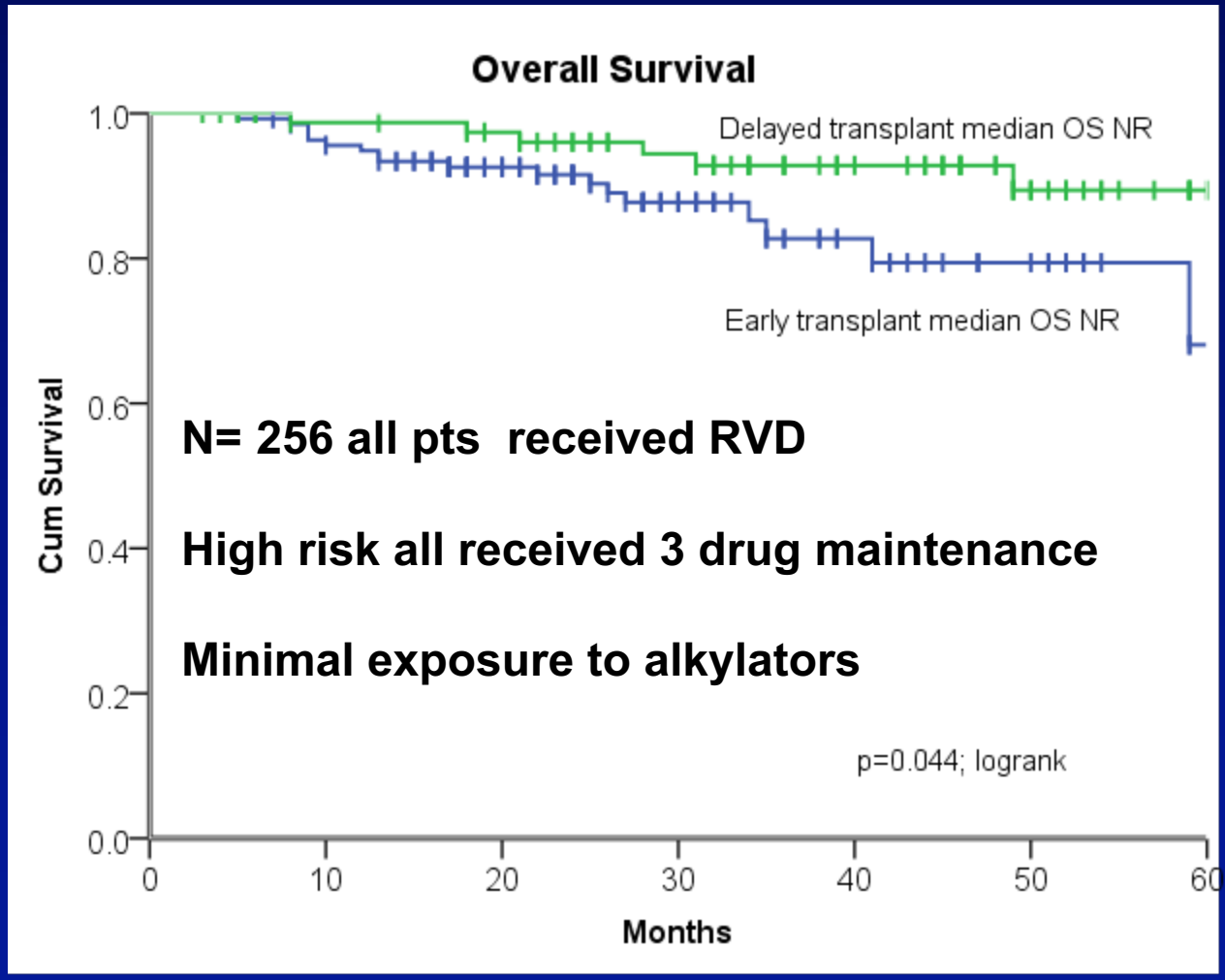
[1]Institut Universitaire du Cancer , Toulouse-Oncopole, France; [2]The Myeloma Unit, Department of Hematology, University of Turin, Turin, Italy; [3]Roswell Park Cancer Institute, Buffalo, NY; [4]University La Sapienza, Rome, Italy; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Bordeaux Hospital University Center (CHU), Bordeaux, France; [7]Seràgnoli Institute of Hematology and Medical Oncology, Bologna University, Bologna, Italy; [8]Dijon University Hospital Center, Dijon, France; [9]University of Torino, Torino, Italy; [10]University Hospital Hôtel-Dieu, Nantes, France; [11]Centre Hospitalier Universitaire, Bordeaux, France; [12]Celgene Corporation, Summit, NJ; [13]Blood and Marrow Transplant Program, Roswell Park Cancer Institute, Buffalo, NY

Overall Survival: Hazard Ratios



- The size of the box is related to the size of the individual study. The confidence interval is a function of the overall sample size. HR, hazard ratio.

Early Versus Late Transplant



Nooka et al, *Leukemia* 2014

DETERMINATION

DFCI 10-106 / IFM DFCI 2009 / BMT CTN 1304

Delayed vs. Early Transplant with Revlimid Maintenance and Antimyeloma Triple therapy

Objectives

1) Compare progression-free survival between Arm A and Arm B for patients with newly diagnosed symptomatic MM
2) Evaluate the impact of lenalidomide maintenance given until progression

Eligibility

Multiple myeloma diagnosis based on IMF 2003 Diagnostic Criteria
Diagnostic assessments w/in 21 days of protocol therapy
Age 18 to 65 years

REGISTRATION

INITIAL THERAPY
Lenalidomide+ bortezomib + dexamethasone (RVD)
1 Cycle (21 days)

RANDOMIZATION
Stratify according to:
- ISS stage (stage I, II or III)
- Cytogenetics: standard vs. high-risk vs FISH failures. High-risk is defined as presence of del(17p), or t(4:14), or t(14;16) using FISH.

ARM A

- **RVD q 21 days (2 cycles)**
- **Collection of peripheral blood stem cells (PBSCs)** using cyclophosphamide and filgrastim or G-CSF type Granocyte® or equivalent
- **RVD q 21 days (5 cycles)**
- **Maintenance Lenalidomide** q28 days (until disease progression)

ARM B

- **RVD q 21 days (2 cycles)**
- **Collection of peripheral blood stem cells (PBSCs)** using cyclophosphamide and filgrastim or G-CSF type Granocyte® or equivalent
- **Autologous stem cell transplant**
  - Melphalan: infused over two days or as a single infusion
  - Re-infusion of PBSCs
- **RVD q 21 days (2 cycles)**
- **Maintenance Lenalidomide** q28 days (until disease progression)

- ***Study treatment provided free of charge to all study participants***
- ***BMT CTN accrual credit provided to all BMT CTN centers***

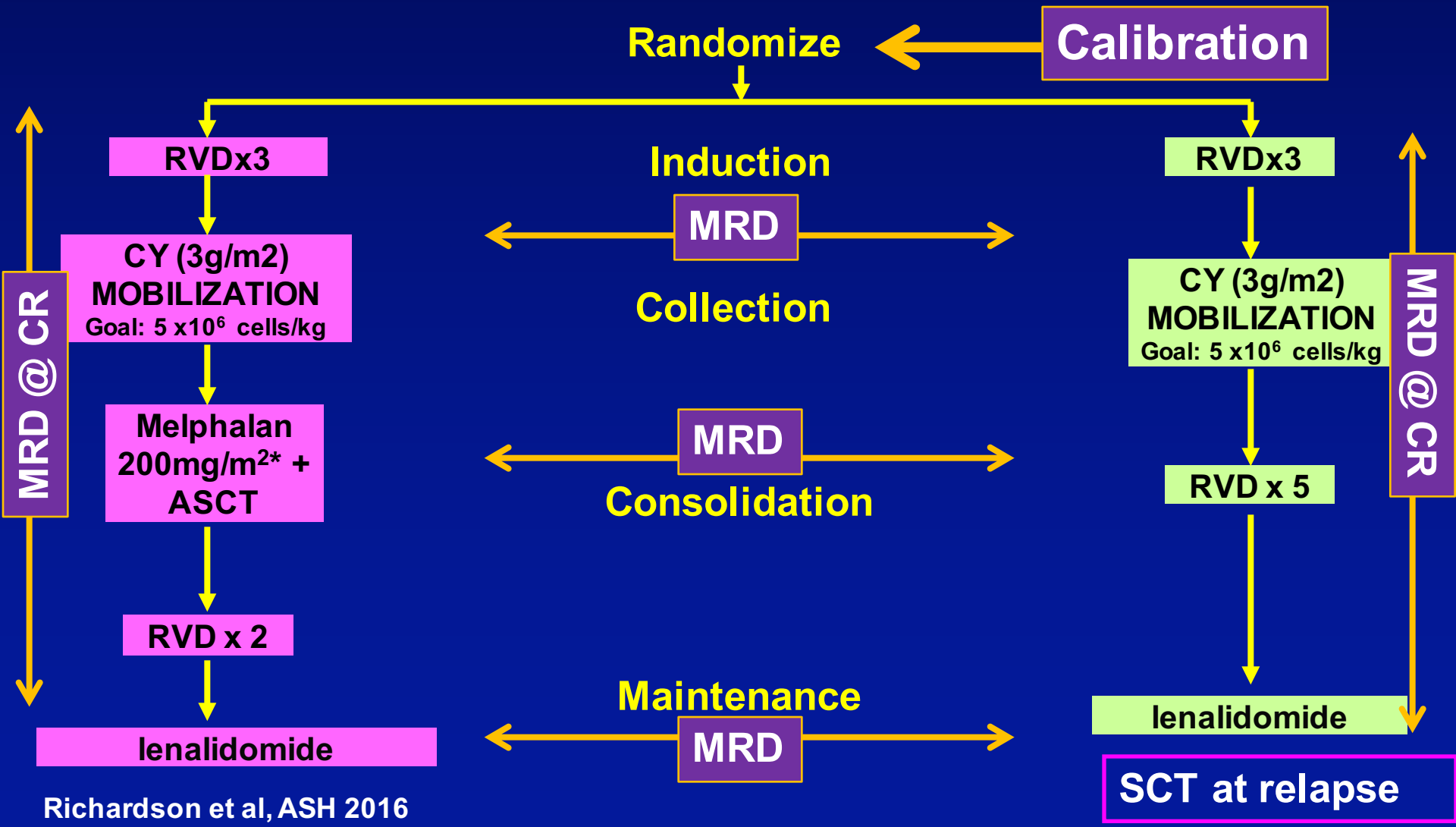
Protocol Chair: PG Richardson: paul_richardson@dfci.harvard.edu
Protocol Coordinator: A Zeytoonjian: andreaA_zeytoonjian@dfci.harvard.edu
BMT CTN Project Manager: Ann Foley, MA, CCRP: afoley@nmdp.org

To view the entire protocol, go to www.bmtctn.net Posted to http://clinicaltrials.gov/ as NCT01208662

DANA-FARBER CANCER INSTITUTE

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IFM/DFCI 2009 Study (US and France)
Newly Diagnosed MM (N=1,420)



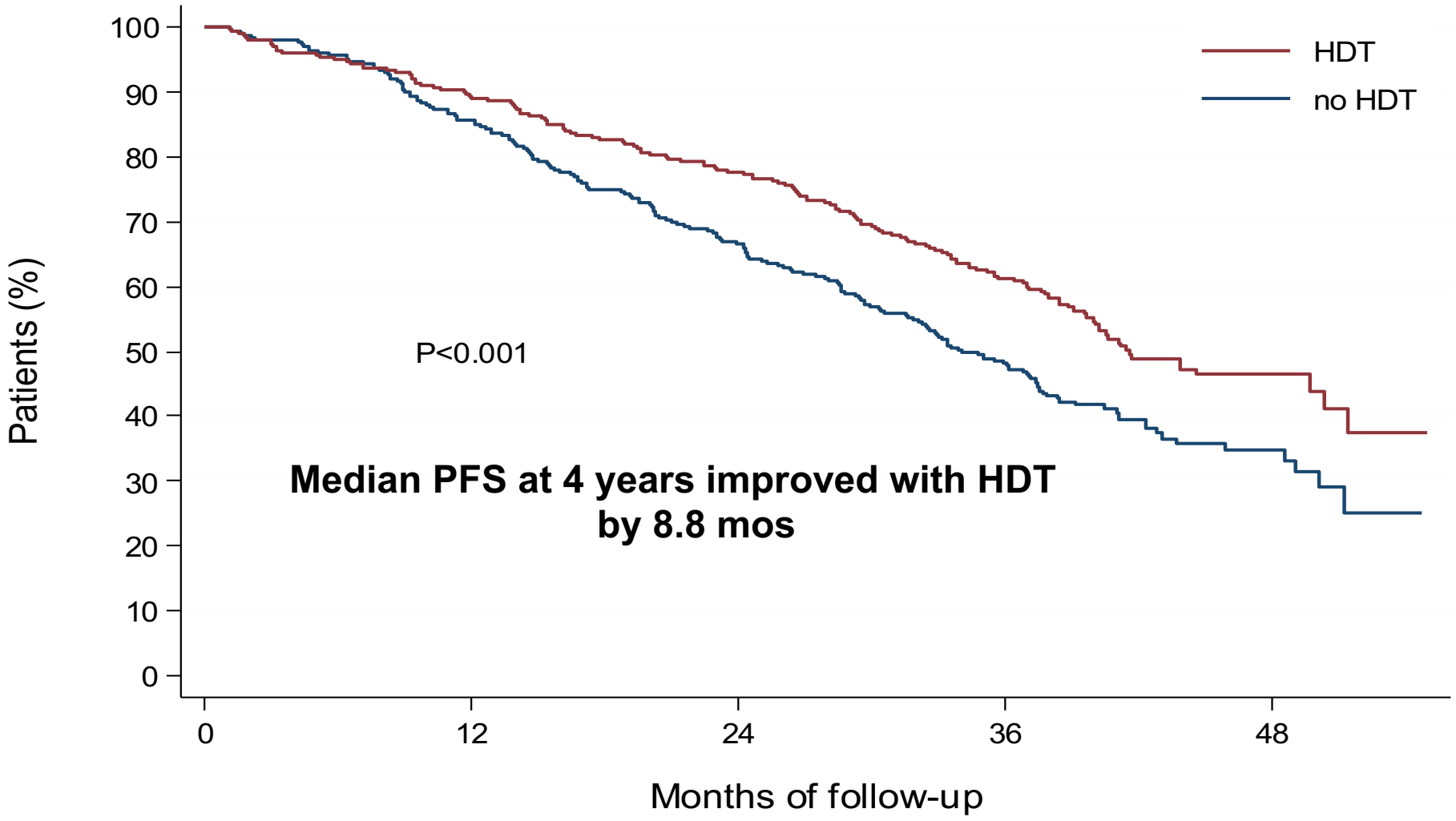
Richardson et al, ASH 2016

ASH 2015: IFM 2009: Best Response

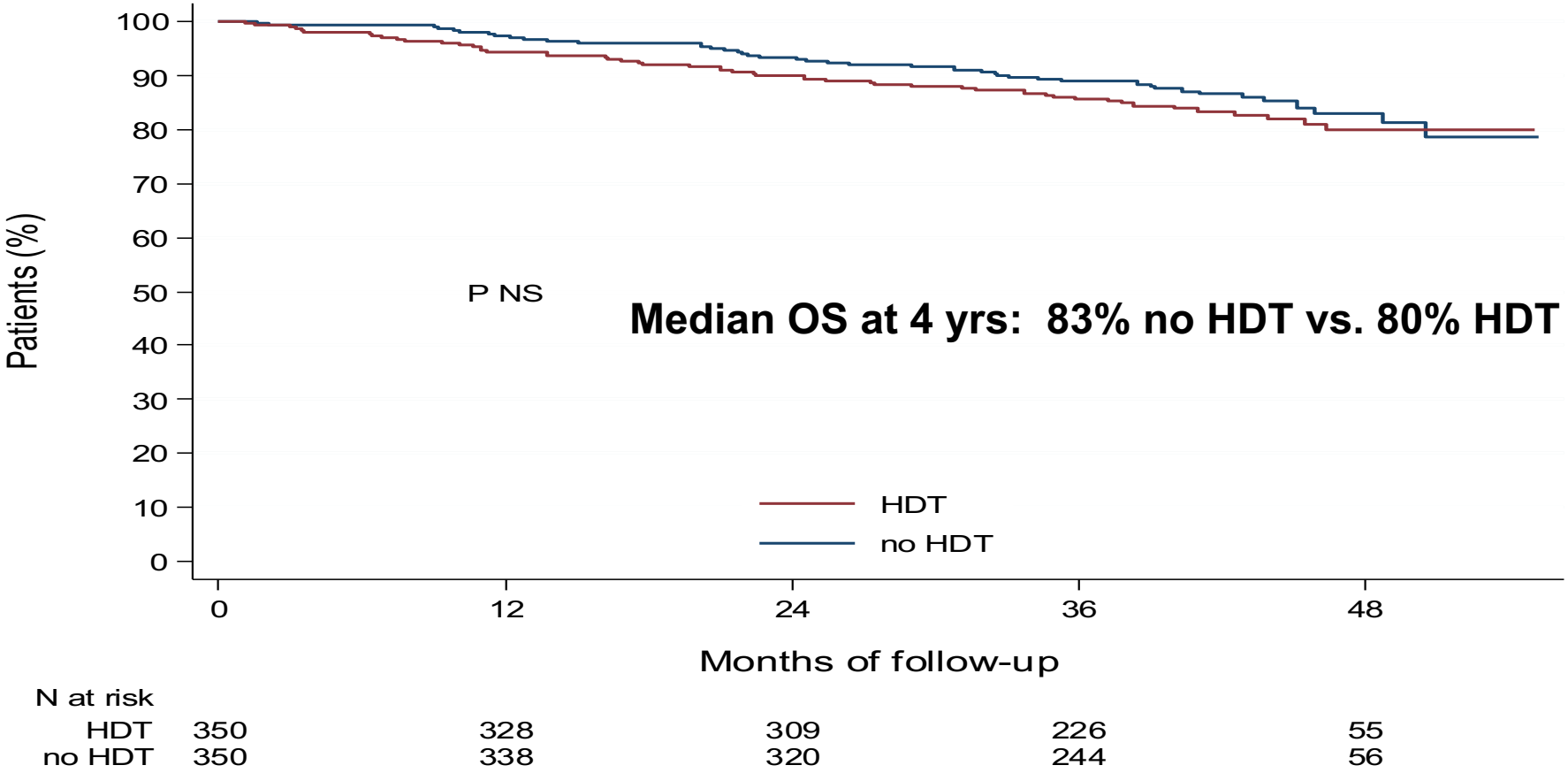
	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

Attal et al, *NEJM* 2017 (in press)

ASH 2015 (Attal et al): IFM 2009: PFS (9/2015)



IFM 2009: OS (9/2015)



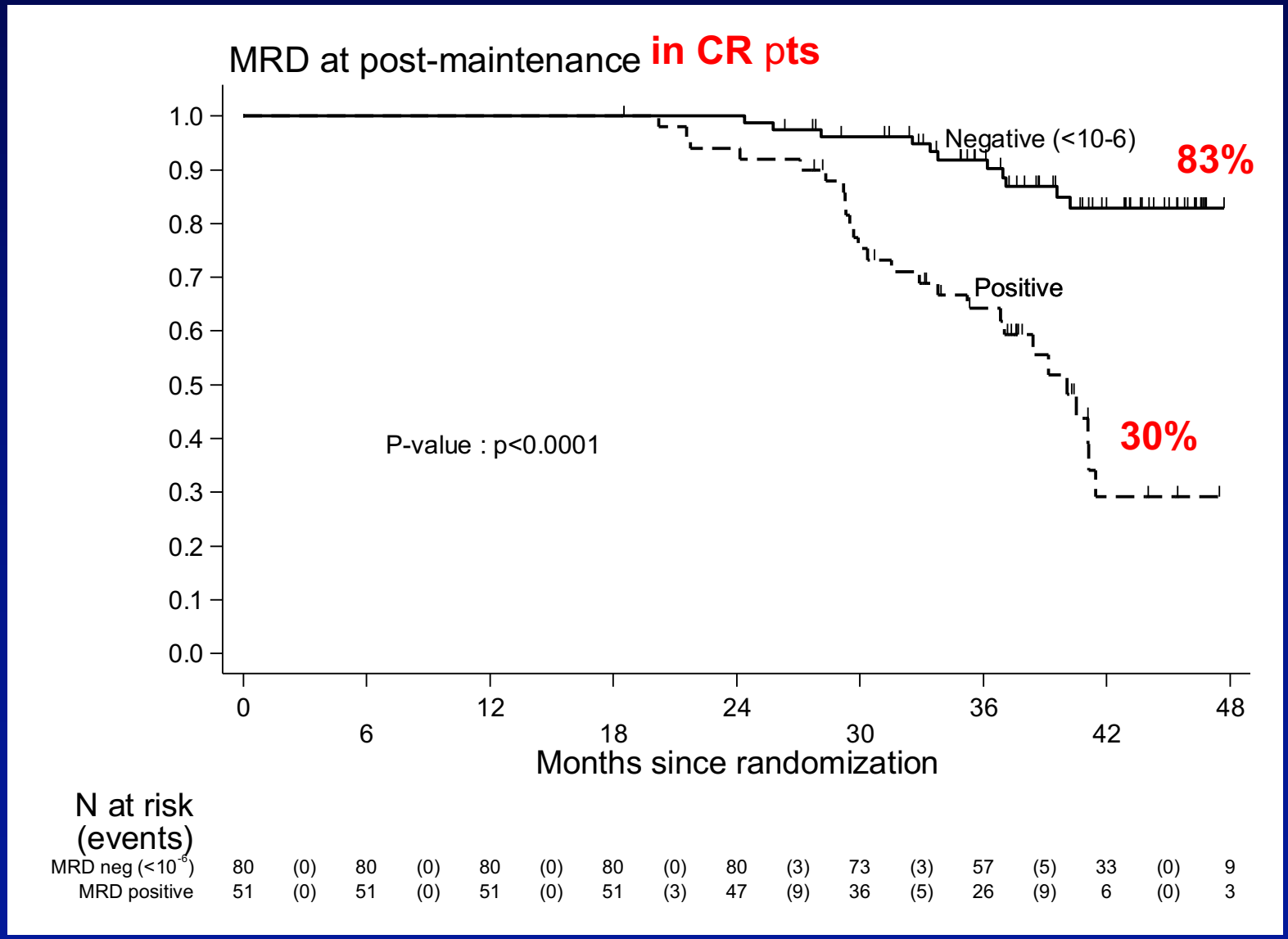
Attal et al, *NEJM* 2017 (in press)

ASH 2015: IFM 2009: Causes of Mortality (9/2015)

	RVD arm N=48	Transplant N=54
Myeloma, n (%)	40/48 (83%)	35/54 (65%)
Toxicity, n (%)	4/48 (8%)	9/54 (16%)
SPM (AML/MDS)	1/48 (2%)	6/54 (11%)
Others	3/48 (6%)	4/54 (7%)

Attal et al, *NEJM* 2017 (in press)

IFM DFCI 2009 update - 375 CR/sCR, 131 MRD pts



Avet-Loiseau et al, ASH 2015; Attal et al, *NEJM* 2017 (in press)

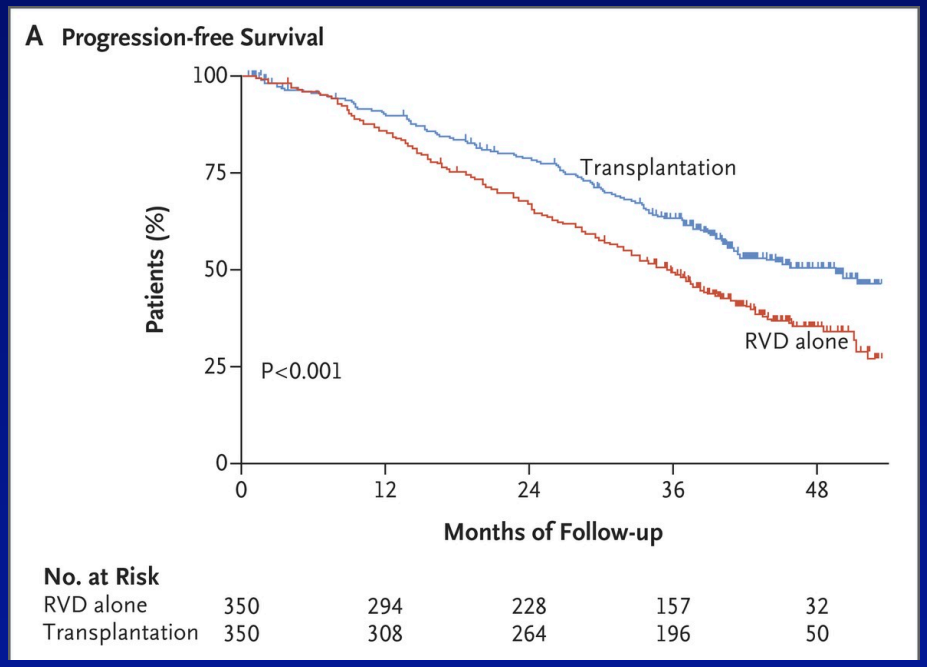
The NEW ENGLAND JOURNAL of MEDICINE

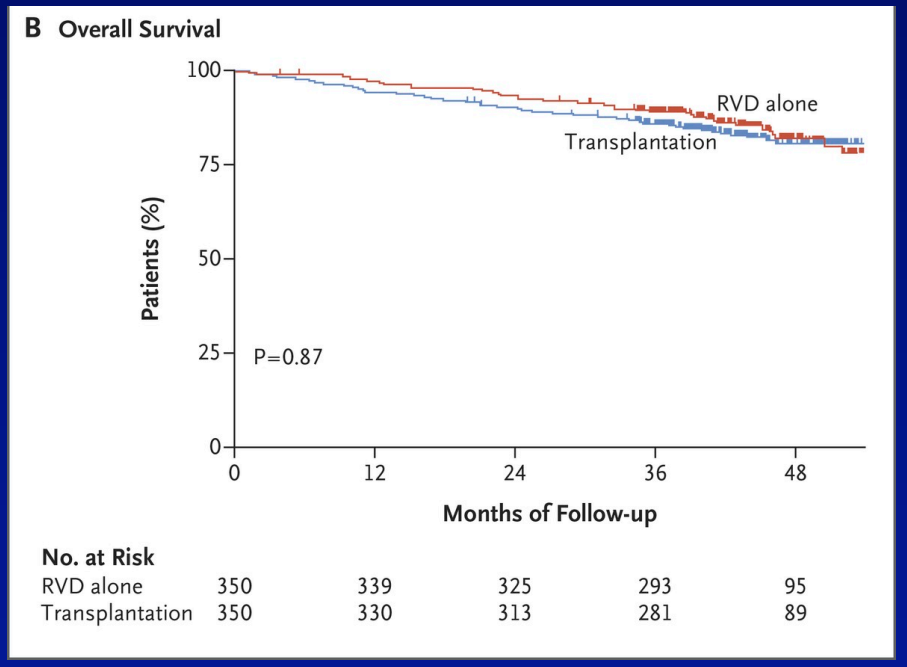
ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study*

Kaplan–Meier Curves for Progression-free Survival and Overall Survival





Attal M et al. N Engl J Med 2017;376:1311-1320

Response to Treatment

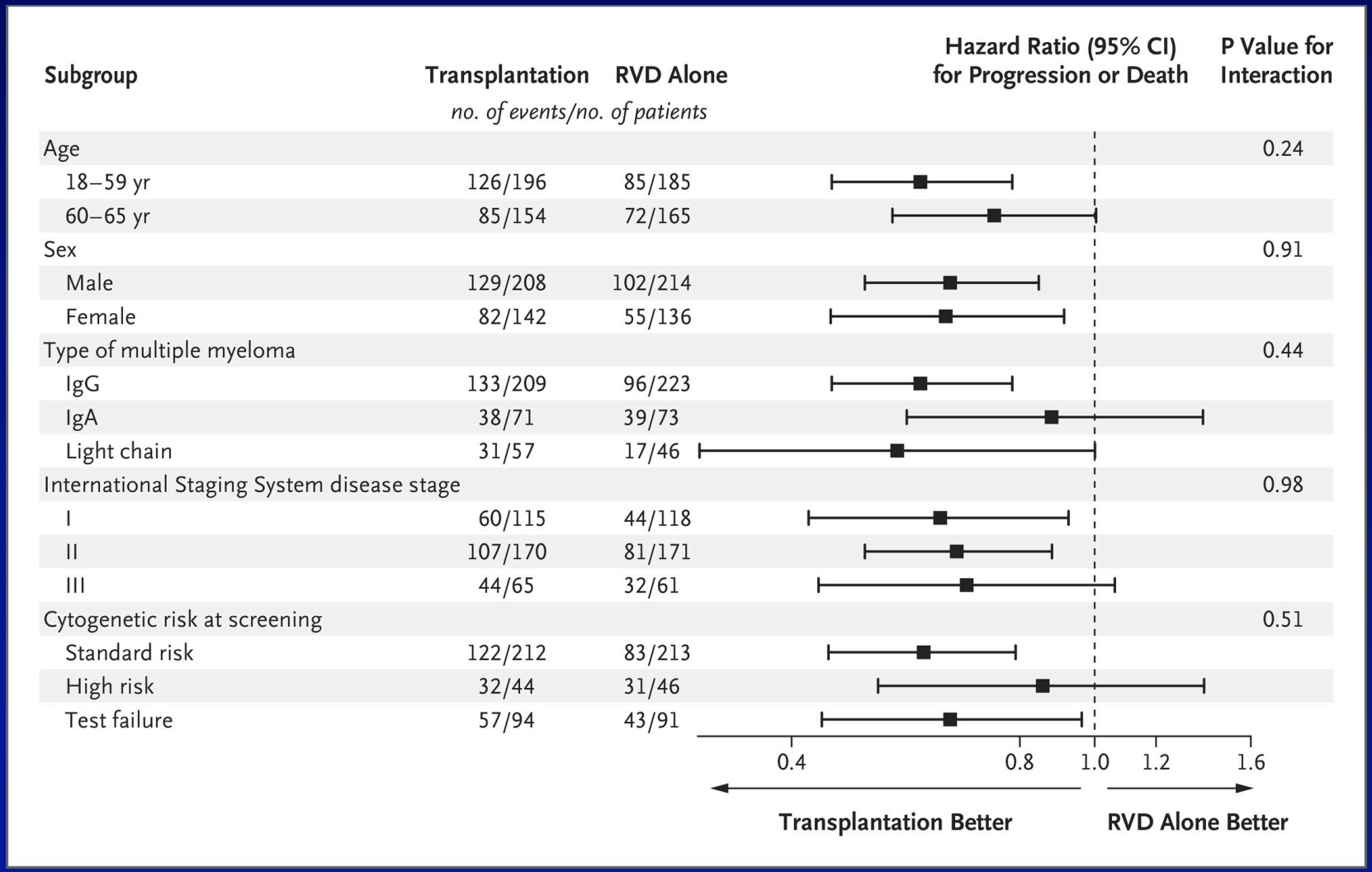
Table 2. Response to Treatment.*

Outcome	RVD-Alone Group (N=350)	Transplantation Group (N=350)	Adjusted P Value†
Best response during the study — no. (%)			0.02
Complete response	169 (48)	205 (59)	
Very good partial response	101 (29)	102 (29)	
Partial response	70 (20)	37 (11)	
Stable disease	10 (3)	6 (2)	
Complete response — no. (%)	169 (48)	205 (59)	0.03
Complete response or very good partial response — no. (%)	270 (77)	307 (88)	0.001
Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
‡ Minimal residual disease was detected by means of flow cytometry. As a result of decisions made by the patient or the investigator, 5 patients in the RVD-alone group and 29 patients in the transplantation group were not tested.

Attal M et al. N Engl J Med 2017;376:1311-1320

Subgroup Analyses of Progression-free Survival



Attal M et al. N Engl J Med 2017;376:1311-1320

Baseline Characteristics of the Patients Who Underwent Randomization

Table 1. Baseline Characteristics of the Patients Who Underwent Randomization.*

Characteristic	RVD-Alone Group (N=350)	Transplantation Group (N=350)
Country — no. (%)		
France	343 (98)	345 (99)
Belgium	6 (2)	5 (1)
Switzerland	1 (<1)	0
Age — yr		
Median	59	60
Range	29–66	30–66
Male sex — no. (%)	208 (59)	214 (61)
Type of myeloma — no. (%)		
IgG	209 (60)	223 (64)
IgA	71 (20)	73 (21)
Light chain	57 (16)	46 (13)
Other	13 (4)	8 (2)
International Staging System disease stage — no. (%)		
I	115 (33)	118 (34)
II	170 (49)	171 (49)
III	65 (19)	61 (17)
Serum β_2-microglobulin level — no. (%)		
<3.5 mg/liter	169 (48)	178 (51)
3.5–5.5 mg/liter	116 (33)	111 (32)
>5.5 mg/liter	65 (19)	61 (17)
Cytogenetic abnormalities — no./total no. of patients who could be evaluated†		
t(4;14) translocation	26/256	28/259
17p deletion	15/256	16/258
t(14;16) translocation	6/256	6/258
t(4;14) or t(14;16) translocation or 17p deletion	44/256	46/259

* RVD therapy consists of lenalidomide, bortezomib, and dexamethasone. Percentages may not total 100 because of rounding.
† Data were obtained by means of fluorescence in situ hybridization. Patients could have more than one abnormality. For technical reasons, 94 patients in the RVD-alone group and 91 patients in the transplantation group could not be evaluated. Also, for technical reasons or because of an insufficient number of plasma cells, 1 additional patient in the transplantation group could not be evaluated for the 17p deletion, and 1 for the t(14;16) translocation.

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Response to Treatment

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Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡	171/265 (65)	220/278 (79)	<0.001

* Responses were assessed according to the International Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† P values were adjusted for multiplicity with the use of the Holm procedure to control the family-wise error rate at 0.05.
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Grade 3 and 4 Adverse Events That Occurred in At Least 2% of Patients.

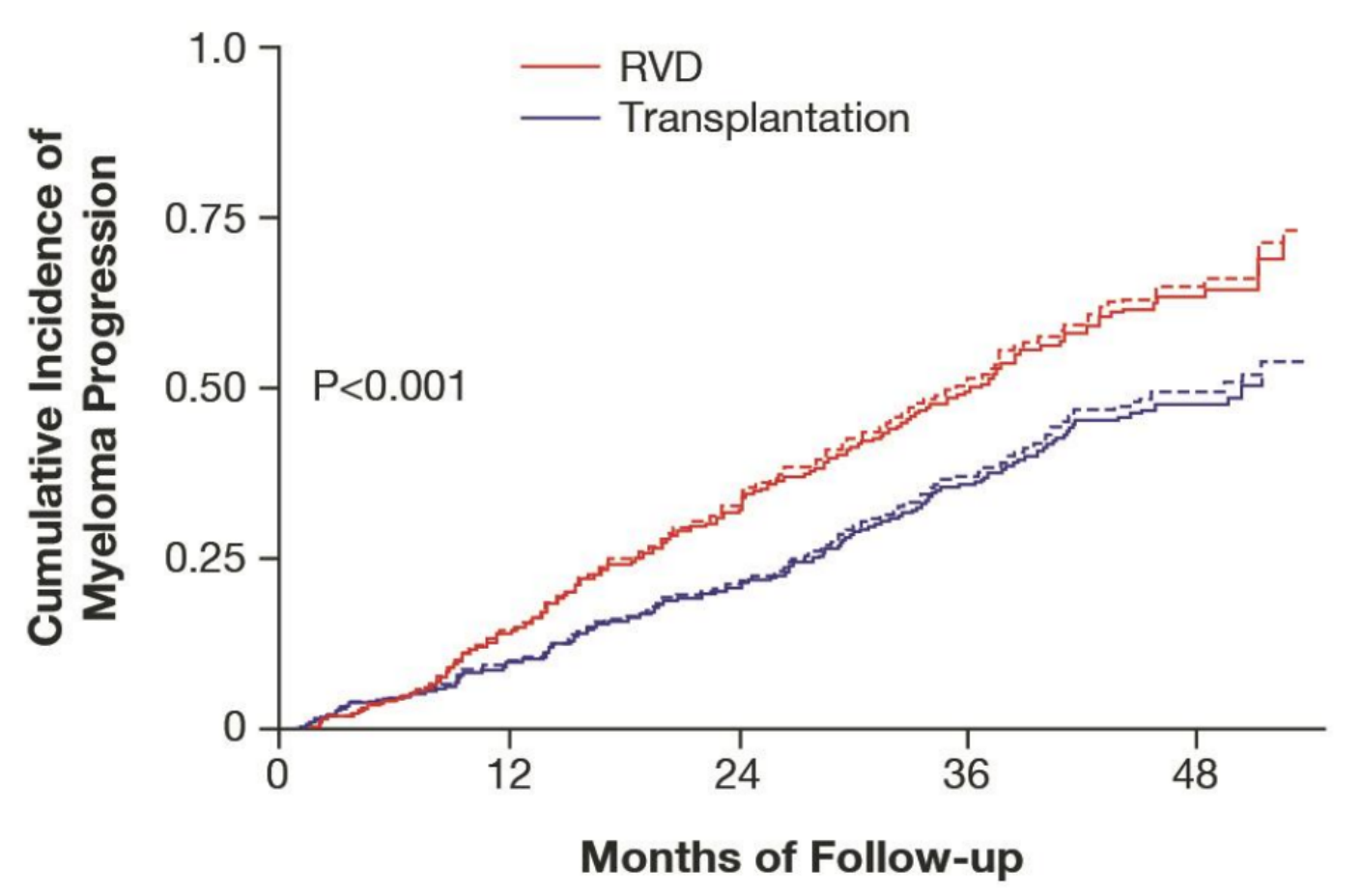
Table 3. Grade 3 and 4 Adverse Events That Occurred in At Least 2% of Patients.

Event	RVD-Alone Group (N=350)	Transplantation Group (N=350)
	number (percent)	
Any event	292 (83.4)	340 (97.1)
Blood and lymphatic system disorders	223 (63.7)	332 (94.9)
Neutropenia	166 (47.4)	322 (92.0)
Febrile neutropenia	12 (3.4)	52 (14.9)
Anemia	31 (8.9)	69 (19.7)
Thrombocytopenia	50 (14.3)	291 (83.1)
Gastrointestinal disorders	24 (6.9)	97 (27.7)
Nausea and vomiting	5 (1.4)	25 (7.1)
Stomatitis	0	59 (16.9)
Diarrhea	10 (2.9)	15 (4.3)
Hepatobiliary disorders	14 (4.0)	16 (4.6)
Cytolytic hepatitis	11 (3.1)	7 (2.0)
General disorders	22 (6.3)	30 (8.6)
Fatigue	7 (2.0)	6 (1.7)
Pyrexia	1 (0.3)	13 (3.7)
General deterioration of physical health	7 (2.0)	2 (0.6)
Infections	31 (8.9)	71 (20.3)
Respiratory tract infection	14 (4.0)	23 (6.6)
Sepsis	6 (1.7)	18 (5.1)
Nervous system disorders	48 (13.7)	59 (16.9)
Peripheral neuropathy	42 (12.0)	45 (12.9)
Grade 2 painful neuropathy	3 (0.9)	8 (2.3)
Skin disorders	18 (5.1)	11 (3.1)
Rash	7 (2.0)	4 (1.1)
Vascular disorders	11 (3.1)	14 (4.0)
Deep-vein thrombosis	5 (1.4)	10 (2.9)
Any thromboembolic event*	13 (3.7)	19 (5.4)

* Thromboembolic events include deep-vein thrombosis, pulmonary embolism, ischemic cardiopathy, and ischemic stroke.

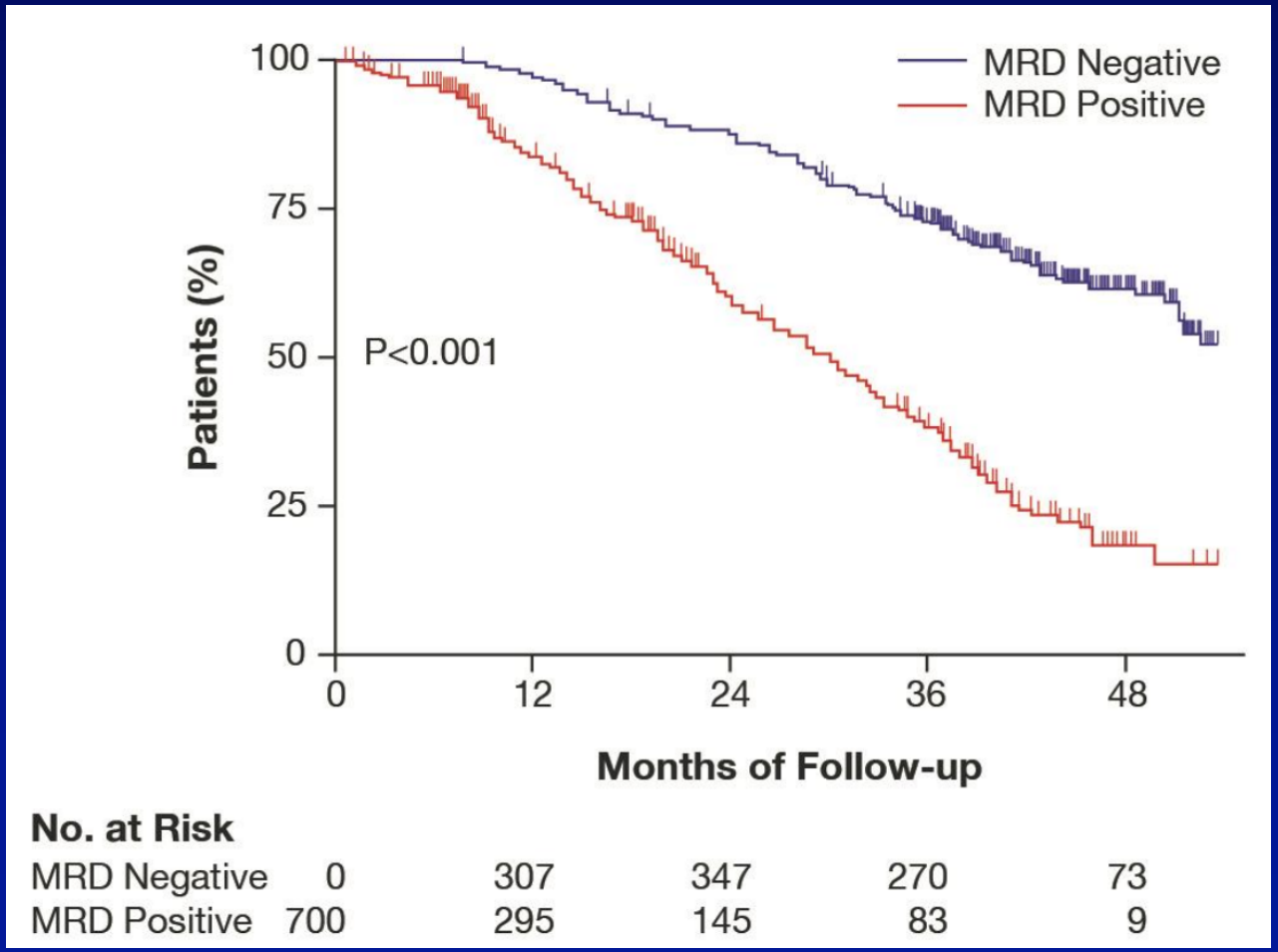
Attal M et al. N Engl J Med 2017;376:1311-1320

Cumulative Incidence of Myeloma Progression by Treatment Arm using the Kaplan-Meier Approach Without Accounting for Competing Risk Events (Dashed Lines) and Cumulative Incidence After Adjusting for Competing Risk Events (Solid Lines)



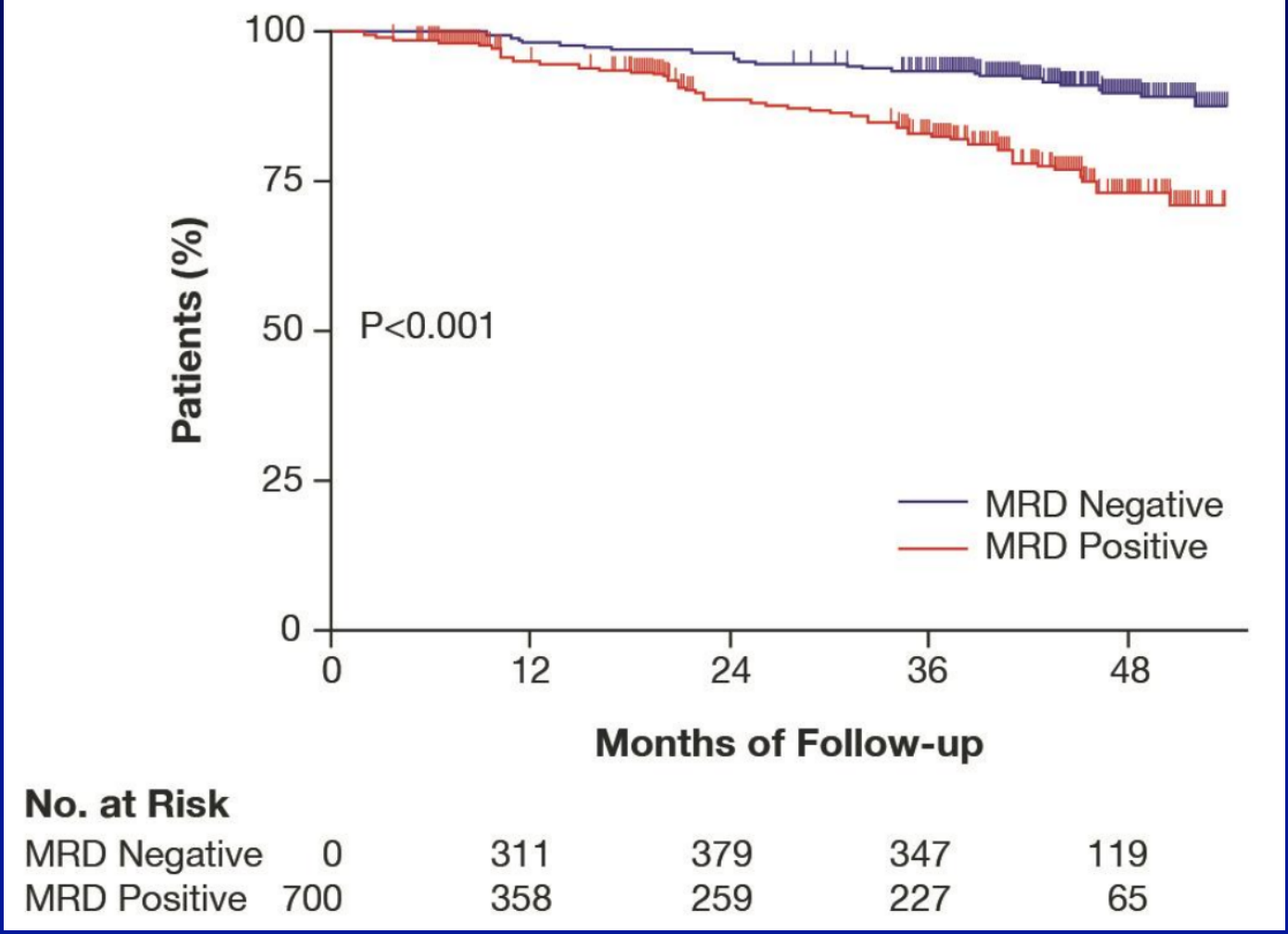
Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-54.
Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.

Kaplan-Meier Curves for Progression-free Survival According to Minimal Residual Disease (MRD) Status



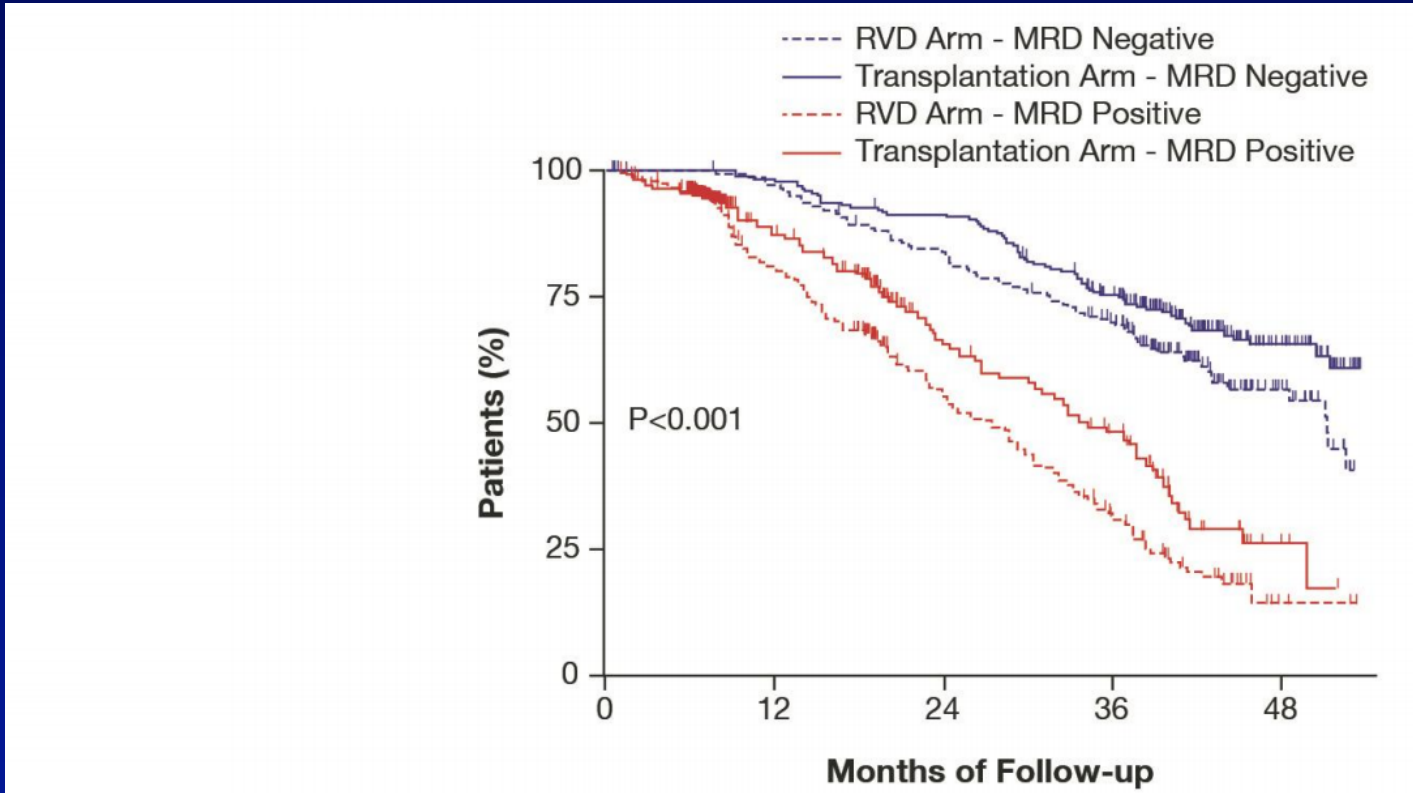
Progression-free survival was prolonged in patients who were MRD negative versus those who were MRD positive (adjusted hazard ratio, 0.30; 95% confidence interval, 0.23 to 0.37;

Kaplan-Meier Curves for Overall Survival According to Minimal Residual Disease (MRD) Status



Overall survival was prolonged in patients who were MRD negative versus those who were MRD positive (adjusted hazard ratio, 0.34; 95% confidence interval, 0.22 to 0.51;

Kaplan-Meier Curves for Progression-free Survival according to Minimal Residual Disease (MRD) Status and Treatment Arm



No. at Risk					
RVD Arm – MRD Negative	0	136	145	115	28
Transplantation Arm – MRD Negative	0	171	202	155	45
RVD Arm – MRD Positive	350	158	83	42	4
Transplantation Arm – MRD Positive	350	137	62	41	5

Regardless of MRD status, progression-free survival was prolonged in the transplantation group versus the RVD group (adjusted hazard ratio, 0.72; 95% confidence interval, 0.58 to 0.88; P< 0.001). The interaction between treatment group and MRD status was not significant (P=0.852 for interaction; P=1.00 after multiple adjustment correction).

Salvage therapy

	RVD Group (N = 350)	Transplantation Group (N = 350)	Total (N = 700)
Second-line therapy for symptomatic progression— n	172	123	295
Pomalidomide-based	61	53	114
Lenalidomide-based	3	4	7
Bortezomib-based	72	47	119
Alternative novel agent-based	5	4	9
Conventional chemotherapy	31	15	46
Second-line therapy followed by salvage transplantation— n (%)	136 (79)	21 (17)	157 (53)

Updated Analysis of the Types of Lesions in Patients with at Least One Second Primary Malignancy (SPM) as of September 2016.

	RVD Group (N = 350)	Transplantation Group (N = 350)	Total (N = 700)
Patients with at least one SPM — n (%)	26 (7.4)	31 (8.9)	57 (8.1)
Patients with at least one invasive SPM — n (%)	17 (4.9)	23 (6.6)	40 (5.7)
Patients with at least one hematologic SPM — n (%)	1 (0.3)	5 (1.4)	6 (0.9)
Acute myeloid leukemia	1	4	5
Myelodysplastic syndromes	1	1	2
Patients with at least one solid tumor — n (%)	16 (4.6)	1 18 (5.1)	34 (4.9)
Breast cancer	2	2	4
Colon cancer	2	2	4
Gastric cancer	0	2	2
Glioblastoma	0	2	2
Lip and/or oral cavity cancer	1	0	1
Lung neoplasm malignant	0	1	1
Malignant melanoma	3	0	3
Pancreatic carcinoma	1	2	3
Pituitary tumour	1	0	1
Porocarcinoma	0	1	1
Prostate cancer	3	3	6
Renal cell carcinoma	1	1	2
Salivary gland cancer	1	0	1
Thyroid cancer	1	3	4
Patients with at least one non-invasive SPM— n (%)	11 (3.1)	8 (2.3)	19 (2.7)
Basal cell carcinoma	9	7	16
Bowen's disease	0	1	1
Squamous cell carcinoma	2	0	2

58th ASH® Annual Meeting & Exposition
December 3-6, 2016 | San Diego, CA

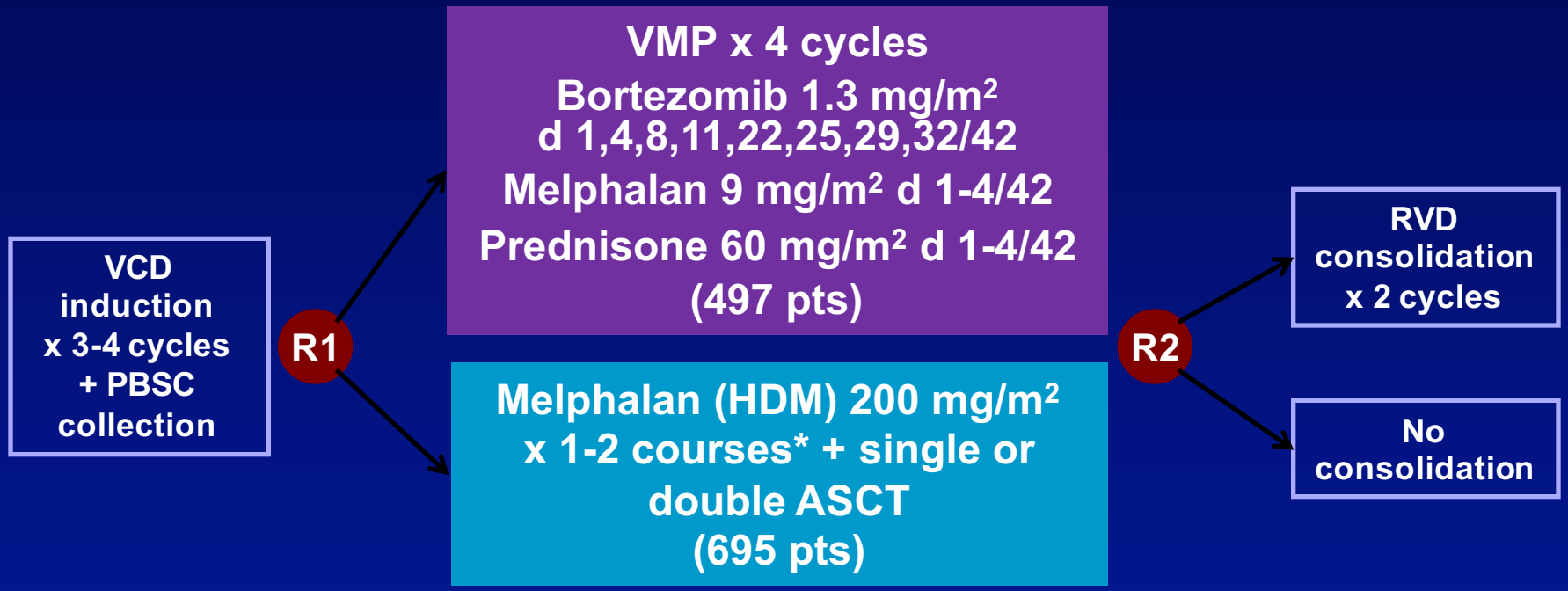
Intensification Therapy with Autologous Stem Cell Transplantation (ASCT) Versus Bortezomib-Melphalan-Prednisone for Newly Diagnosed Multiple Myeloma Patients: An Intergroup, Multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial) ASH 2016

Michele Cavo*, Meral Beksac, Meletios A. Dimopoulos, Lucia Pantani, Francesca Gay, Roman Hájek, Ulf-Henrik Mellqvist, Francesca Patriarca, Vittorio Montefusco, Monica Galli, Hans Erik Johnsen, Heinz Ludwig, Sonja Zweegman, Ruth Wester, Ka Lung Wu, Christoph Driessen, Rossella Troia, Petra Cornelisse, Bronno van der Holt, Antonio Palumbo and Pieter Sonneveld

On behalf of EMN02/HO95 MM Trial participants

*Seràgnoli Institute of Hematology, Bologna University School of Medicine, Italy

EMN02/HO95 MM trial: study design



All pts received lenalidomide maintenance until R/P

Stratification: ISS I vs. II vs. III

Randomization to VMP *vs* HDM (1:1) in centers with a fixed single ASCT policy

Randomization to VMP *vs* HDM-1 vs HDM-2 (1:1:1) in centers with a double ASCT policy

Study endpoints

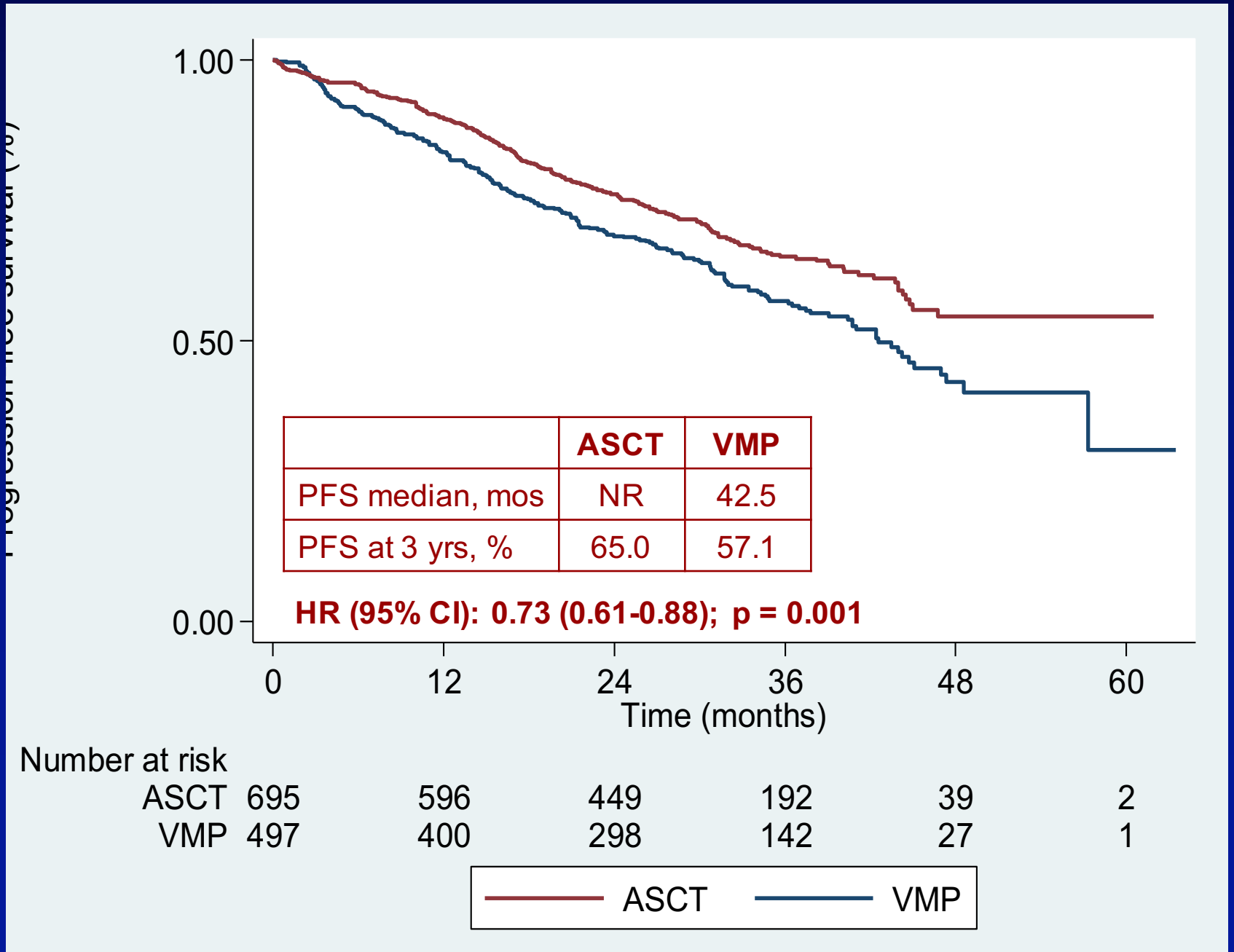
PRIMARY

- PFS from R1: ASCT *vs* VMP
- PFS from R2: VRD consolidation *vs* no consolidation

SECONDARY

- PFS from R1: HDM-1 *vs* HDM-2
- Rates of response to ASCT or VMP
- OS from R1: ASCT *vs* VMP
- Toxicities with ASCT and VMP

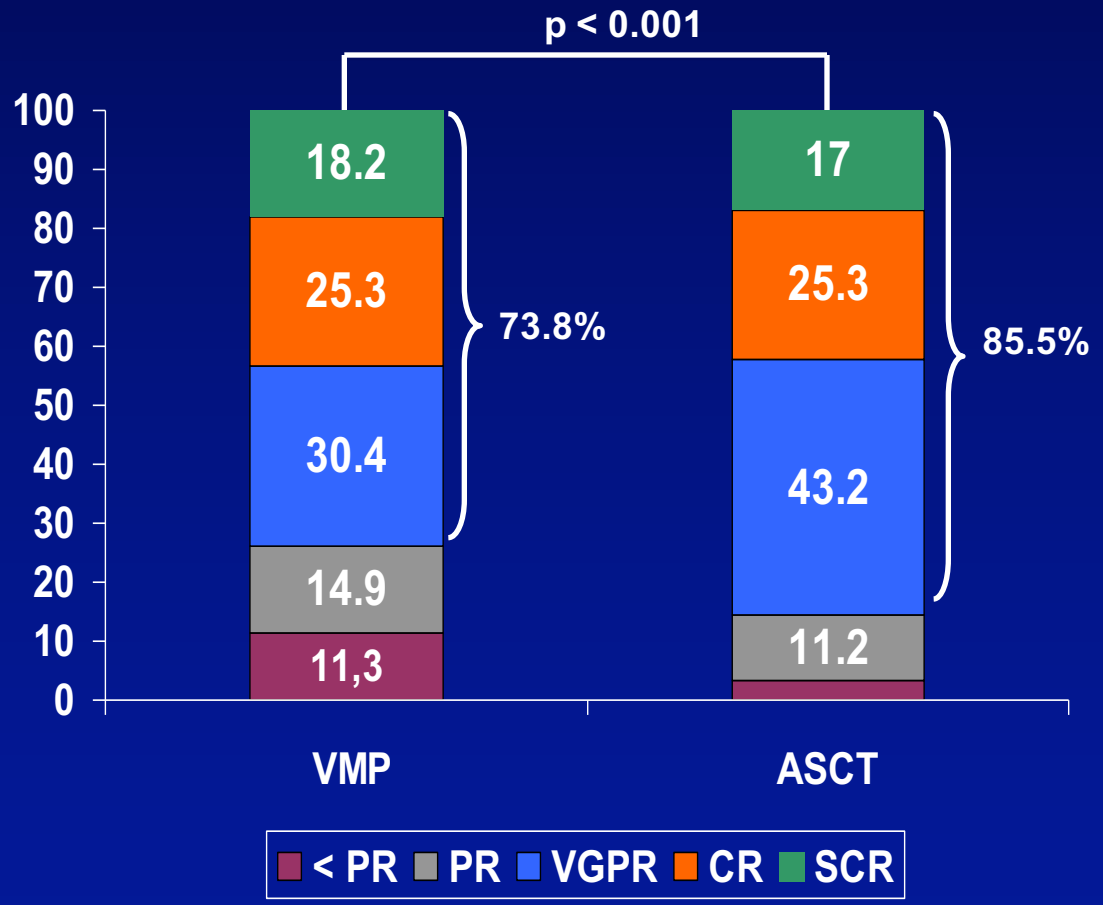
PFS by randomization 1 (VMP *vs.* ASCT)



	ASCT	VMP
PFS median, mos	NR	42.5
PFS at 3 yrs, %	65.0	57.1

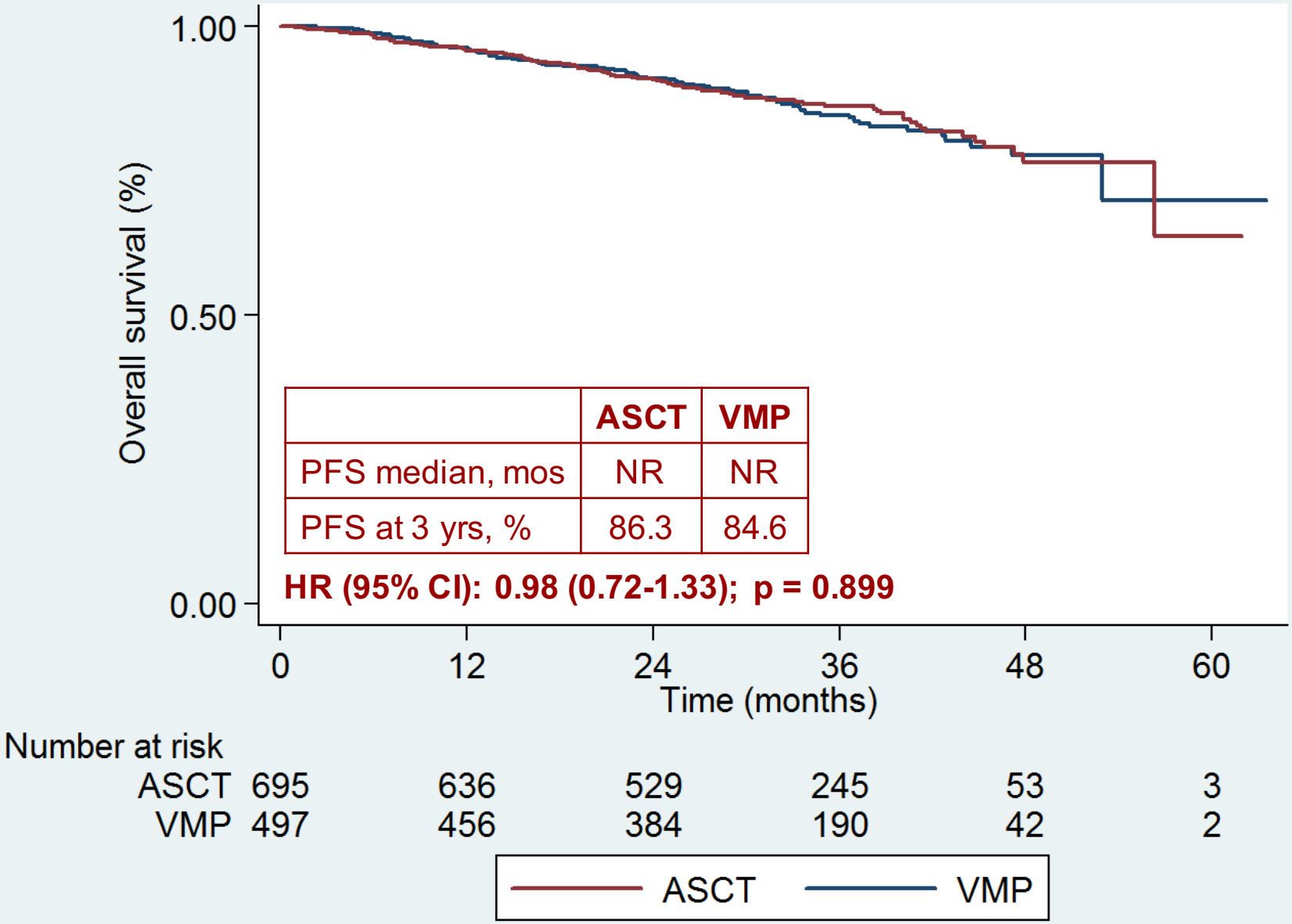
Best response rates

	VMP (n = 451)	ASCT (n = 641)
Response	(%)	(%)
sCR	18.2	17.0
CR	25.3	25.3
VGPR	30.4	43.2
PR	14.9	11.2
< PR	11.3	3.3



As reported by study investigators. Central reassessment of response categories is ongoing

OS by randomization 1 (VMP vs ASCT)



	ASCT	VMP
PFS median, mos	NR	NR
PFS at 3 yrs, %	86.3	84.6

HR (95% CI): 0.98 (0.72-1.33); p = 0.899

Conclusions

- Upfront ASCT was associated with a significant improvement in PFS *vs* VMP in the overall patient population
- Superior PFS with ASCT *vs* VMP was retained across prespecified subgroups of patients at low and high risk
- PFS benefit with ASCT in the overall patient population was retained in a multivariate analysis
- The superiority of ASCT over VMP was further supported by the significant improvement in the rate of VGPR or higher quality responses
- Upfront HDM and ASCT continues to be a treatment choice for fit patients with NDMM, but there is no OS difference seen to date

Restoring Immune function (ASH 2016):

Immunomodulatory drugs, other small molecules (e.g. HDACi's)

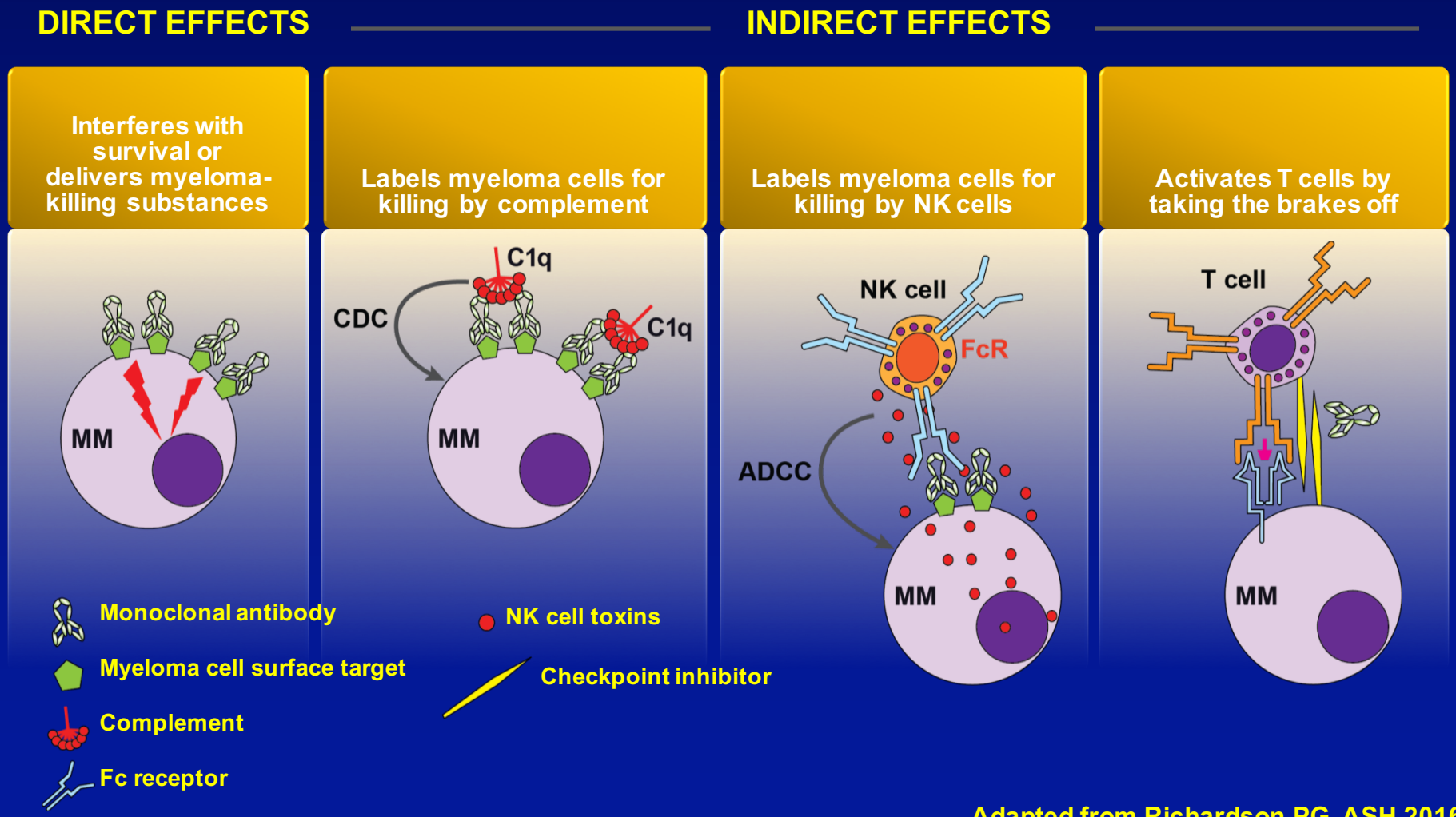
Monoclonal antibodies

Checkpoint inhibitors

Vaccines

Cellular therapies

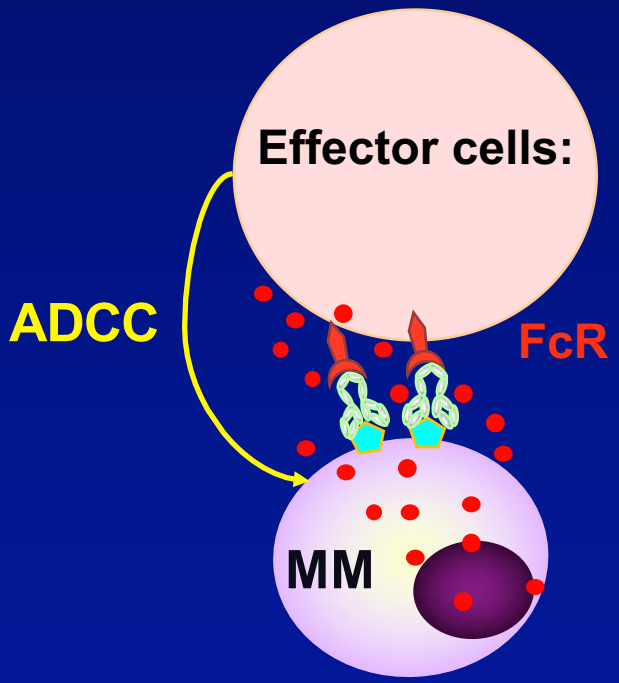
Monoclonal Antibodies Kill MM Through Multiple Mechanisms



Adapted from Richardson PG, ASH 2016

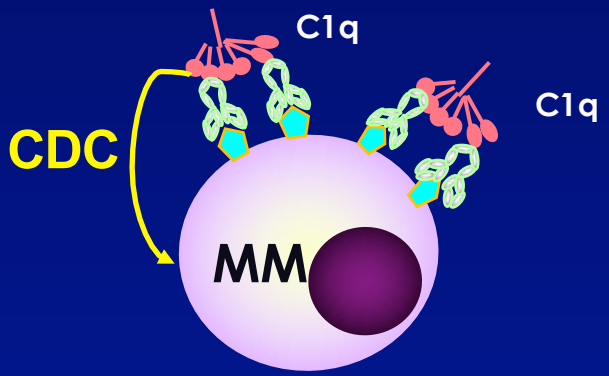
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)



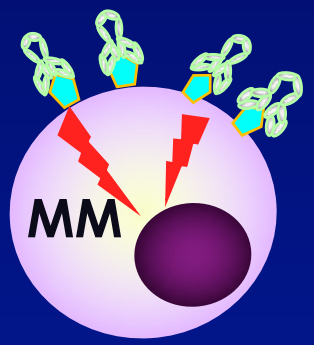
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1; SLAMF7)
- Daratumumab, SAR650984, MOR 202 (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)



- Daratumumab
- SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways



- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- Siltuximab (1339) (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab, SAR650984, MOR 202 (CD38)

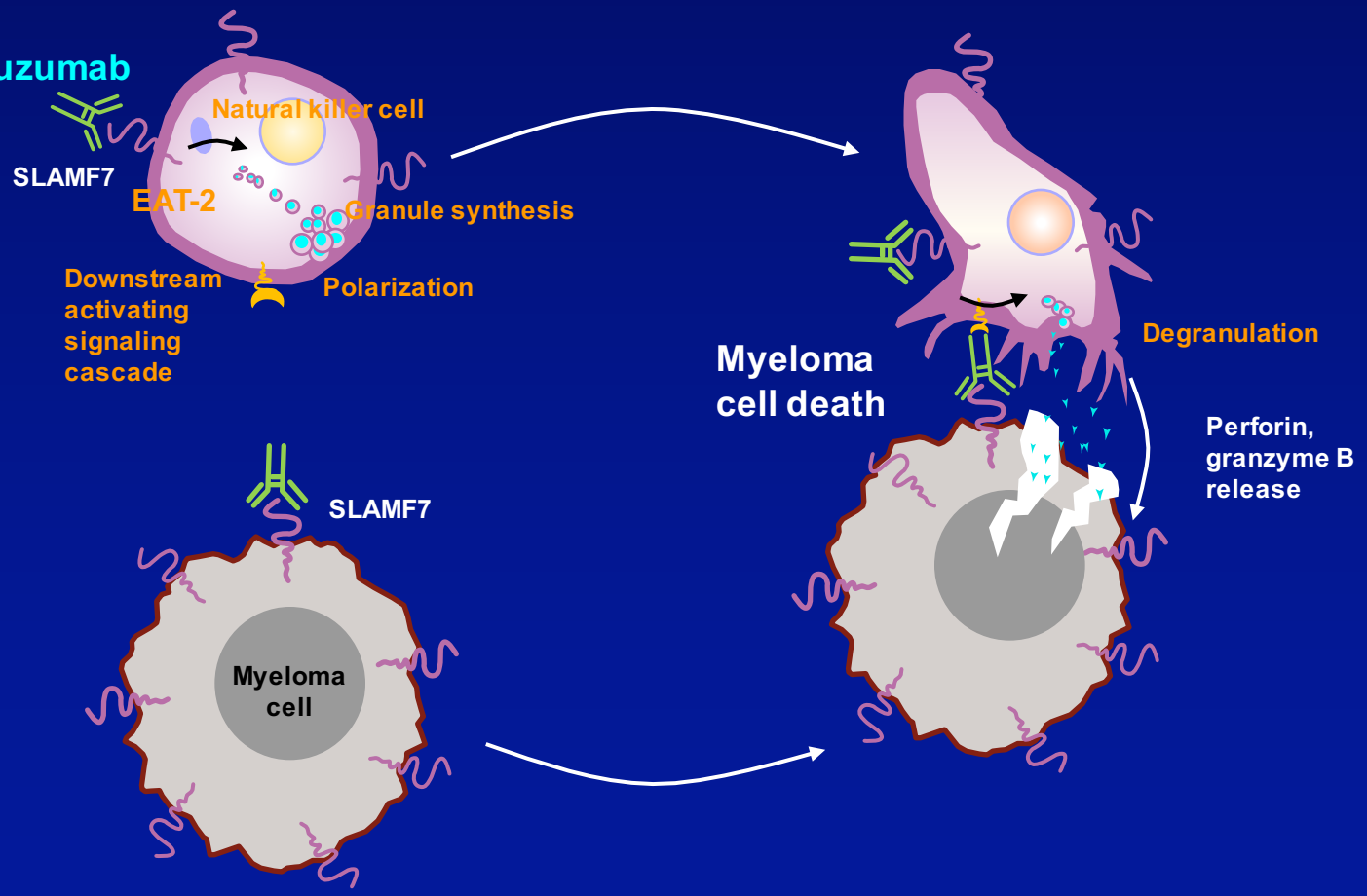
Adapted from Tai & Anderson Bone Marrow Research 2011

Elotuzumab: Immunostimulatory Mechanism of Action

- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7, a protein highly expressed by myeloma and natural killer cells[1]
- Elotuzumab causes myeloma cell death via a dual mechanism of action[2]

A Directly activating natural killer cells

B Tagging for recognition (ADCC)



1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9.
ADCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7

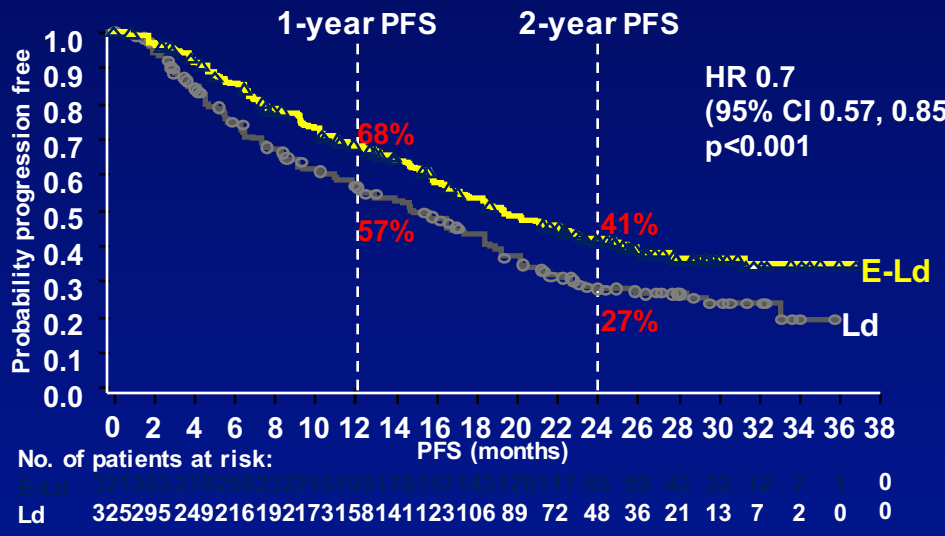
ELOQUENT-2: Primary Analysis

ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

Co-primary endpoint: PFS



From *N Engl J Med*, Lonial S et al, Elotuzumab therapy for relapsed or refractory multiple myeloma, 373, 621–31.

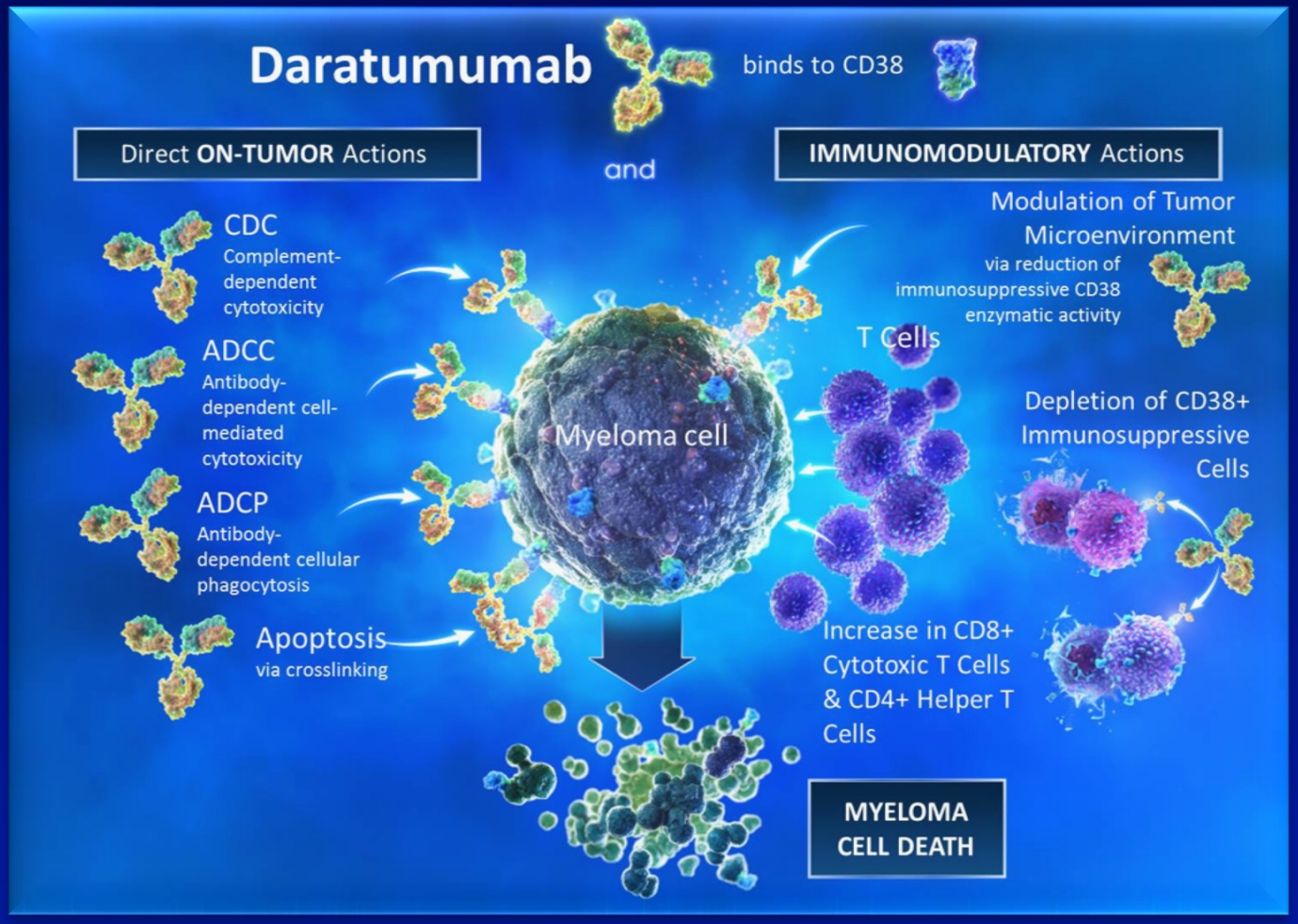
Co-primary endpoint: ORR	E-Ld	Ld
%	79	66
95% CI	74, 83	60, 71

ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone[1]

1. Lonial S et al. *N Engl J Med* 2015;373:621–31.

Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



1. Lammerts van Bueren J, et al. *Blood.* 2014;124:Abstract 3474.
2. Jansen JMH, et al. *Blood.* 2012;120:Abstract 2974.
3. de Weers M, et al. *J Immunol.* 2011;186:1840-8.
4. Overdijk MB, et al. *MAbs.* 2015;7:311-21.
5. Krejcik J, et al. *Blood.* 2016. Epub ahead of print.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

H.M. Lokhorst, T. Plesner, J.P. Laubach, H. Nahi, P. Gimsing, M. Hansson, M.C. Minnema, U. Lassen, J. Krejcik, A. Palumbo, N.W.C.J. van de Donk, T. Ahmadi, I. Khan, C.M. Uhlar, J. Wang, A.K. Sasser, N. Losic, S. Lisby, L. Basse, N. Brun, and P.G. Richardson

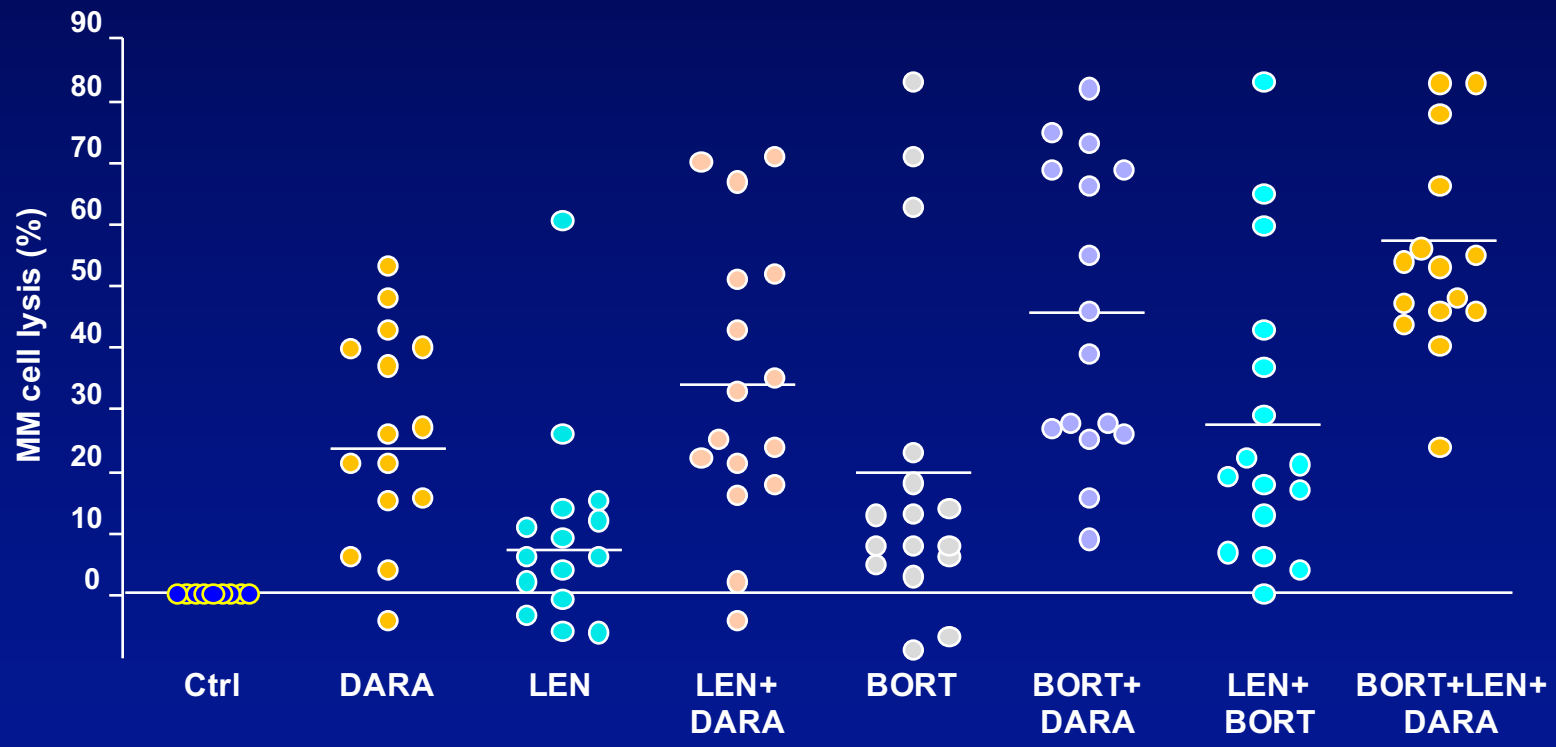
THE LANCET Oncology

Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, Richard LeBlanc, Michael Sebag, Natalie Callander, Andrzej Jakubowiak, Darrell White, Javier de la Rubia, Paul G Richardson, Steen Lisby, Huaibao Feng, Clarissa M Uhlar, Imran Khan, Tahamtan Ahmadi, Peter M Voorhees

N Engl J Med 2015 Sep 24;373(13):1207-19; *Lancet* 2016 Apr 9;387(10027):1551-60.

Synergistic With Other Standard MM Therapies, Including Bortezomib and Lenalidomide



LEN: 3 μM lenalidomide
BORT: 3 nM bortezomib
DARA: 10 μg/mL daratumumab

BM-MNC, n = 16
All DARA combinations vs alone, P <0.001.
BM-MNC, bone marrow mononuclear cells.

van der Veer MS, et al. *Blood Cancer J*. 2011;1(10):e41.

The NEW ENGLAND JOURNAL of MEDICINE

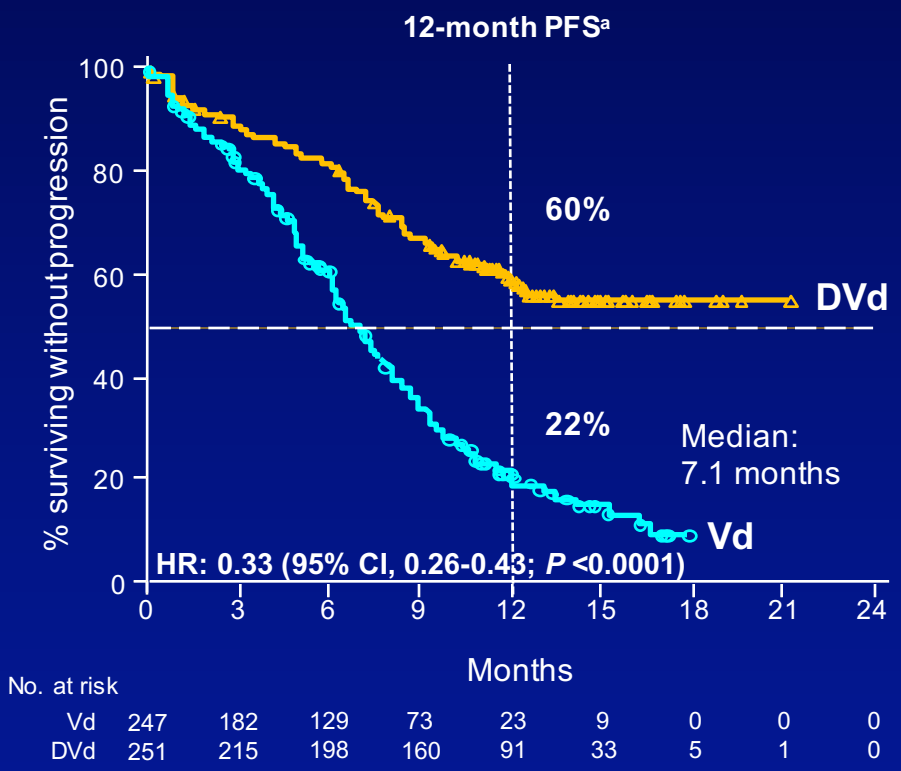
ORIGINAL ARTICLE

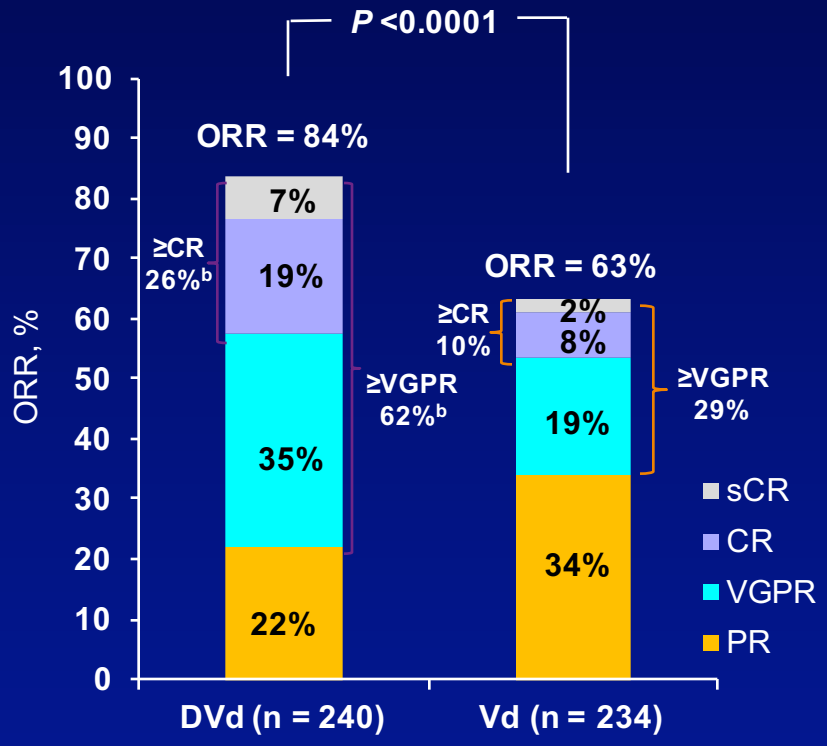
Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

Palumbo A et al. *N Engl J Med.* 2016;375:754

Updated Efficacy; ASH 2016





- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow up

Responses continue to deepen in the DVd group with longer follow-up

ITT, intent to treat.
Note: PFS: ITT population; ORR: response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.

Conclusions

- PFS benefit continues to be maintained with DVd over time
- DVd is superior to Vd regardless of prior lines of therapy
- Largest magnitude of benefit with DVd is observed in patients with 1 prior line of therapy
  - 78% reduction in risk of progression or death for DVd versus Vd
- More patients in DVd achieved deeper responses with longer follow-up
  - Higher CR and MRD-negative rates
  - MRD negativity translated into longer PFS
- DVd is superior to Vd regardless of cytogenetic risk or time since last therapy
- No new safety signals were reported

These data further support the use of this newly approved regimen of DVd in RRMM, with most benefit in patients with 1 prior line of therapy

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ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

Dimopoulos M et al. *N Engl J Med*. 2016;375:1319.

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

RANDOMIZE 1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
- Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Rd (n = 283)

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

Primary endpoint

- PFS

Secondary endpoints

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

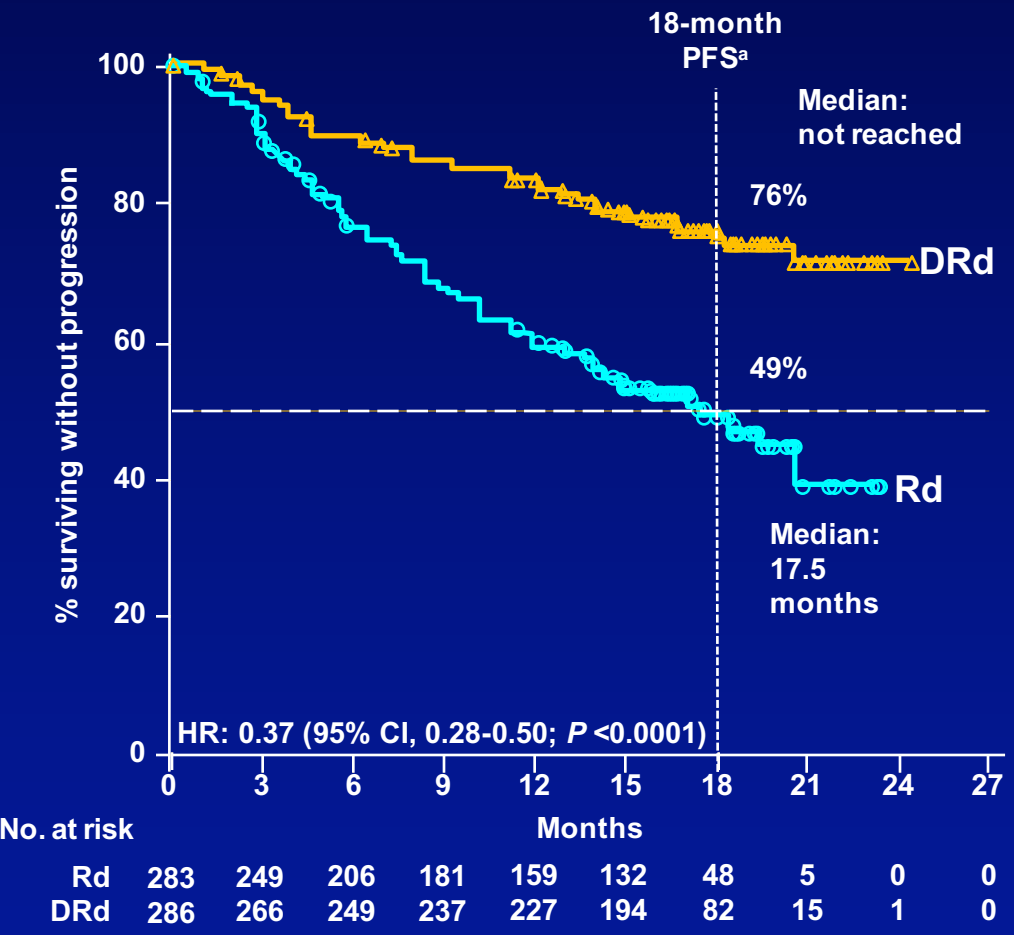
Statistical analyses

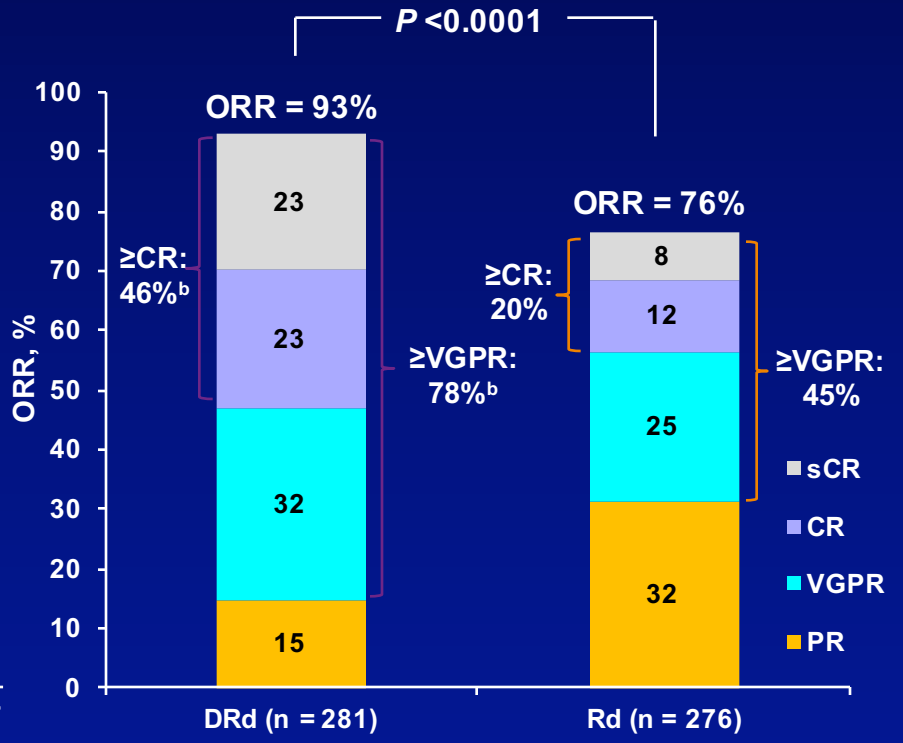
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

Updated Efficacy; ASH 2016



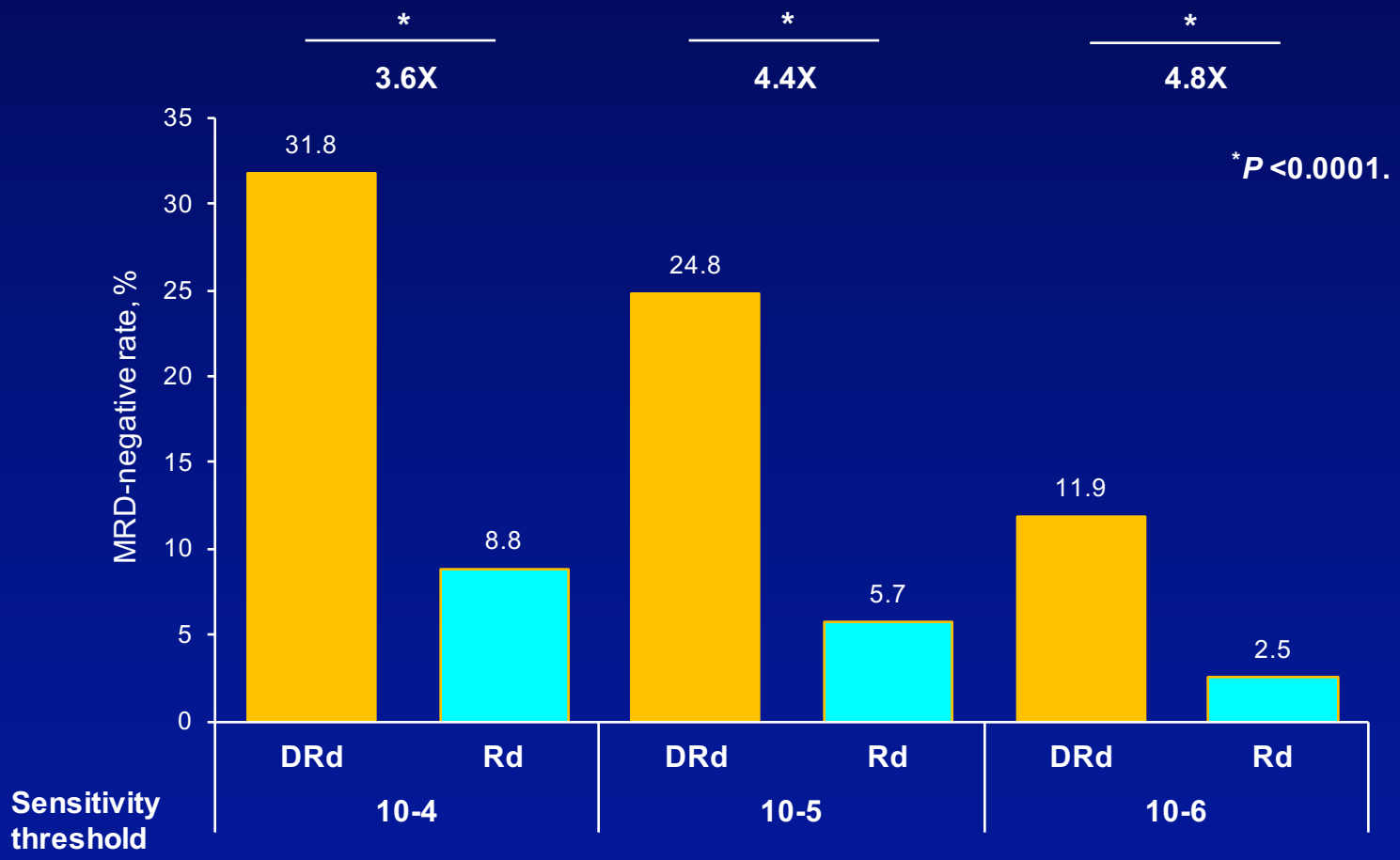


- **Median (range) follow-up: 17.3 (0-24.5) months**

Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate;
[b]*P* <0.0001 for DRd vs Rd.

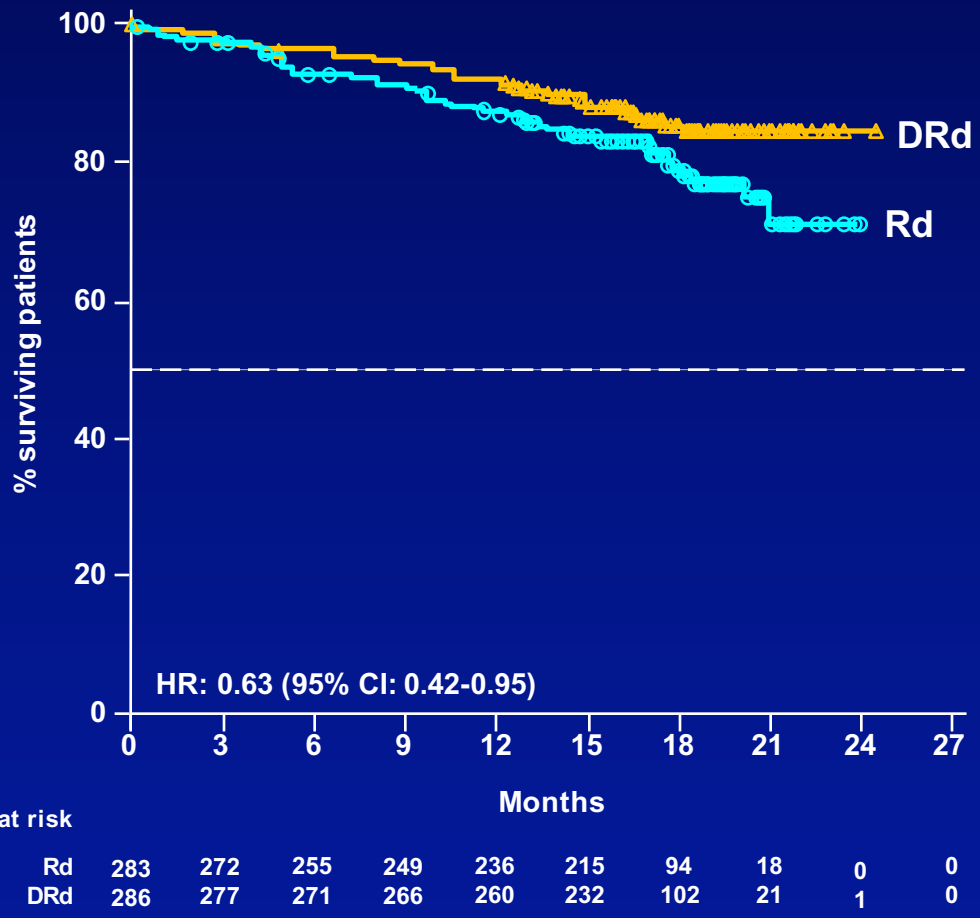
MRD-negative Rate; ASH 016



MRD-negative rates were >3-fold higher at all thresholds

Intent-to-treat population.
P values are calculated using likelihood-ratio chi-square test.

OS; ASH 2016



- OS events[a]
  - 40 (14%) in DRd
  - 56 (20%) in Rd

Curves are beginning to separate, but OS data are immature

Intent-to-treat population.
Median OS was not reached; results did not cross the prespecified stopping boundary.

Conclusions

- Daratumumab-Rd significantly improved PFS in comparison with Rd alone
  - DRd was associated with a 63% reduction in the risk of progression or death
- Treatment benefit of DRd versus Rd was consistent across subgroups
- DRd doubled CR/sCR rates and quadrupled MRD-negative rates
- DRd has a manageable safety profile consistent with the known safety profile of daratumumab or Rd alone

Daratumumab combined with Rd potentially represents a new standard of care for myeloma patients after ≥1 prior treatment

Lenalidomide-based Studies

	POLLUX DRd vs Rd	ASPIRE KRd vs Rd[1]	ELOQUENT-2 Elo-Rd vs Rd[2,3]	TOURMALINE-MM1 RId vs Rd[4]
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥VGPR	76%	70%	33%	48%
≥CR	43%	32%	4%	14%
Duration of response, mo	NE	28.6	20.7	20.5
OS HR (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

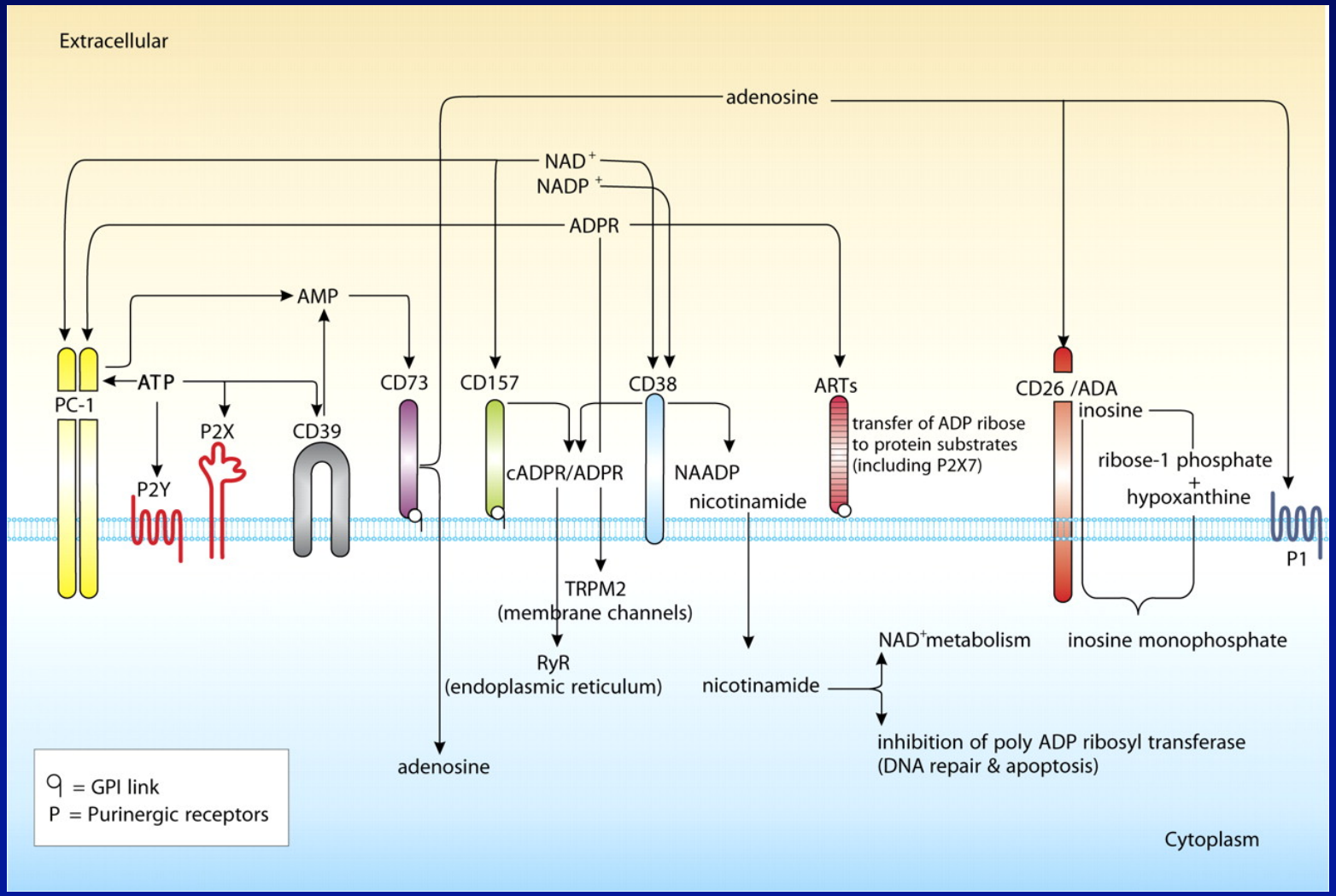
1. Stewart AK, et al. *N Engl J Med.* 2015;372(2):142-152.
2. Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631.
3. Dimopoulos MA, et al. *Blood.* 2015;126(23):Abstract 28.
4. Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634.

K, carfilzomib; E, elotuzumab; N, ixazomib.

Enhancing the efficacy of CD 38 targeting MoAbs in MM

BM contains a panel of growth-permissive and restrictive signals from the tumor microenvironment: these signals likely co-evolve with the tumor.

Is there a role for ectoenzymes in this intricate network?



Malavasi F et al. ASH 2016; Malavasi F et al. *Physiol Rev*. 2008 Jul;88(3):841-86. M.V. Dhodapkar, *Blood* 2016

Anti-CD38 antibody-mediated therapy in myeloma: some unbeaten paths of potential application (ASH 2016, Malavasi F et al.)

1) Can the enzymatic activities exerted by CD38 play a role in these events?

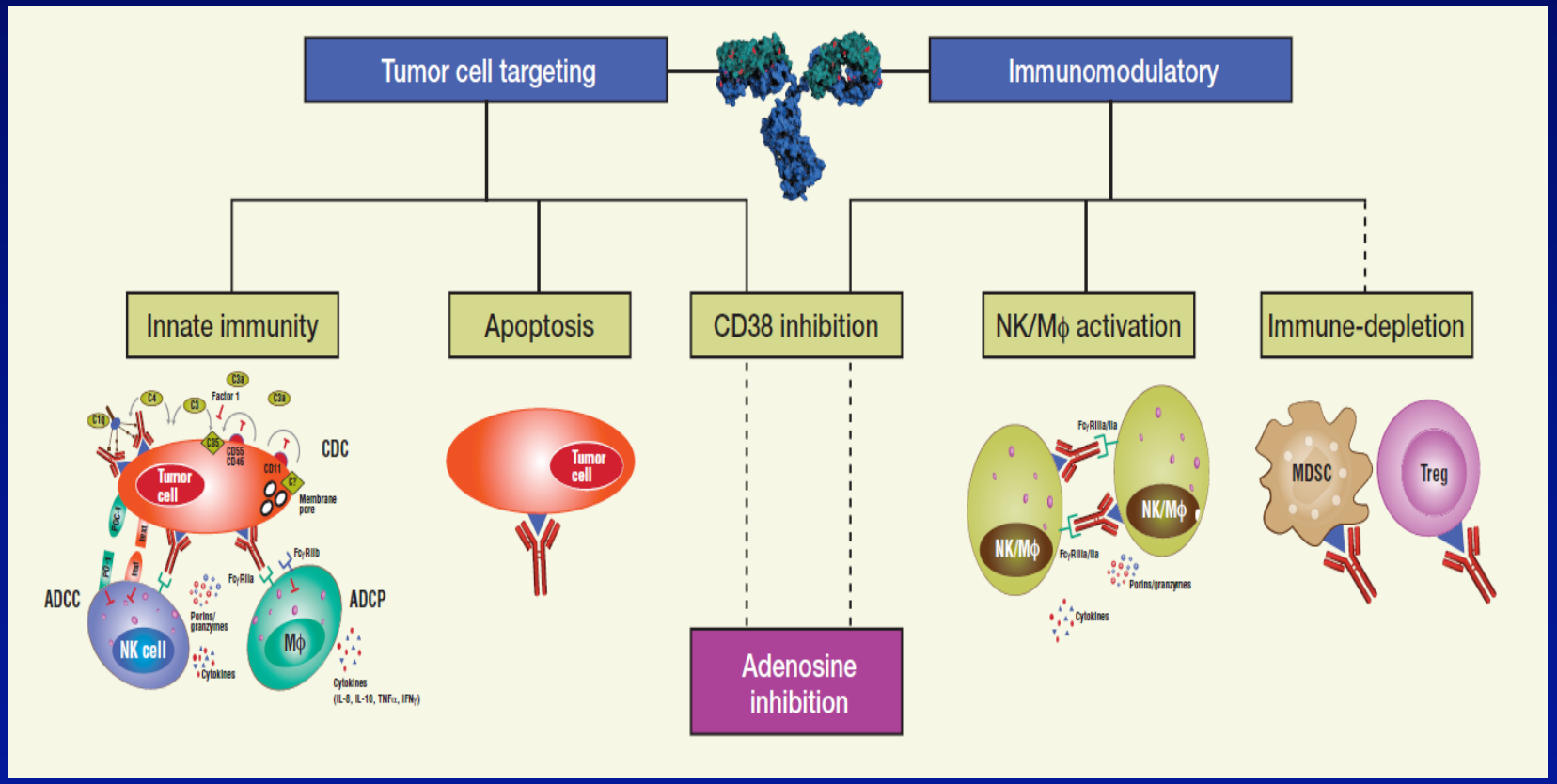
2) Does the enzymatic activities of CD38 collaborate with other ectoenzymes in the bone marrow niche?

3) Do therapeutic anti-CD38 antibodies interfere with the enzymatic activities ruled by CD38?

4) Do the products derived from the ectoenzymes operate outside the niche?

ASH 2016 – ISA POM DEX (Richardson PG et al.)
Introduction

Modes of action of isatuximab

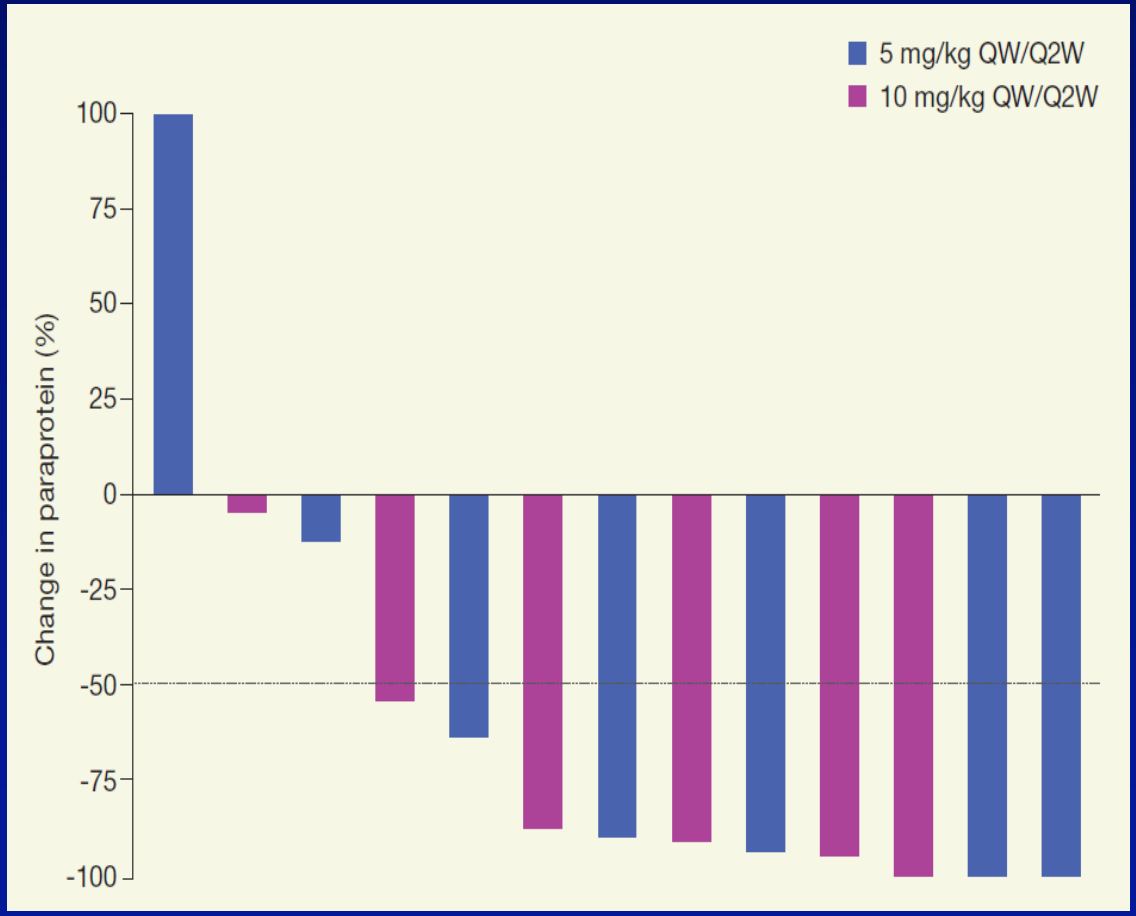


ADCC/CP, antibody-dependent cellular cytotoxicity/phagocytosis; CDC, complement-dependent cytotoxicity; Mφ, macrophage; MDSC, myeloid-derived suppressor cell; NK, natural killer cell.

Results: Paraprotein reduction

Reductions in paraprotein levels were recorded in the majority of patients.

Waterfall plot of best percentage change in paraprotein levels

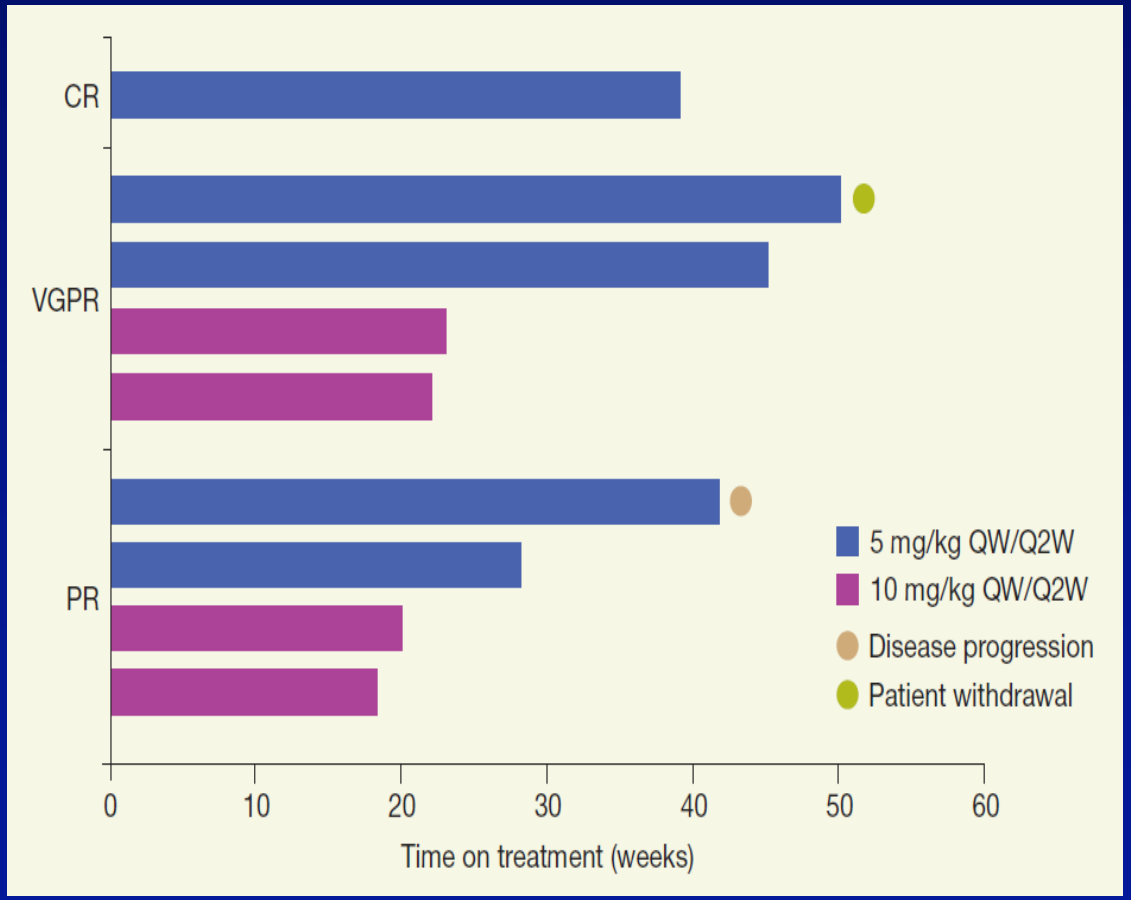


Post-baseline paraprotein data were not available for one patient in the 5 mg/kg cohort.
QW, weekly; Q2W, once every 2 weeks.

Results: Time on treatment

Seven patients who achieved at least PR remained on treatment at data cutoff.

Time on treatment by best confirmed response (at least PR)



CR, complete response; PR, partial response; QW, weekly; Q2W, once every 2 weeks; VGPR, very good partial response.

Summary

- The combination of isatuximab with Pom/Dex is generally well tolerated in patients with RRMM.
  - The AEs observed are generally consistent with the known safety profiles of the individual agents.
- IARs were all Gr 1/2 in intensity and tended to occur with the first infusion.
- The PK parameters of isatuximab do not appear to be affected by Pom/Dex co-administration.
- The combination of isatuximab with Pom/Dex was clinically active in this heavily pretreated patient population.
  - Confirmed ORR was 64%; confirmed ORR with isatuximab 10 mg/kg was 67%.
  - Confirmed ORR in IMiD-refractory patients was 64%.
- The MTD for this combination was not reached at the highest isatuximab dose level tested; 10 mg/kg was the selected dose for the expansion cohort based on these preliminary clinical, efficacy, safety, and PK data.
- A global Phase III study of isatuximab plus Pom/Dex is planned to start in 2016.

First in Human Study with GSK2857916, An Antibody Drug Conjugated to Microtubule-disrupting Agent Directed Against B-cell Maturation Antigen, in Patients with Relapsed/Refractory Multiple Myeloma: Results from Study BMA117159 Part 1 Dose Escalation

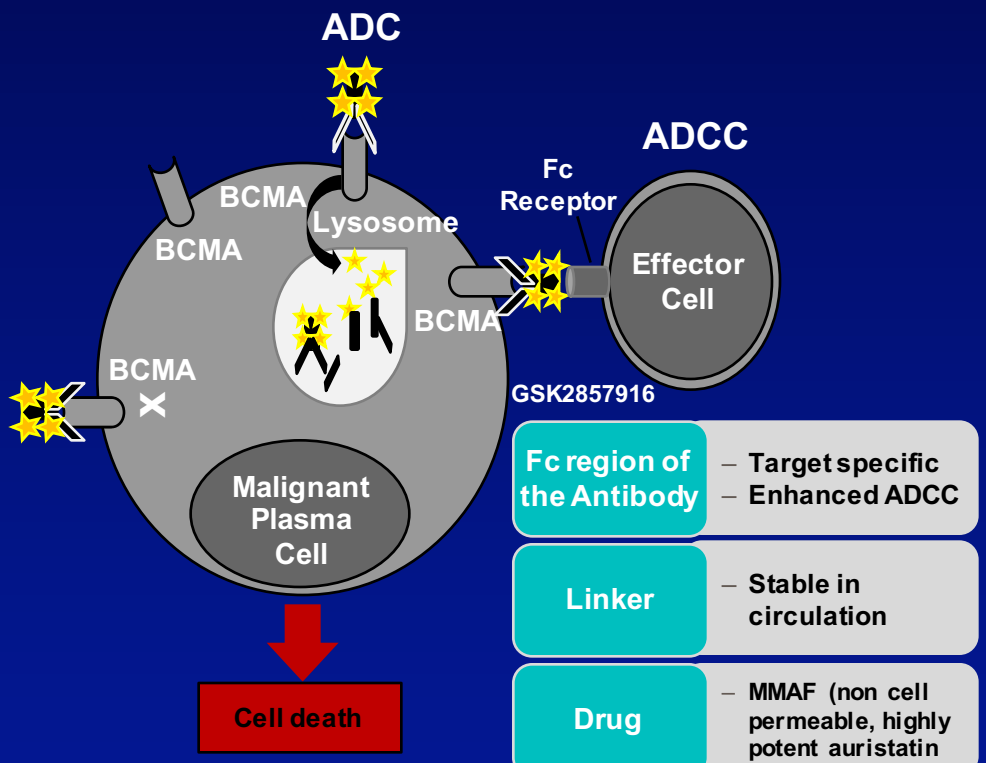
ASH 2016

Adam D. Cohen[1], Rakesh Popat[2], Suzanne Trudel[3], Paul G. Richardson[4], Edward N. Libby[5], Nikoletta Lendvai[6], Larry D. Anderson Jr[7] , Heather J. Sutherland[8], Daren Austin[9], Stephen DeWall[9], Catherine E. Ellis[9], Zangdong He[9], Jolly Mazumdar[9], Catherine Wang[9], Joanna Opalinska[9], Peter M. Voorhees[10]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [2]University College London Hospitals NHS Foundation Trust, London, UK; [3]Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Seattle Cancer Care Alliance, Seattle, WA, USA; [6]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [7]University of Texas Southwestern, Dallas, TX, USA; [8]Vancouver General Hospital, Vancouver, BC, Canada; [9]GlaxoSmithKline, USA/UK; [10] Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Background

- BCMA expression is restricted to B cells at later stages of differentiation and is requisite for the survival of long lived plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- GSK2857916 is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to a microtubule disrupting agent MMAF via a stable, protease resistant maleimidocaproyl linker
  - Preclinical studies demonstrate its selective and potent activity[1]



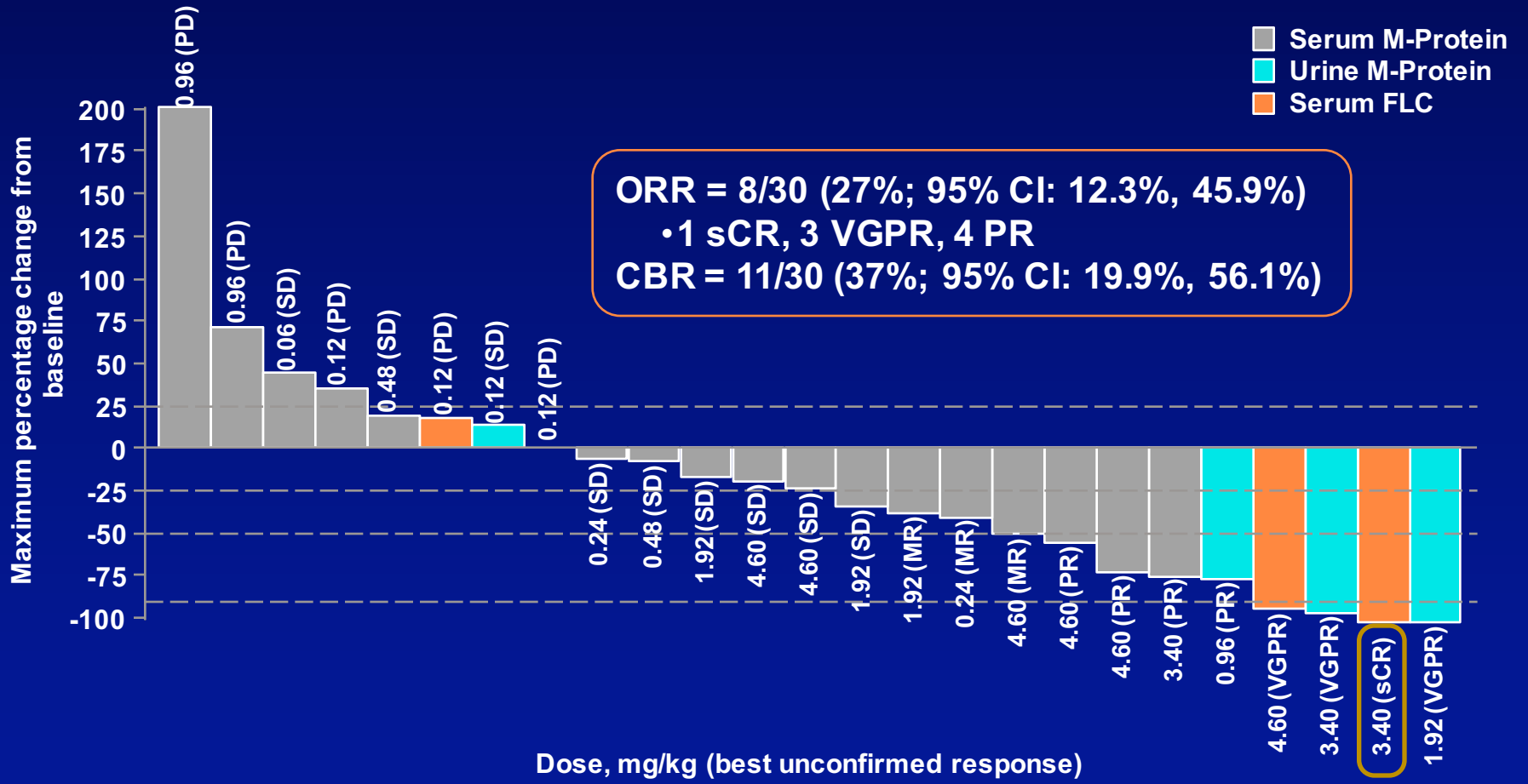
Mechanisms of Action:

1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death
4. BCMA receptor signalling inhibition

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; Fc, Fragment crystallizable; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

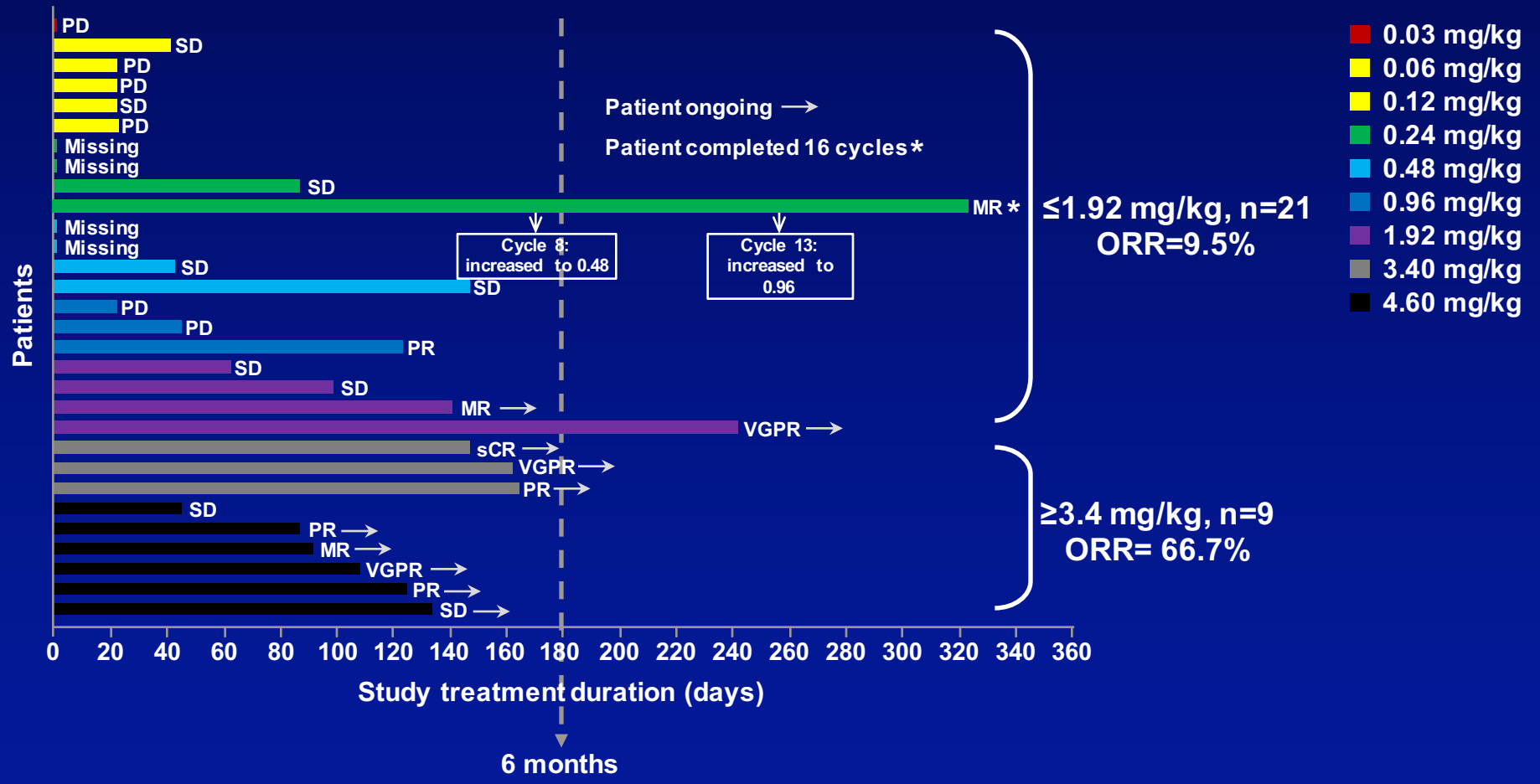
[1]Tai YT, et al. Blood 2014;123(20):3128-38.

Maximum % Change in M-Protein or Free Light Chain



- CBR, clinical benefit rate; CI, confidence interval; FLC, free light chain; M-protein, myeloma protein; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

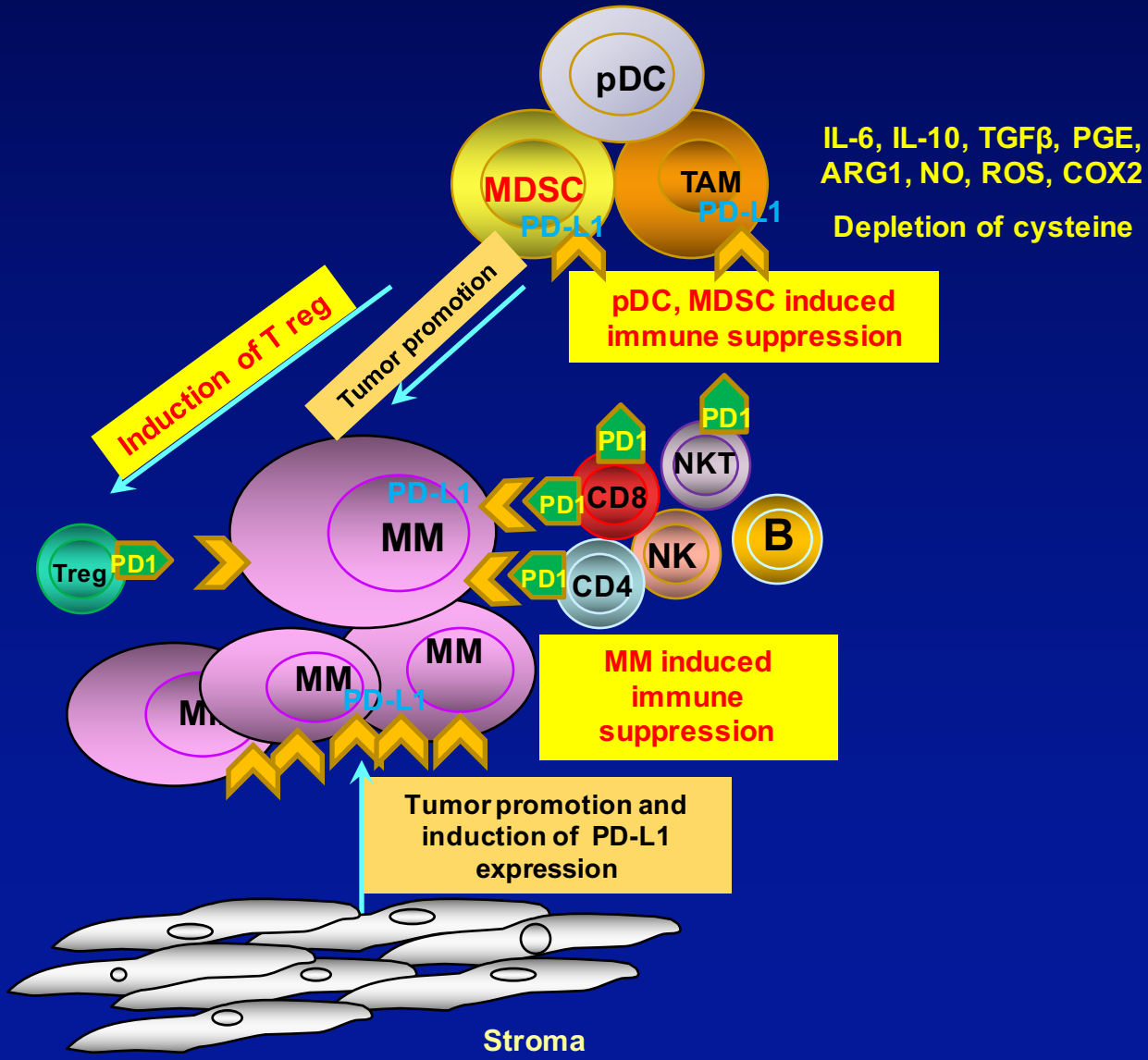
Part 1: Summary of Clinical Activity and Duration on Study



Conclusions

- GSK2857916 was well tolerated with no DLTs up to 4.6 mg/kg q3w; MTD was not reached
- AEs were manageable with ocular toxicity emerging as the most frequent reason for dose modifications
- Hematologic toxicities such as thrombocytopenia and anemia are expected in the disease under study
  - Thrombocytopenia emerged more frequently as treatment-related at higher doses; although events were transient and manageable
- 66.7% ORR including a stringent CR observed at higher doses of GSK2857916 in this refractory population
- 3.4 mg/kg was selected as the dose to investigate in the expansion phase of the study based on the totality of the data from Part 1
- Pharmacodynamic and correlative analyses are ongoing

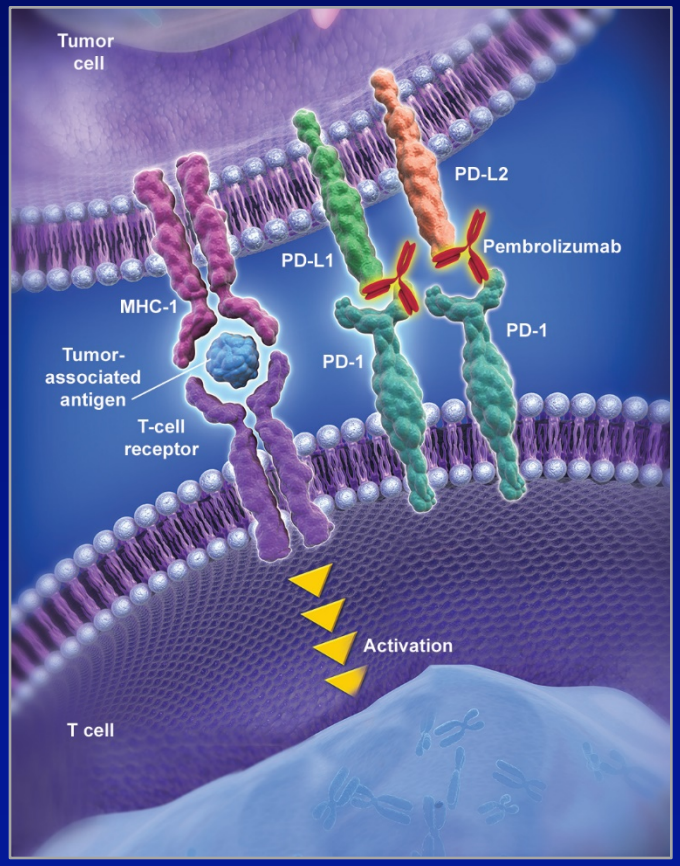
Immune Suppressive Microenvironment in MM



Görgün GT, et al. *Blood* 2013;121:2975-87

Pembrolizumab and the PD-1 Pathway

- The PD-1 pathway is often exploited by tumors to evade immune surveillance[1-3]
- Role of PD-1 inhibitors in MM[1-2]
- Pembrolizumab blocks interaction between PD-1 and PD-L1/PD-L2[4-6]
- Rationale for the combination of IMiDs and PD-L1 blockade[7]
  - Lenalidomide reduces PD-L1 and PD-1 expression on MM cells and T- and myeloid-derived suppressor cells
  - Lenalidomide enhances checkpoint blockade–induced effector cytokine production in MM bone marrow and induced cytotoxicity against MM cells



1. Liu J et al. *Blood*. 2007;110:296. 2. Tamura H et al. *Leukemia*. 2013;27:464. 3. Paiva B et al. *Leukemia*. 2015;29:2110. 4. Keir ME et al. *Annu Rev Immunol*. 2008;26:677. 5. Hallett WH et al. *Biol Blood Marrow Transplant*. 2011;17:1133. 6. Homet Moreno B, Ribas A. *Br J Cancer*. 2015;112:1421. 7. Görgün G et al. *Clin Cancer Res*. 2015;21:4607.

Pembrolizumab + REV/DEX

- Patients had heavily pretreated RRMM (median four prior therapies); 86% had received a stem cell transplant and 75% were refractory to lenalidomide
  - 49% were unresponsive to two, three, or four medications
- Acceptable safety profile, with AEs similar to those seen in patients using pembrolizumab in solid tumors
- ORR was 50% and disease control rate (CR, PR, or SD) was 98%

Conclusion: results are promising; phase 3 studies of pembrolizumab are now under way.

Mateos M-V et al. *J Clin Oncol.* 2016;34(suppl):abstr 8010. NCT02036502.

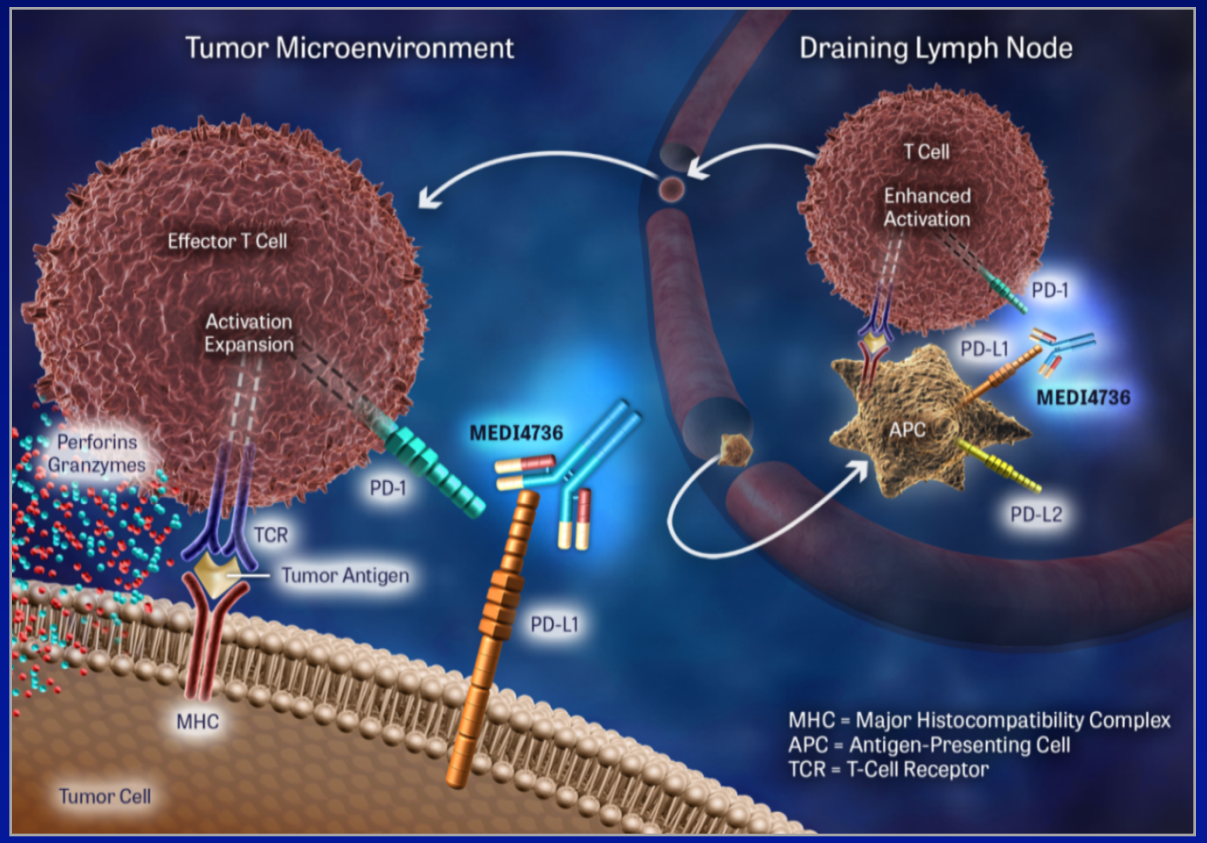
Pembrolizumab in Combination with Pomalidomide and Dexamethasone for RR MM

- Phase II study of 48 pts
  - Pembro 200 mg Q 2 weeks Pom 4 mg Q21 Dex 40mg QW
  - Median of 3 prior lines, 80% double refractory
  - High risk cytogenetics 38%
  - Interstitial pneumonitis 13%; hypothyroid 10%
  - ORR 56%; sCR 8%; VGPR 13%; PR 29%
  - Double refractory ORR: 55%
  - Median DOR for responding patients: 8.8 months

Badros et al UMD ASH 2016

ASH 2016: Durvalumab in MM – Combos with DARA, POM , DEX

Durvalumab: Hypothesized Mechanism of Action



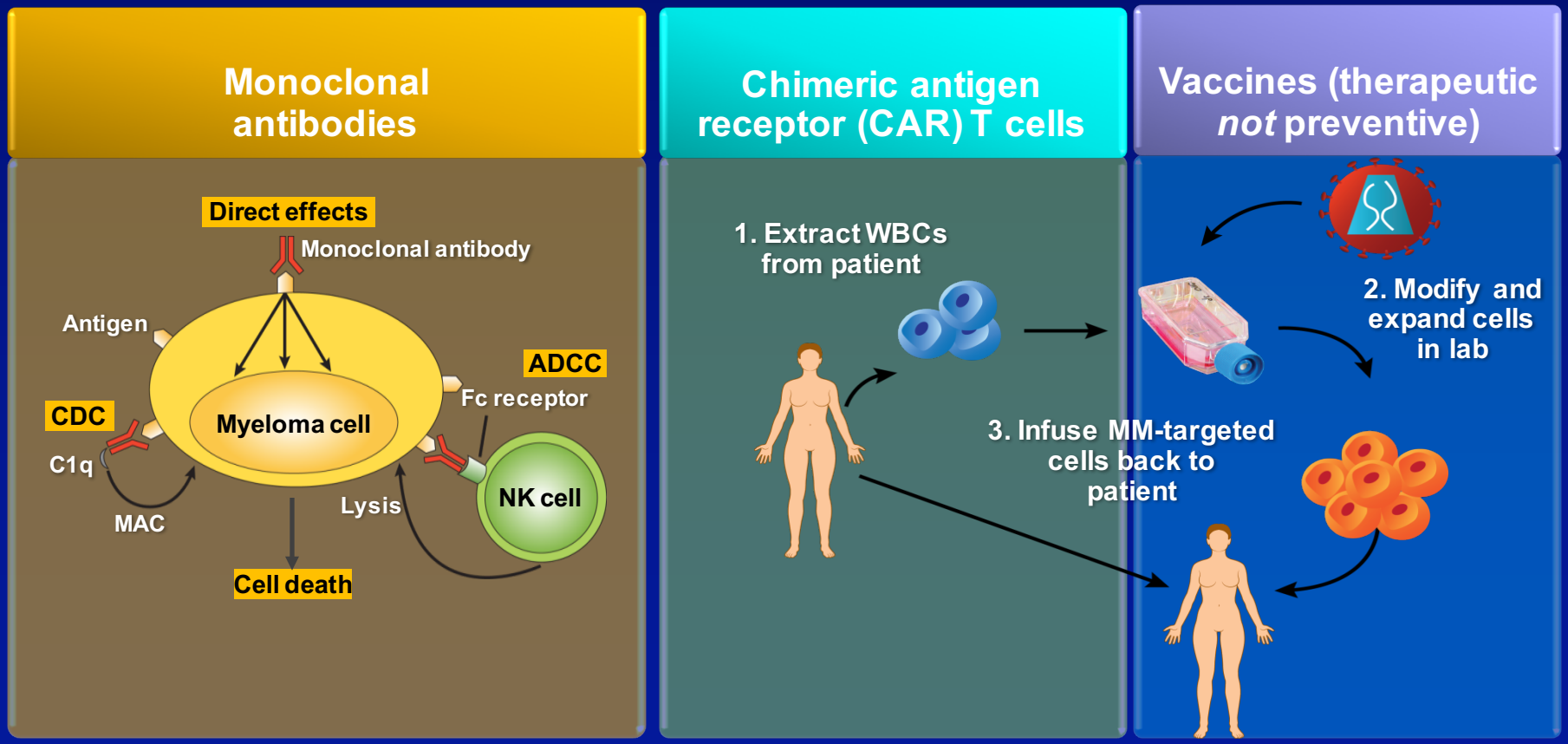
Reprinted from Ibrahim R et al. Semin Oncol. 2015;42(3):474-483, Copyright 2015.

Siegel DS et al. *J Clin Oncol.* 2016; Abstract TPS8072.
Richardson PG et al. ASH 2016, MMRF Symposium

Harnessing the Immune System to Fight Myeloma:

Types of Immunotherapy, Immuno-Oncology

Passive ——— Active



Richardson PG et al, ASH 2016

Myeloma CAR therapy ASH 2016

- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA
- Functional CAR T cells can be generated from MM patients
- CAR T and NK cells have in vitro and in vivo activity against MM
- Clinical trials underway
  - Anecdotal prolonged responses but no robust efficacy data available yet
- Many questions remain about CAR design:
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps 'cocktails' of multiple CARs or CARs + chemotherapy will be required for best outcomes

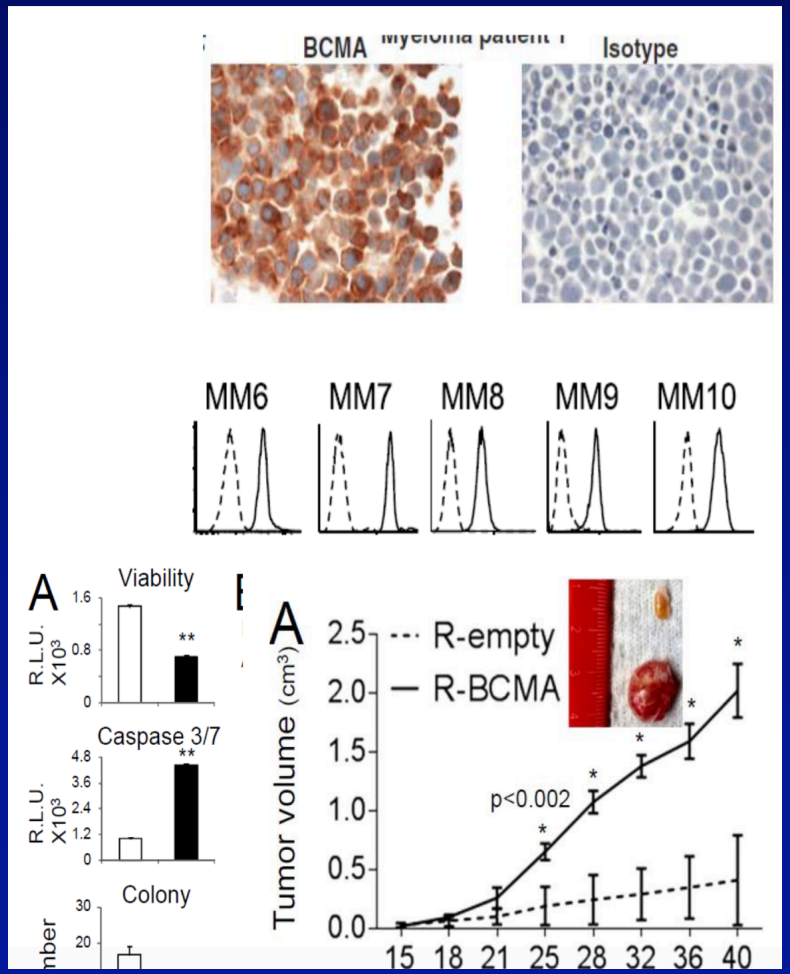
B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) for Multiple Myeloma (MM):Initial Safety and Efficacy from a Phase I Study

Adam D. Cohen, Alfred L. Garfall, Edward A Stadtmauer, Simon Francis Lacey, Eric Lancaster, Dan T. Vogl, Karen Dengel, David E Ambrose, Fang Chen, Gabriela Plesa, Irina Kulikovskaya, Vanessa E Gonzalez, Minnal Gupta, Regina Young, Tenesia Carey, Regina Ferthio, Brendan M. Weiss, Celeste Richardson, Randi E. Isaacs, J. Joseph Melenhorst, Bruce L. Levine, Carl H June and Michael C. Milone

ASH 2016

BCMA (TNFRSF17, CD269)

- Receptor for BAFF (Blys) and APRIL
- Expressed on plasma cells, some mature B cell subsets, and plasmacytoid DC's
  - Maintains plasma cell homeostasis
  - Not on other normal tissues
- Expressed consistently on myeloma cells
  - Varying intensity
- Promotes MM pathogenesis



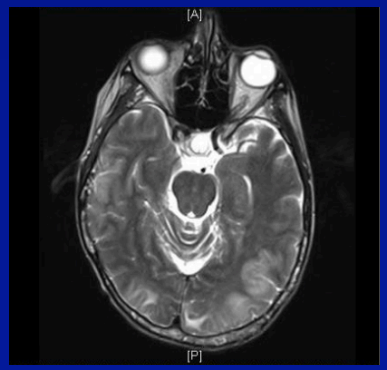
Patient Characteristics – Cohort 1 (n=9)

Characteristic	Median (range) or %
Age	57 (44 – 70)
Gender	67% male; 33% female
Isotype	IgG (33%), IgA (44%), LC (22%)
Prior lines of therapy	9 (4-11)
Lenalidomide	100% (refractory: 78%)
Bortezomib	100% (refr: 89%)
Pomalidomide	100% (refr: 89%)
Carfilzomib	100% (refr: 89%)
Autologous SCT	78%
Cyclophosphamide	100% (refr: 67%)
Daratumumab	44% (refr: 44%)
Anti-PD1	33% (refr: 33%)
High-risk genetics -17p or *TP53* mutation	100% 67%
Extramedullary dz	33%

Safety (n=9)

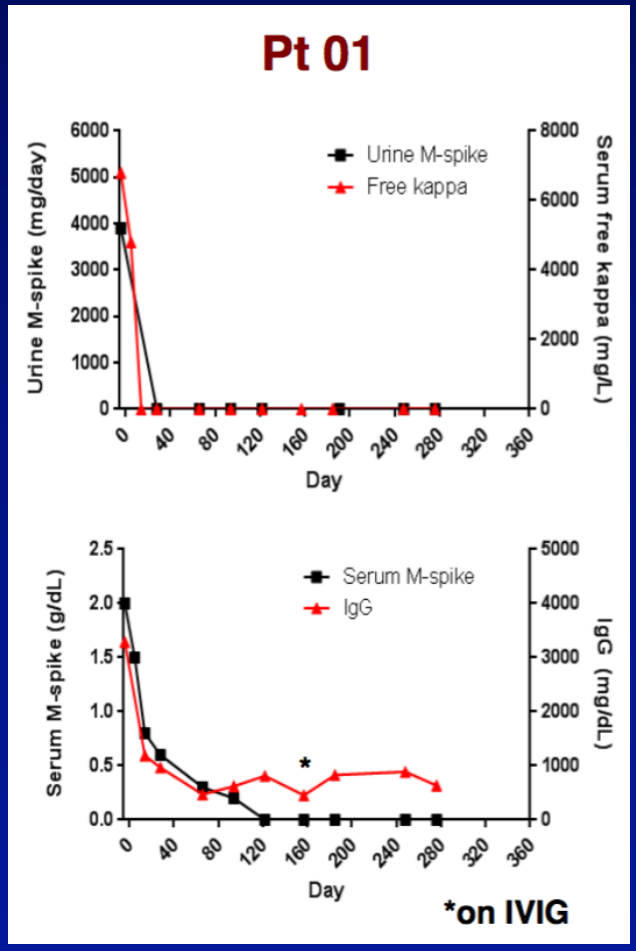
- Cytokine release syndrome in 8/9 (89%)
  - Grade 1 (n=1); Grade 2 (n=4); Grade 3 (n=2); Grade 4 (n=1)
  - 4/9 received tocilizumab
  - Median hospital stay = 9 days (range 3-40)

- Dose-limiting toxicity (pt. 03):
  - Grade 4 PRES (posterior reversible encephalopathy syndrome)
    - Recurrent seizures, obtundation
    - MRI brain: diffuse enhancement w/ swelling and sulcal effacement
    - Rapid peripheral CART expansion
    - Solumedrol 1 g/d x 3 → Cytoxan 1.5 g/m2 day 17
    - Rapid improvement, resolution of MRI changes and neuro deficits



Clinical Responses

Pt	BM PC %	Cytogenetics	CART dose received (% of planned)	CRS grade	Time to 1st response (days)	Best Heme response	PFS (mos.)
01	70	+11 -17p -16q	2 x 10e8 (40%)	3 (toci)	14	sCR*	12+
02	60	+1q +4p -17p	5 x 10e8 (100%)	1	14	MR	2
03	95	+1q t(4;14) -16q	2 x 10e8 (40%)	3 (toci)	15	VGPR*	5
09	15	t(11;14)-16q -17p	5 x 10e8 (100%)	2	-	SD	2
10	95	+1q t(11;14)	1.8 x 10e8 (100%)	-	-	PD	0.5
11	80	+1q t(4;14) -17p	5 x 10e8 (100%)	2	25	MR	2.5
07	15	+1q, +11, -4, -14, -16	5 x 10e8 (100%)	2	14	uPR**	1.5
08	80	-1p +1q, -4 -17p	5 x 10e8 (100%)	4 (toci)	-	PD	0.5
15	90	+1q, t(11;14)	5 x 10e8 (100%)	2 (toci)	14	VGPR*	2+

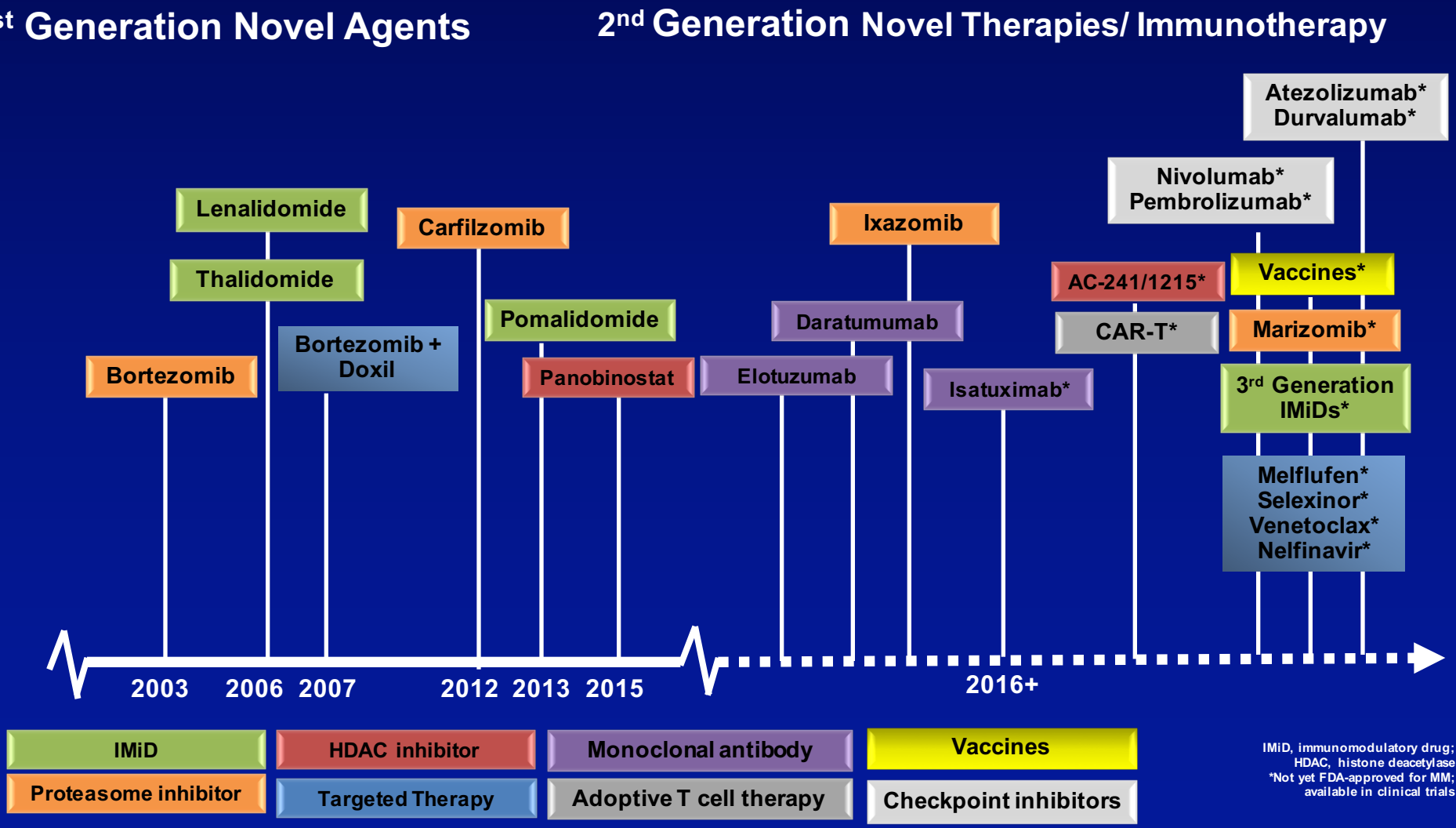


*No MM by flow
**unconfirmed; 24 hour UPEP not repeated

ASH 2016: Integration and Impact of Novel Agents, including Immune Therapies

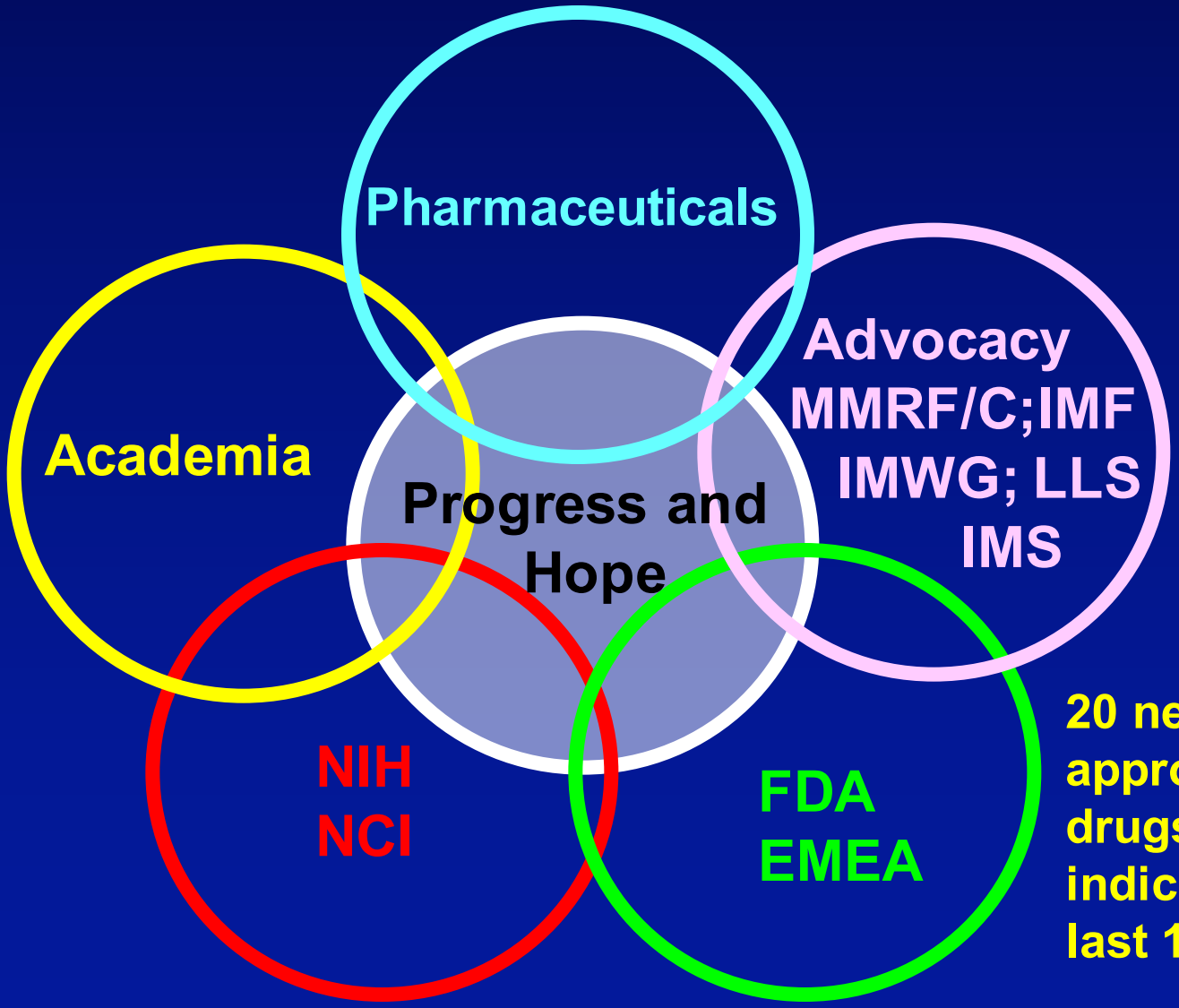
- Innovations (PIs, IMiDs) to date have produced significant improvements in PFS, OS: recent approvals (e.g. Carfilzomib, Ixazomib, HDACi, MoAbs) will augment this, with the next wave of therapies agnostic to mutational thrust
- Baseline immune function appears a key barrier to success and is targetable (e.g. use of PD1/PDL1 blockade)
- MoAbs (Elo, DARA, ISA, MOR 202) active in high risk disease, represent true new novel mechanisms, as well as other immuno-therapeutics (e.g. checkpoint inhibitors, vaccines)
- New insights to mechanisms of drug action (e.g. IMiDs, Ixazomib, Marizomib, Panobinostat, AC 241) will further expand therapeutic opportunities
- Numerous other small molecule inhibitors, targeted chemotherapeutics show promise (e.g. HDACi's, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/Myc, DUBs, MEK, melflufen) – with nelfinavir, venetoclax, melflufen and selexinor showing promise moving forward into advanced phase studies
- Further refinement of prognostics and MRD will guide therapy

Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016- 2017



IMiD, immunomodulatory drug; HDAC, histone deacetylase
*Not yet FDA-approved for MM; available in clinical trials

Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside



20 new FDA-approved drugs/combos/ indications in last 14 yrs

The Impact Of Novel Therapies in MM ~ 2016

2009 –
Patient DG, age 62 years
High Risk IgG kappa MM
DSS 3, ISS 2,
Elevated LDH
17 del positive ,
13 del positive (by FISH) PMH – HTN, nil else.

RD + Zometa => RVD (VGPR) Well tolerated, minimal PN (G1)

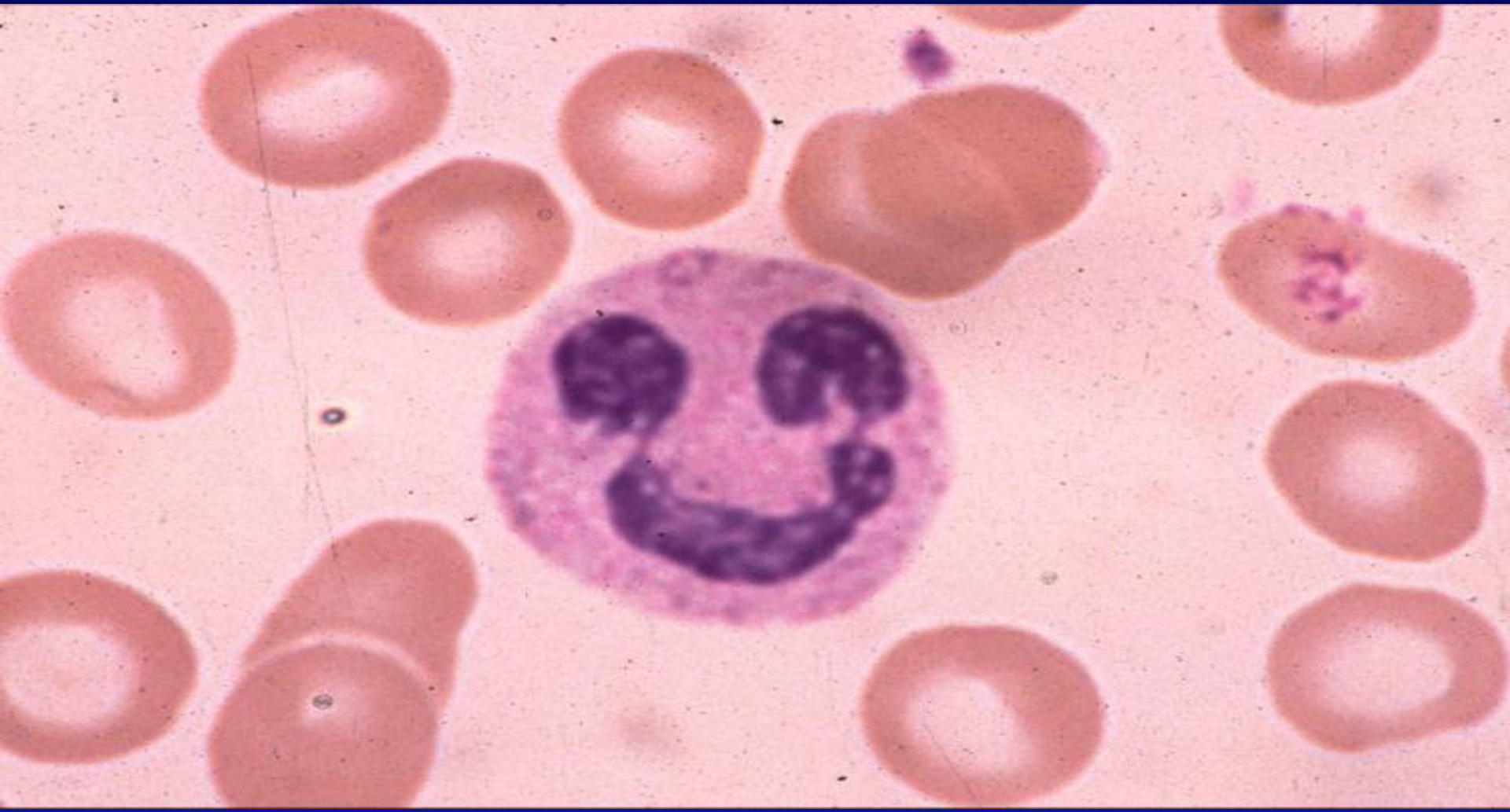
2010 ASCT (CY – HDM) (CR)
R/Z maintenance

2011 PD – RVD (PR)

2012 PD – PomVD (VGPR)

2013 PD (aggressive relapse with extra-medullary disease) DARA [501] 16 mg/kg (CR) to present (> 3 years) "Best I have ever felt since prior to diagnosis"

Thank YOU!!



Slide Courtesy of Phil McCarthy MD

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