Targeting Immune Modulation, Checkpoint Inhibition and Other Immune Based Therapy, including Monoclonal Antibodies, as Disease Therapy in Myeloma

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Key Targets in MM

Excess Protein Production:

- **Target Protein degradation**

Genomic abnormalities:

- **Target and overcome mutations**

Immune Suppression:

- **Restore anti-MM immunity**

Restoring Immune function:

Immunomodulatory drugs, other small molecules

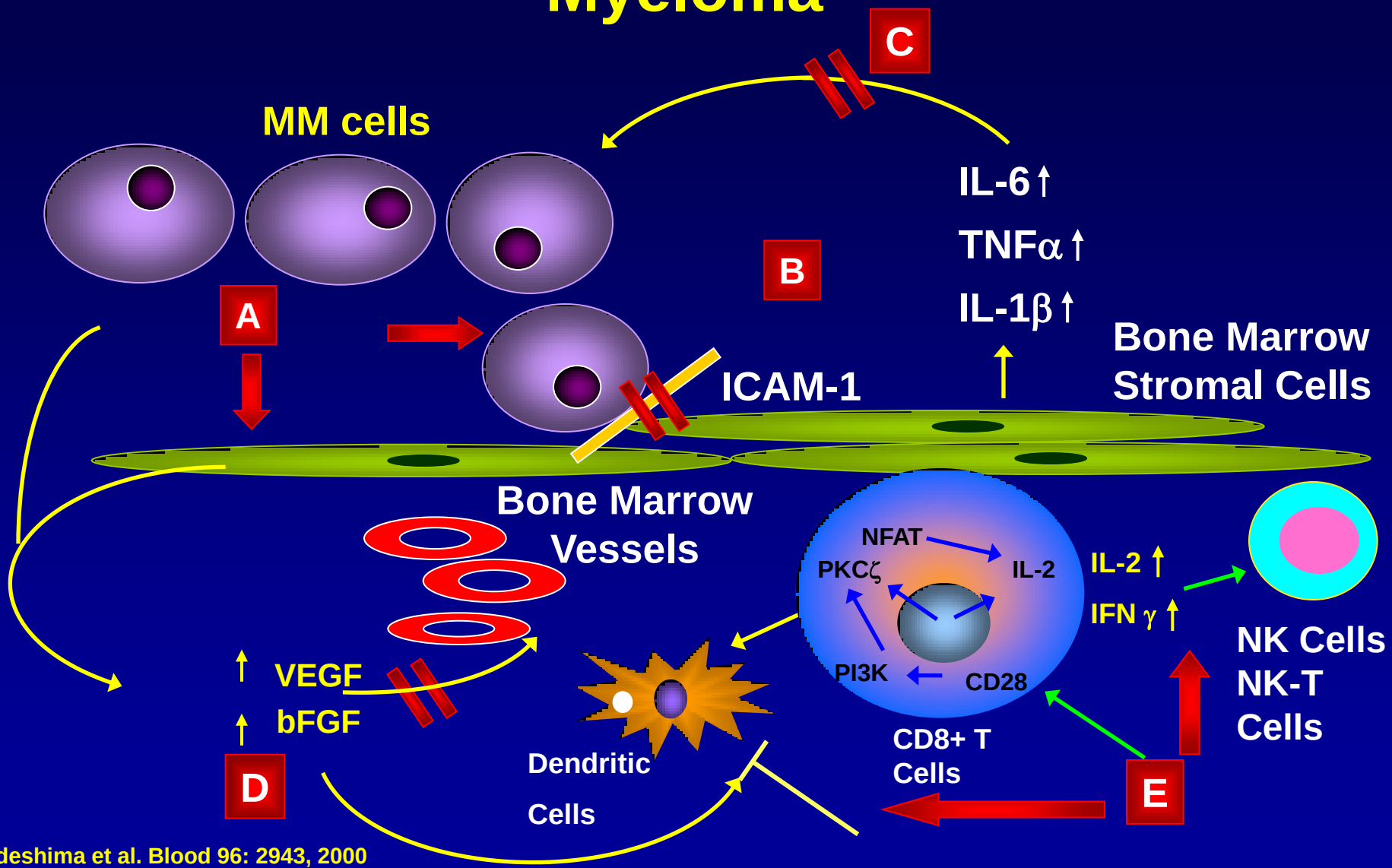
Monoclonal antibodies

Checkpoint inhibitors

Vaccines

Cellular therapies

Lenalidomide and Pomalidomide in Myeloma



Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001
Mitsiades et al. Blood 99: 4525, 2002

Lentzsch et al Cancer Res 62: 2300, 2002
LeBlanc R et al. Blood 103: 1787, 2004
Hayashi T et al. Brit J Hematol 128: 192, 2005

Immunomodulatory agents
IMiDs: mechanism of action

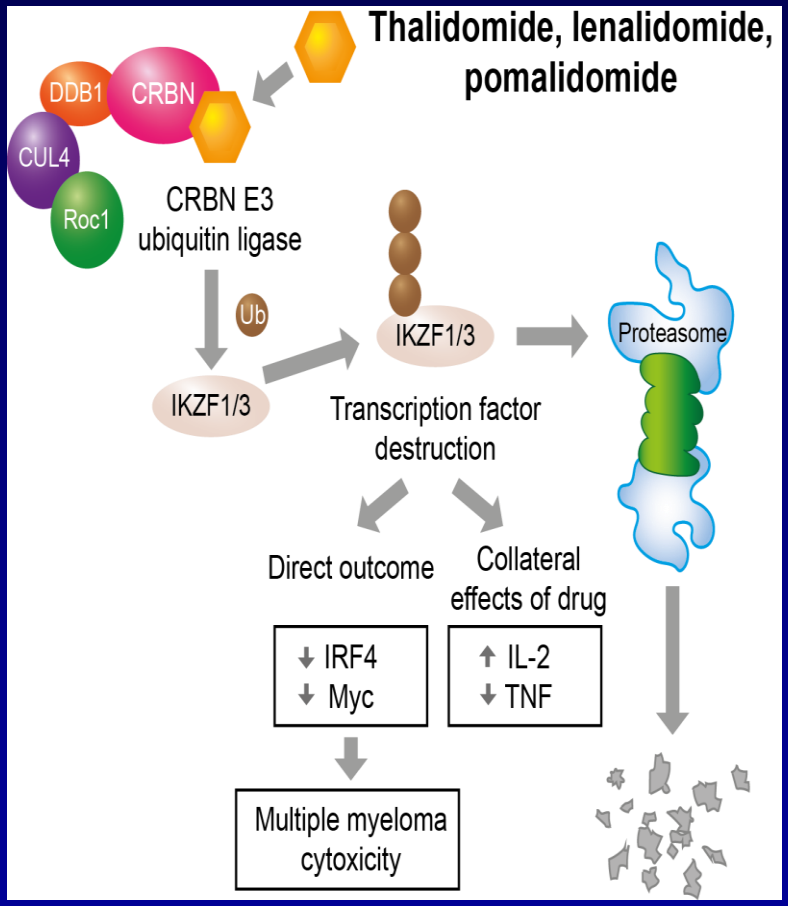
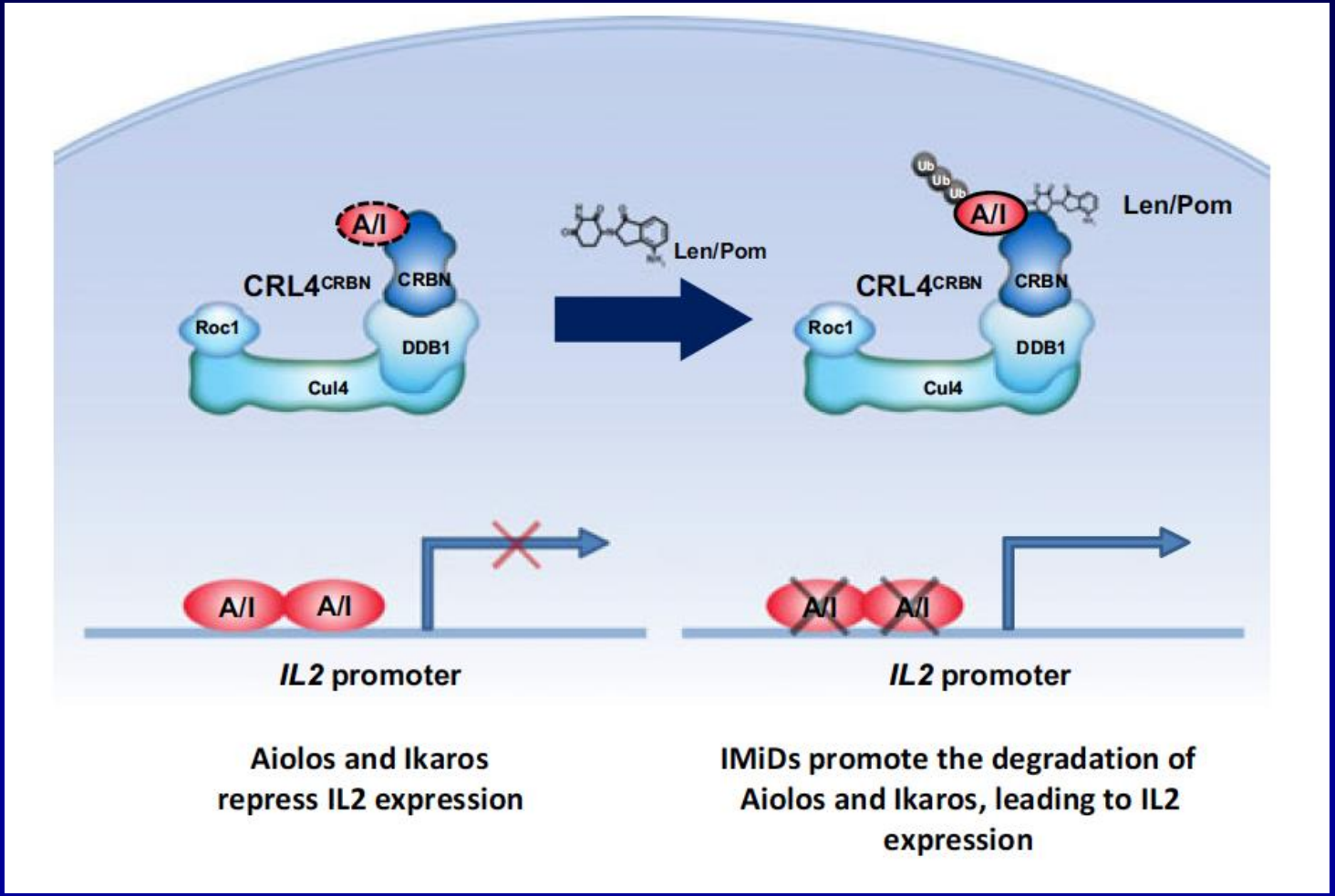


Figure adapted from Stewart KA. *Science* 2014; 343: 256-257.0
Kronke et al, *Science*, 2014
Lu et al, *Science*, 2014

Model of Lenalidomide and Pomalidomide Co-Stimulation of Tcells via Degradation of Aiolos and Ikaros



Gandhi AK et al. Brit J Haematol, 2013

blood®
2006 108: 3458-3464
doi:10.1182/blood-2006-04-015909 originally published online July 13, 2006

A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma

Paul G. Richardson, Emily Blood, Constantine S. Mitsiades, Sundar Jagannath, Steven R. Zeldenrust, Melissa Alsina, Robert L. Schlossman, S. Vincent Rajkumar, K. Raman Desikan, Teru Hideshima, Nikhil C. Munshi, Kathleen Kelly-Colson, Deborah Doss, Mary L. McKenney, Svetlana Gorelik, Diane Warren, Andrea Freeman, Rebecca Rich, Anfang Wu, Marta Olesnyckyj, Kenton Wride, William S. Dalton, Jerome Zeldis, Robert Knight, Edie Weller and Kenneth C. Anderson

blood®
2009 114: 772-778
doi:10.1182/blood-2008-12-196238 originally published online May 26, 2009

Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma

Paul Richardson, Sundar Jagannath, Mohamad Hussein, James Berenson, Seema Singhal, David Irwin, Stephanie F. Williams, William Bensinger, Ashraf Z. Badros, Robert Vescio, Laurie Kenvin, Zhinuan Yu, Marta Olesnyckyj, Jerome Zeldis, Robert Knight and Kenneth C. Anderson

Blood 2006 Nov 15;108(10):3458-64.
Blood 2009 Jul 23;114(4):772-8.

The NEW ENGLAND JOURNAL of MEDICINE

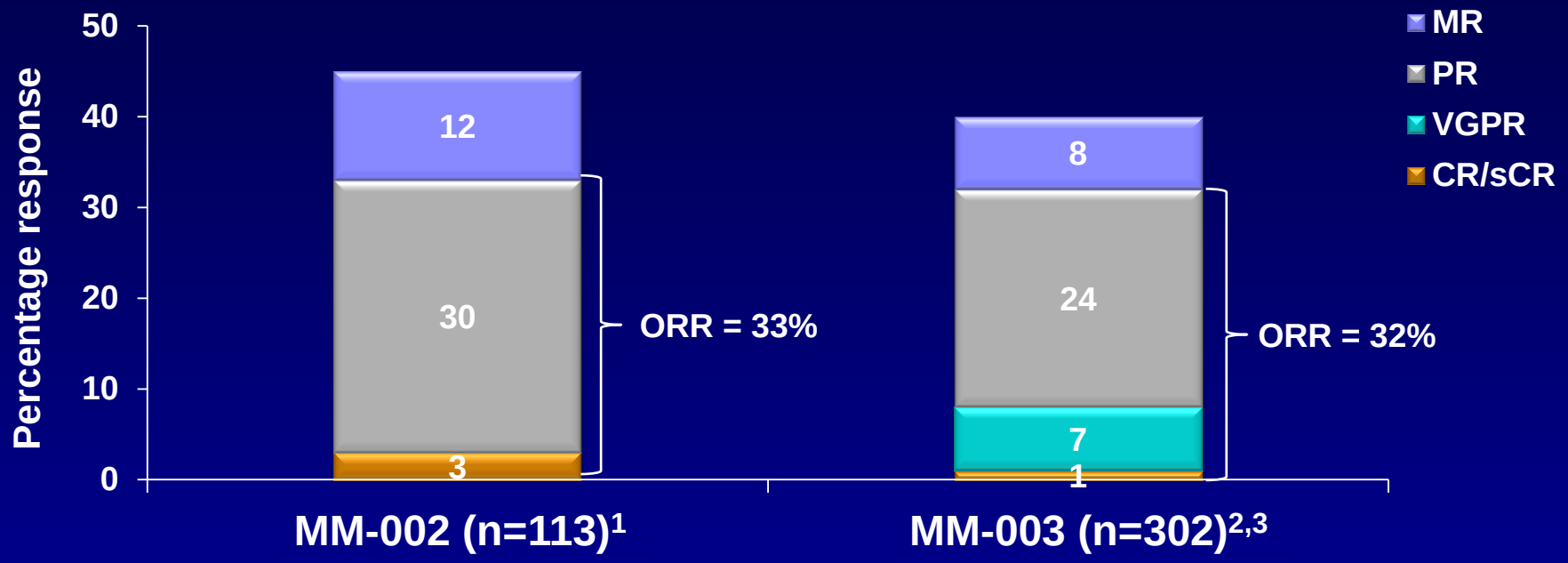
ORIGINAL ARTICLE

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.

Efficacy Results of POMALIDOMIDE + LoDEX in advanced RR MM (Phase II/III: MM002 & MM003)



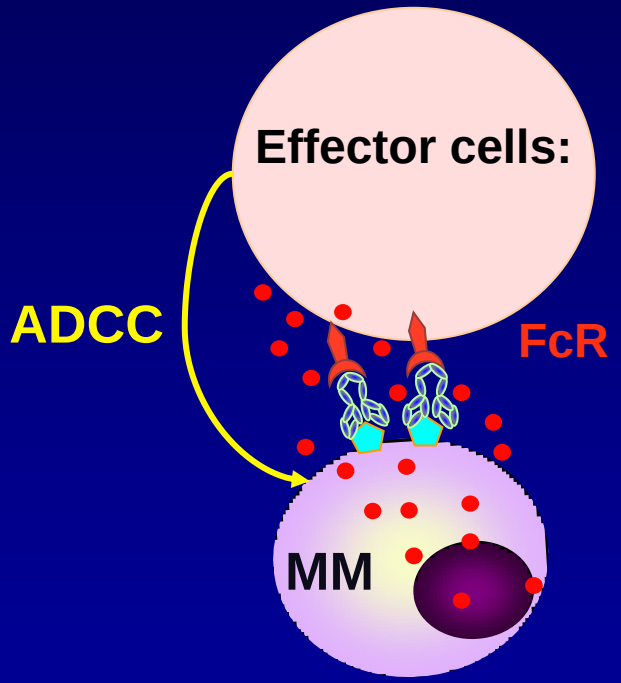
	MM-002[1]	MM-003[2,3]
Median follow-up, months	14.2	15.4
Median DoR, months	8.3	7.5
Median PFS, months	4.2	4.0
Median OS, months	16.5	13.1

CR, complete response; DoR, duration of response; LoDEX, low-dose dexamethasone; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1.Richardson PG, et al. *Blood* 2014;123:1826-32.
2. San Miguel J, et al. *Lancet Oncology* 2013;14:1055-1066.
3. San Miguel et al: ASH 2013; Oral Presentation and Abstract 686.

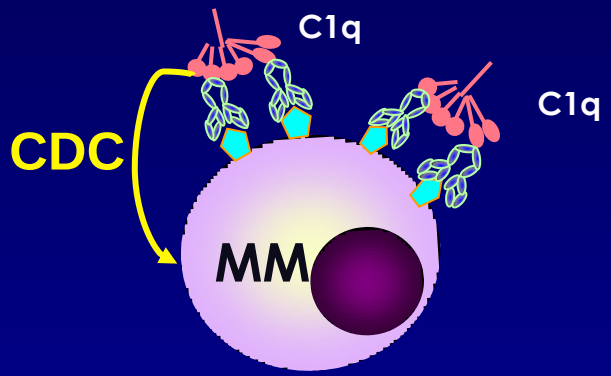
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)



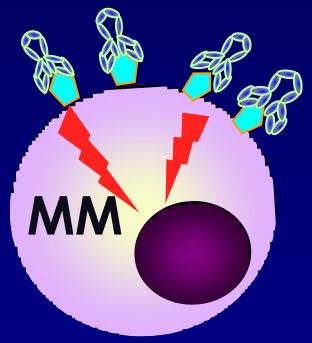
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1; SLAMF7)
- Daratumumab, SAR650984 (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)



- Daratumumab
- SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways

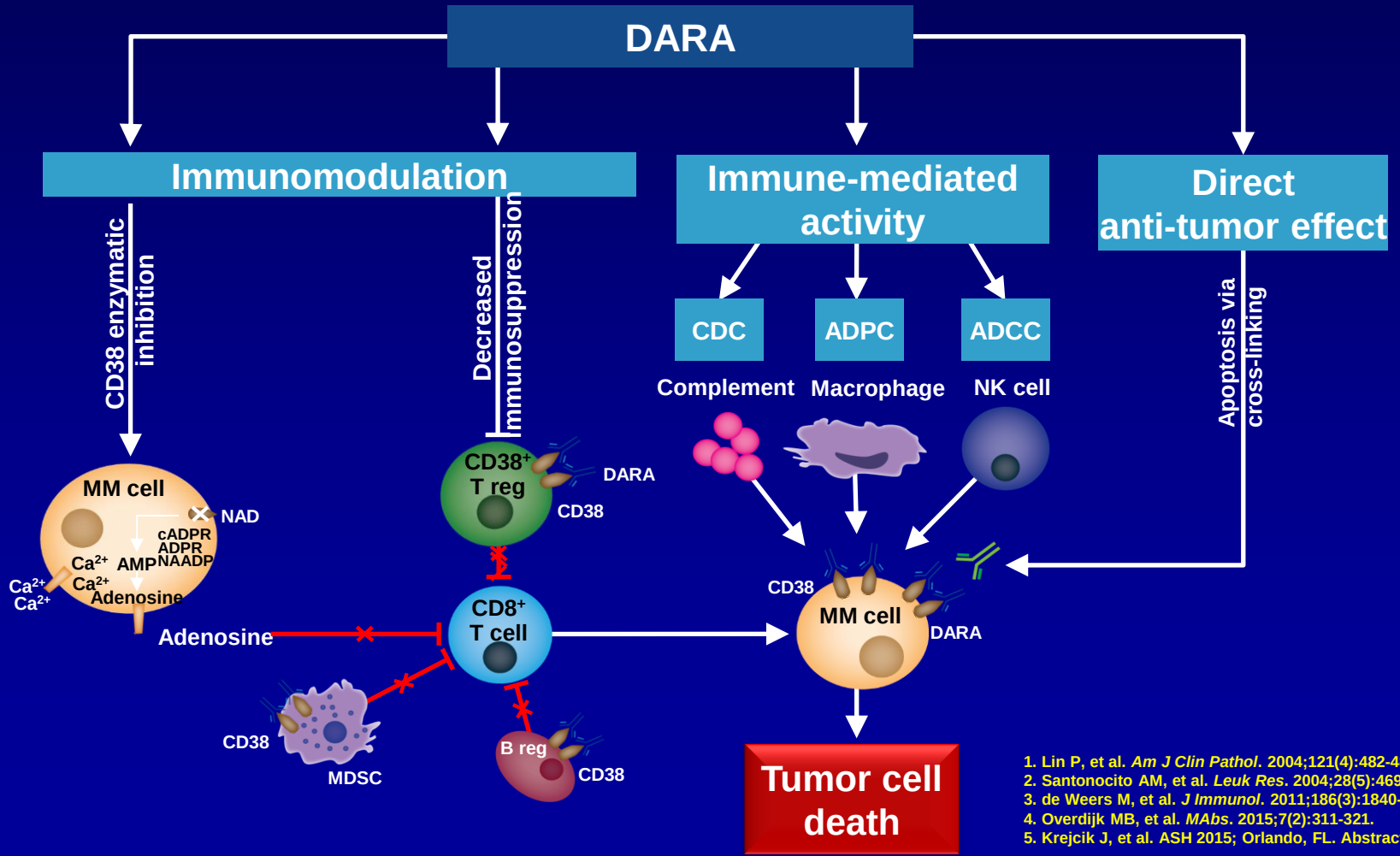


- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- Siltuximab (1339) (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab, SAR650984 (CD38)

Adapted from Tai & Anderson Bone Marrow Research 2011

DARA: Mechanisms of Action

- CD38 is highly and ubiquitously expressed on myeloma cells[1,2]
- DARA is a human IgG1 monoclonal antibody that binds CD38-expressing cells
- DARA binding to CD38 induces tumor cell death through direct and indirect mechanisms[3-5]



1. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488.
2. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Krejcik J, et al. ASH 2015; Orlando, FL. Abstract 3037.

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

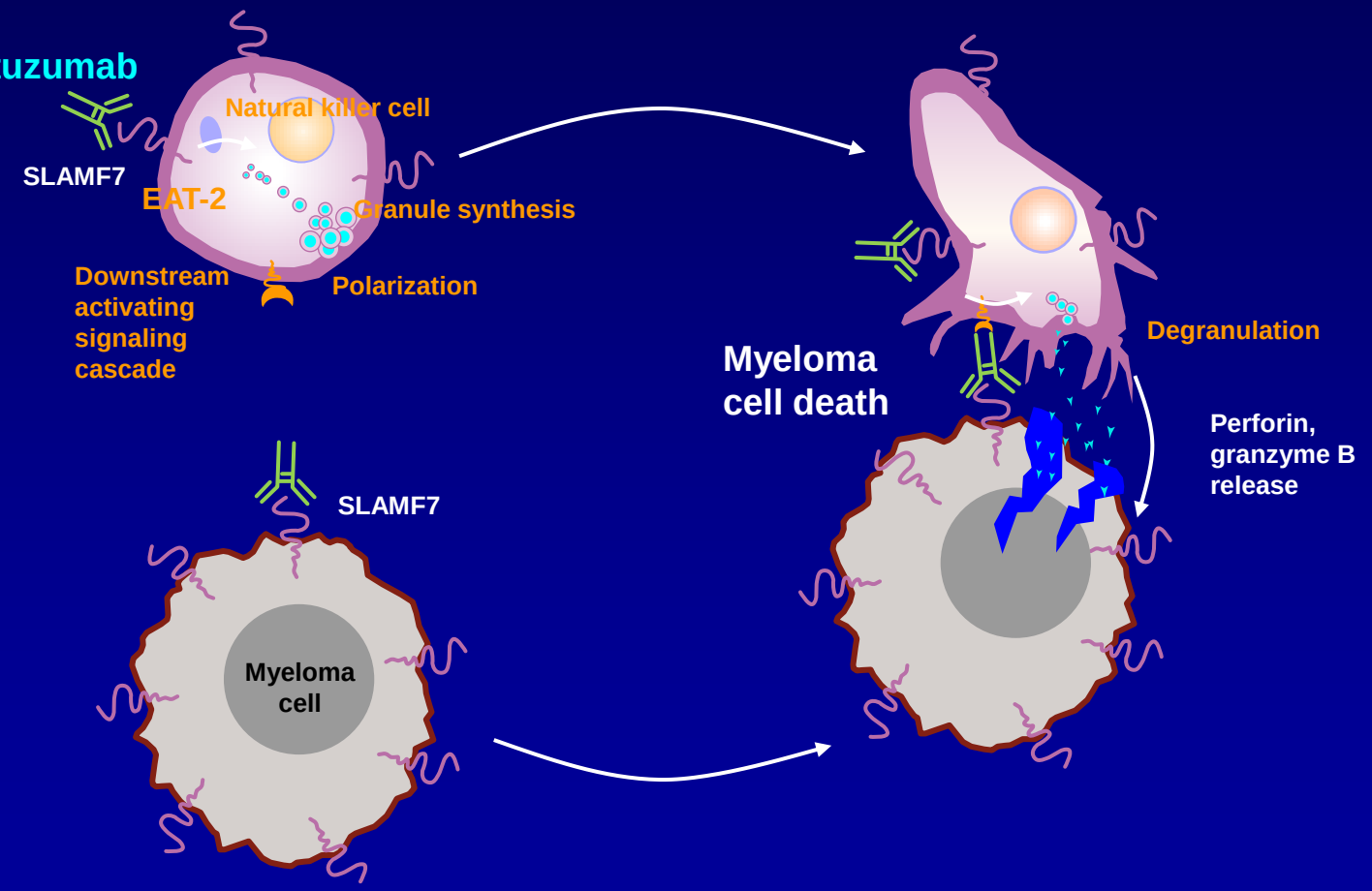
Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

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.**

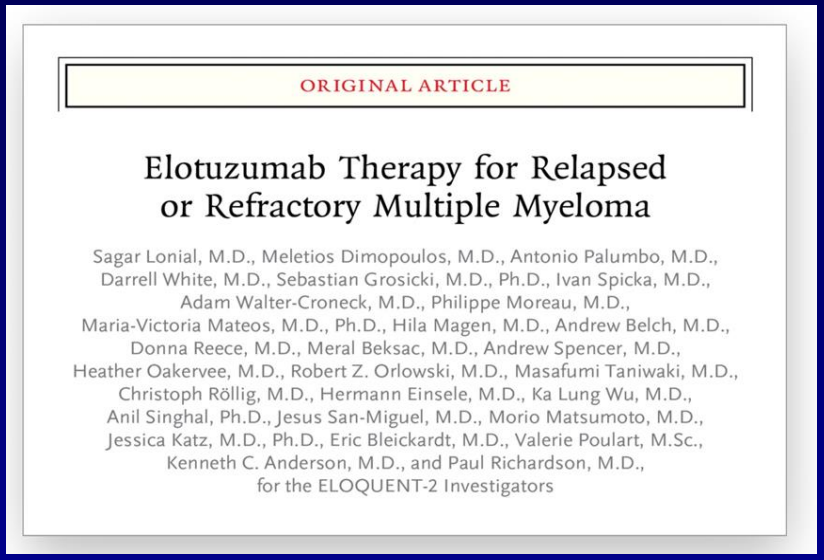
Elotuzumab: Immunostimulatory Mechanism of Action

- 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]



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

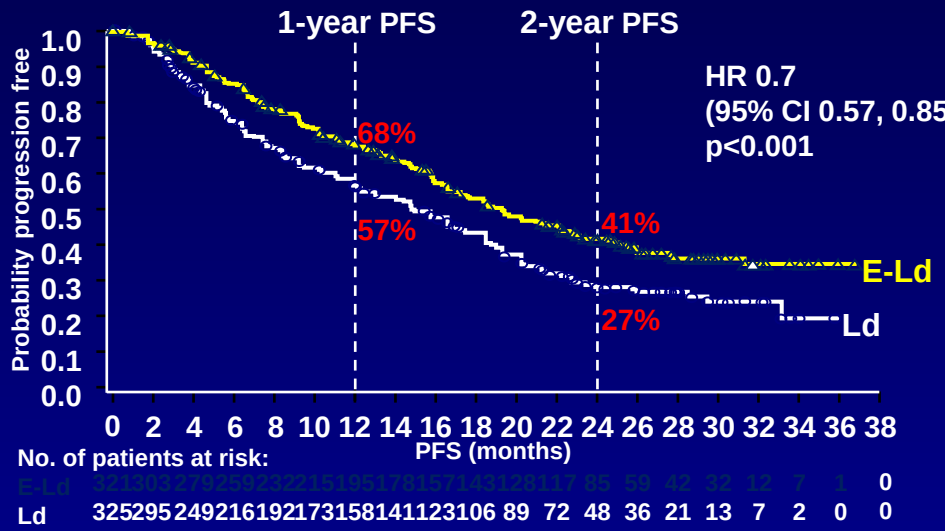


ORIGINAL ARTICLE

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



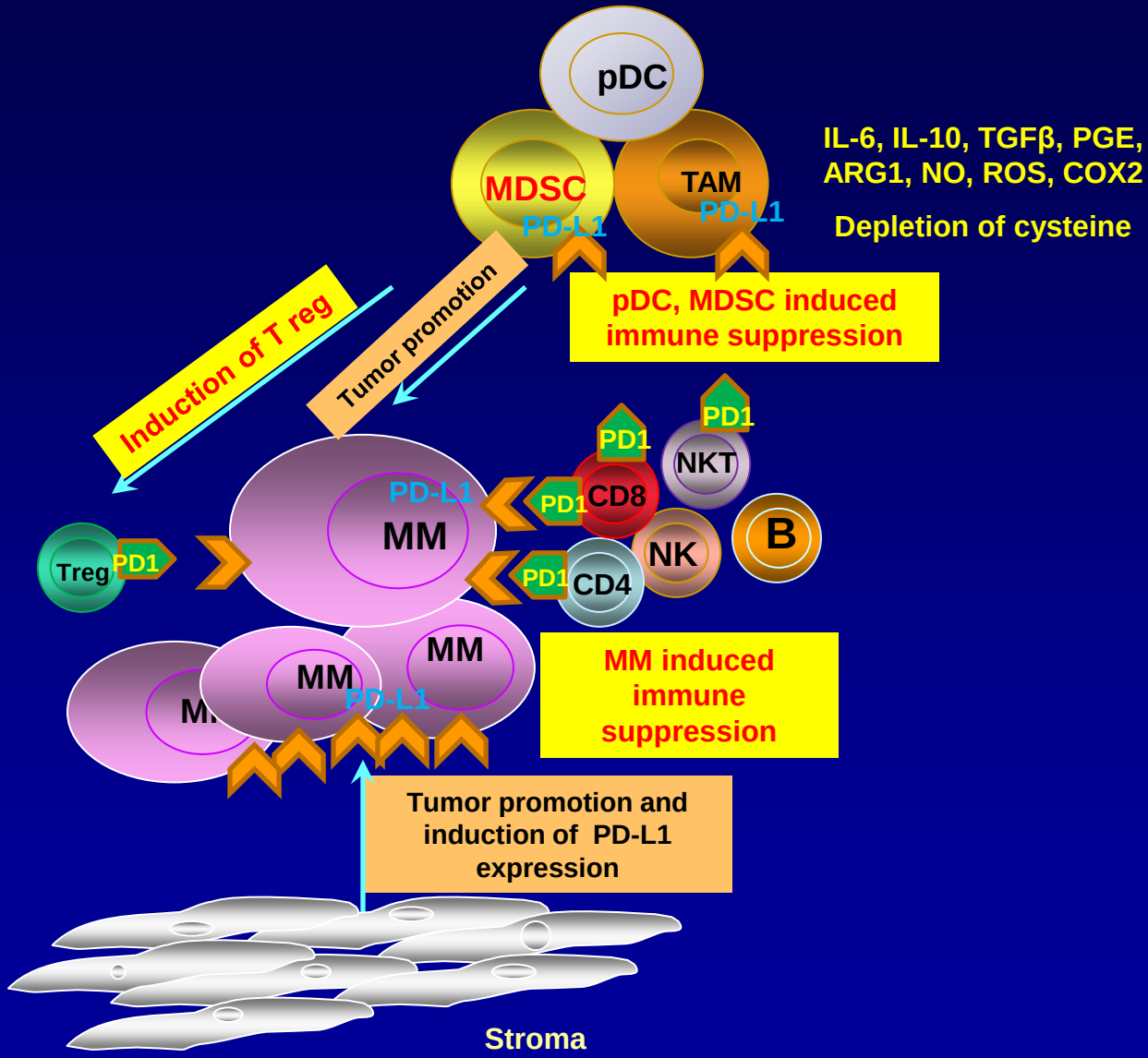
From *N Engl J Med*, Lonial S et al, Elotuzumab therapy for relapsed or refractory multiple myeloma, 373, 621–31. Copyright © 2015, Massachusetts Medical Society. Reprinted with permission

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.

Immune Suppressive Microenvironment in MM



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

Targeting the Multiple Myeloma Immunosuppressive Microenvironment ASH 2015

Blockade of PD1/PD-L1, alone or in combination:

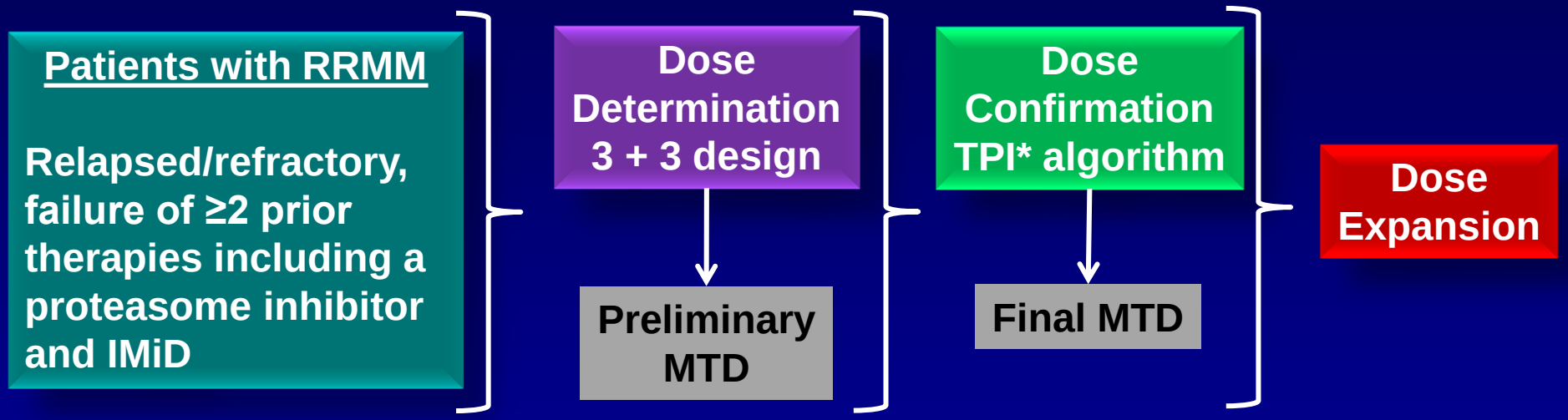
Inhibits accessory (BMSC, MDSC, pDCs) cell and augments immune cell (CD4T, CD8T, NK,NKT,Monocyte/Macrophage) function

Inhibits multiple myeloma (MM) cell growth in the BM milieu.

Trials of ongoing combination therapies : IMiDs, MoAbs, PD-L1/PD-1 blockade, vaccines, and cellular therapies – Len/dex and Pom/dex + PEMBRO
ORR 65% in RRMM, with manageable toxicity

San- Miguel J, et al ASH 2015
Badros A, et al ASH 2015

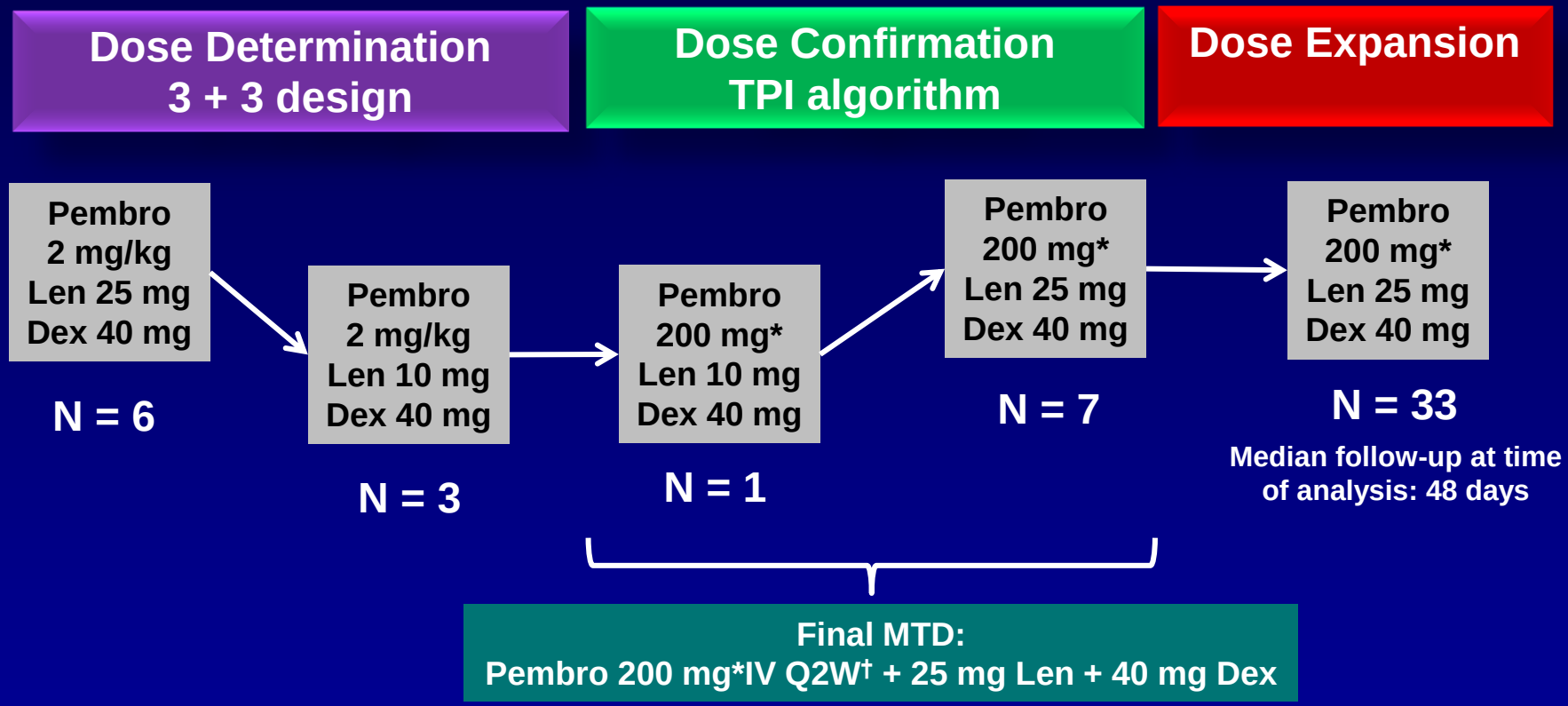
KEYNOTE-023: Phase 1 Trial of Pembrolizumab + Lenalidomide and Low Dose Dexamethasone in RRMM



- Primary end points: Safety and tolerability
- Secondary end points: ORR, DOR, PFS, OS

*TPI = Toxicity Probability Interval (Ji Y et al. Clin Trials. 2007;4:235-244)

KEYNOTE-023: Study Chronology



- Safety analysis: all patients enrolled in the study (N = 50)
- Efficacy analysis: patients in the dose determination and confirmation stages (N = 17)

*Pembrolizumab 2 mg/kg ≈ 200 mg fixed dose Q2W (based upon PK/PD studies)
† Pembrolizumab IV 30 minutes (no premedication) Q2W, lenalidomide 1-21 day, dexamethasone weekly

J. San Miguel, December 7, 2015

KEYNOTE-023: Baseline Characteristics

	Pembro + Len + Dex (N = 50)
Age, median (range)	62 (46-77)
Sex, n (%)	
Male	32 (64)
Female	18 (36)
Cytogenetics, n (%)	
High risk [del17p, t(4:14) and/or t(14:16)]	5 (11)
1q amp	6 (13)
del13q	6 (13)
Standard	29 (63)
Not available	4
β2-microglobulin, n (%)	
≥5.5 mg/L	8 (16)
≥3.5 - <5.5 mg/L	9 (18)
<3.5 mg/L	33 (66)
LDH, n (%)	
>400 IU/L	22 (44)
≤400 IU/L	28 (56)

Data cutoff date: September 22, 2015

J. San Miguel, December 7, 2015

KEYNOTE-023: Prior Lines of Therapies

	Pembro + Len + Dex N = 50
Prior therapies, median (range)	4 (1-5)
≥3 Lines of therapy, n (%)	36 (**72**)
Prior therapies, n, (%) Lenalidomide Bortezomib Pomalidomide Carfilzomib	 48 (**96**) 48 (**96**) 13 (**26**) 11 (**22**)
Prior ASCT, n (%)	43 (**86**)

	Pembro + Len + Dex N = 50	
Refractory to lenalidomide, n (%)*	38 (**76**)	
Double refractory	15 (30)	50%
Triple refractory	6 (12)	
Quadruple refractory	4 (8)	
Refractory to bortezomib, n (%)	32 (64)	
Refractory, last line, n (%)	40 (**80**)	
Refractory to lenalidomide as last line, n (%)	10 (20)	

***Double refractory = Len/Bort**
Triple refractory = Len/Bort/Pom or Len/Bort/Carf
Quadruple refractory = Len/Bort/Pom/Carf

Data cutoff date: September 22, 2015

KEYNOTE-023: Most Common AEs Related to Study Drug

n (%)	Pembro + Len + Dex N = 50	
	All AEs	Grade 3/4
All AEs	36 (72)	23 (46)
AEs in ≥4 Patients		
Neutropenia	12 (24)	11 (22)
Thrombocytopenia	14 (28)	4 (8)
Diarrhea	8 (16)	1 (2)
Fatigue	7 (14)	1 (2)
Anemia	6 (12)	4 (8)
Pruritus	6 (12)	0 (0)
Hyperglycemia	5 (10)	3 (6)
Muscle spasms	5 (10)	1 (2)
Myalgia	4 (8)	0 (0)
Constipation	4 (8)	0 (0)
Asthenia	4 (8)	0 (0)

- **AEs consistent with individual drug safety profiles for approved indications**
- **AEs associated with pembrolizumab were similar to other indications**
- ***Incidence may be underestimated due to limited drug exposure***

Data cutoff date: September 22, 2015

J. San Miguel, December 7, 2015

KEYNOTE-023: Immune Mediated AEs

	Pembro +Len + Dex N = 50
Adrenal insufficiency	
Grade 2	1 (2)
Hyperthyroidism	
Grade 1	1 (2)
Grade 2	1 (2)
Hypothyroidism	
Grade 1	2 (4)
Thyroiditis	
Grade 1	1(2)

- No dose modification or treatment discontinuation required for management of the reported immune related AEs
- No cases of pneumonitis or colitis were reported
- No infusion reactions were reported

Data cutoff date: September 22, 2015

J. San Miguel, December 7, 2015

KEYNOTE-023: Antitumor Activity

Dose Determination and Dose Confirmation Stages

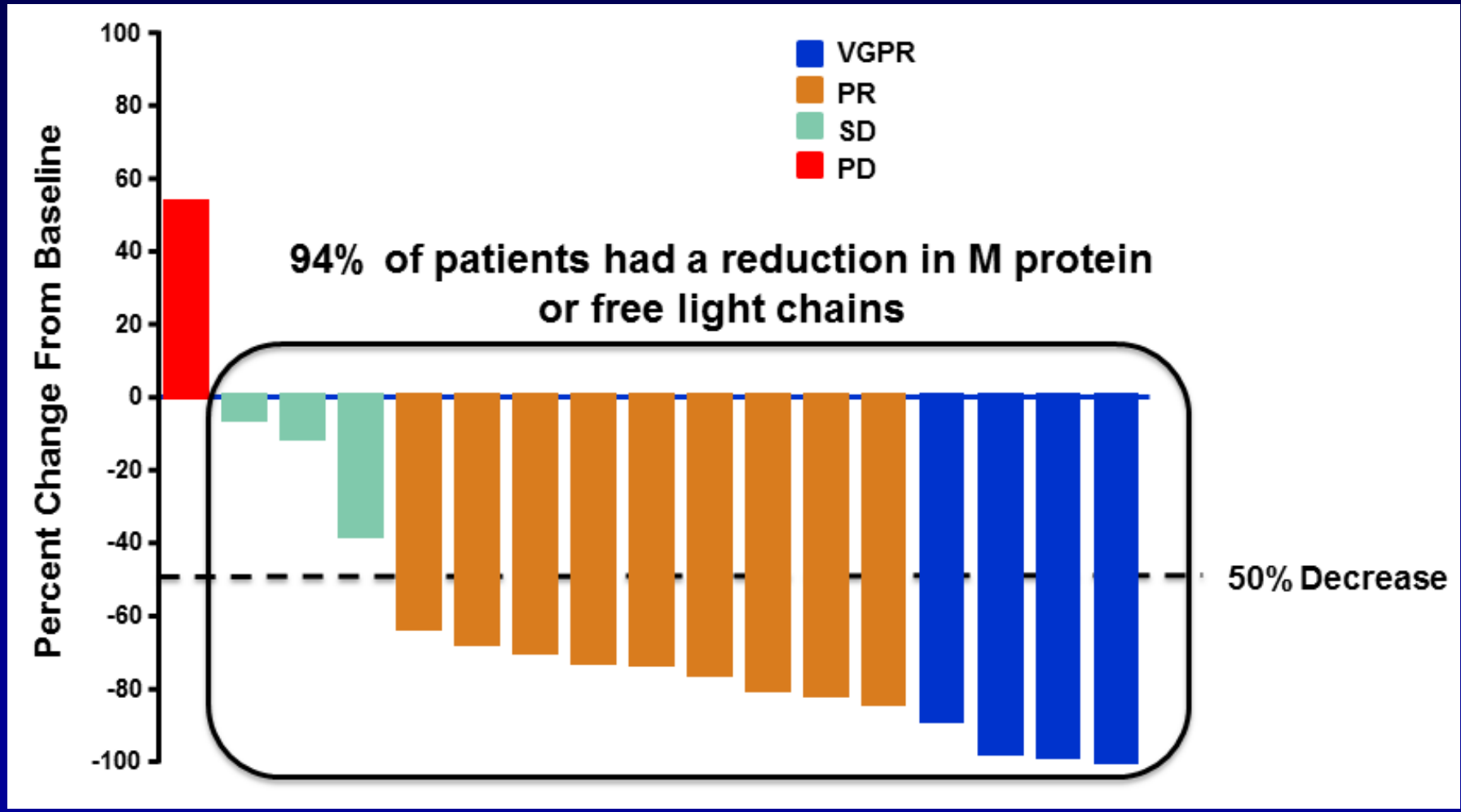
N (%)	Total N = 17	Len Refractory* N = 9
Overall Response Rate	13 (**76**)	5 (**56**)
Very Good Partial Response	4 (**24**)	2 (**22**)
Partial Response	9 (**53**)	3 (**33**)
Disease Control Rate†	15 (**88**)	7 (**78**)
Stable Disease	3 (**18**)	3 (**33**)
Progressive Disease	1 (**6**)	1 (**11**)

*3 patients double refractory and 1 triple refractory (Len/Bor + Pom)
†Disease Control Rate = CR + VGPR + PR + SD > 12 weeks

Data cutoff date: September 22, 2015

J. San Miguel, December 7, 2015

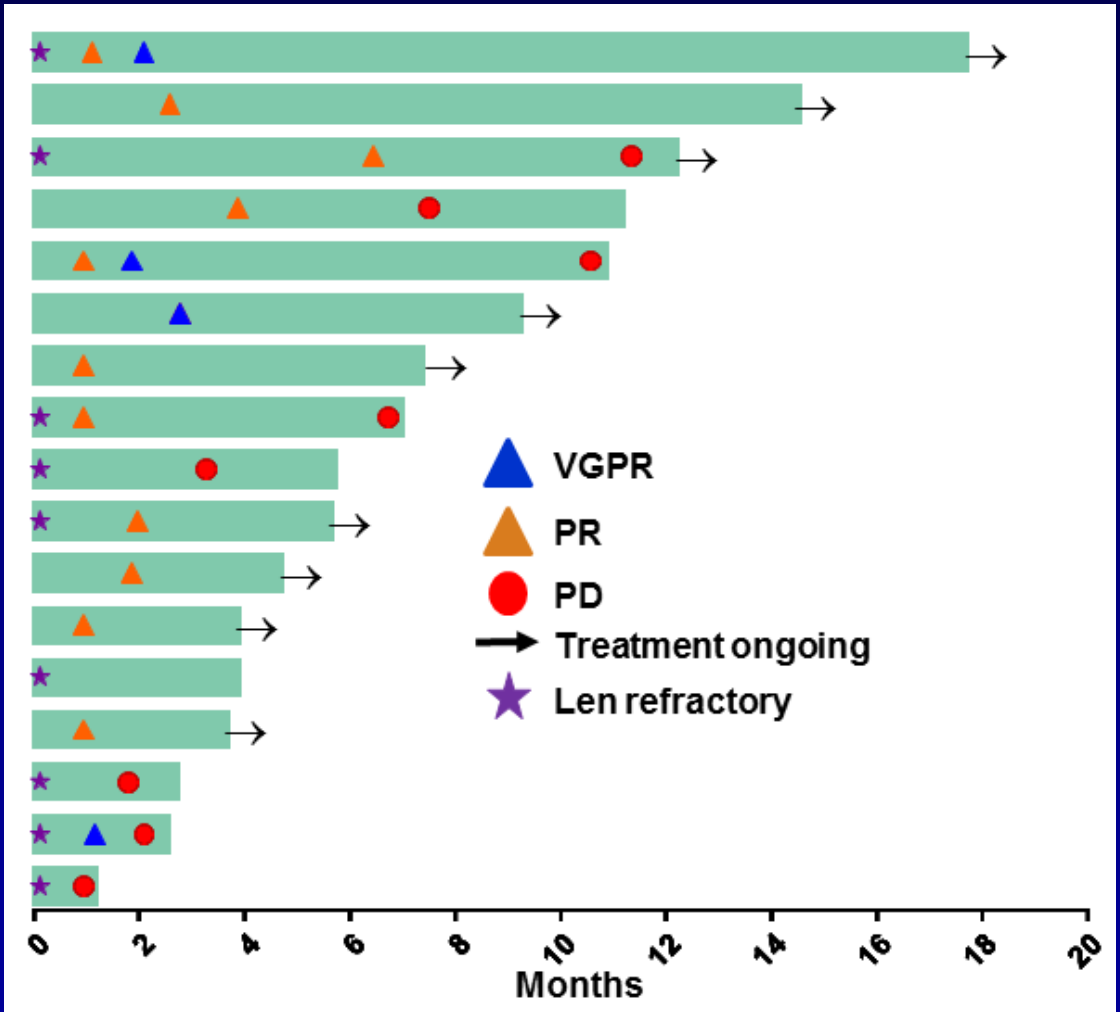
KEYNOTE-023: Maximum Change from Baseline in Level of M Protein or Free Light Chains



Data cutoff date: September 22, 2015

J. San Miguel, December 7, 2015

KEYNOTE-023: Time Since Initiation of Treatment



- Median (range) follow-up
  - 296 days (132-560)
- Median DOR: 9.7 month
- Median (range) time to achieve first objective response
  - 1.2 month (1.0 – 6.5)
- 11% of patients upgraded the quality of response

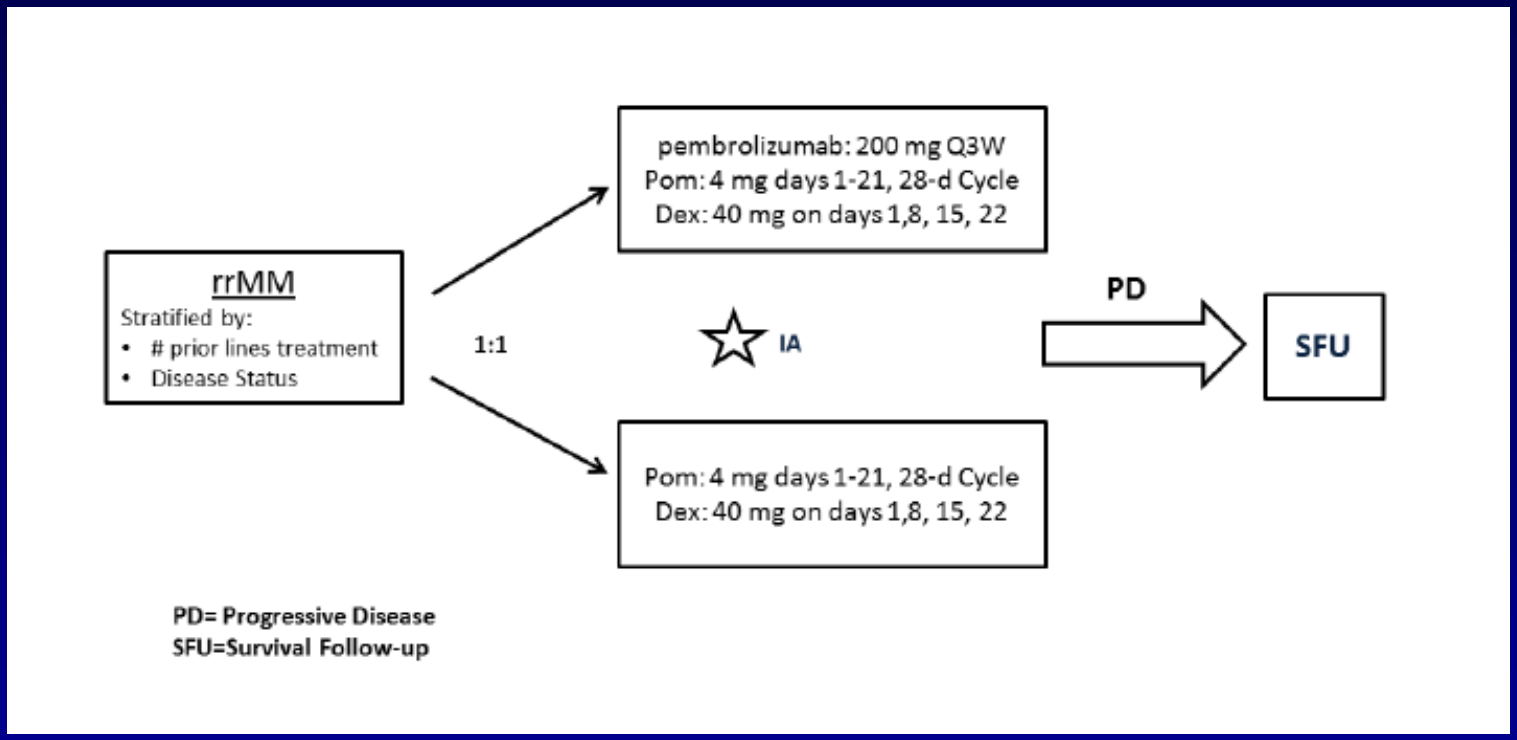
Data cutoff date: September 22, 2015

J. San Miguel, December 7, 2015

Conclusions

- **MTD/MAD was defined as pembrolizumab 200 mg in combination with lenalidomide 25 mg and low-dose dexamethasone 40 mg**
- **Preliminary data suggest that this treatment combination has an acceptable safety and tolerability profile, and is consistent with Aes reported for pembrolizumab in solid tumors**
- **Initial efficacy results show promising activity in heavily pretreated patients with RRMM and support the continued development of pembrolizumab in patients with multiple myeloma**

KEYNOTE-183: A phase III study of Pomalidomide and low dose Dexamethasone with or without Pembrolizumab (MK3475) in refractory or relapsed and refractory Multiple Myeloma (rrMM). (NCT02576977)



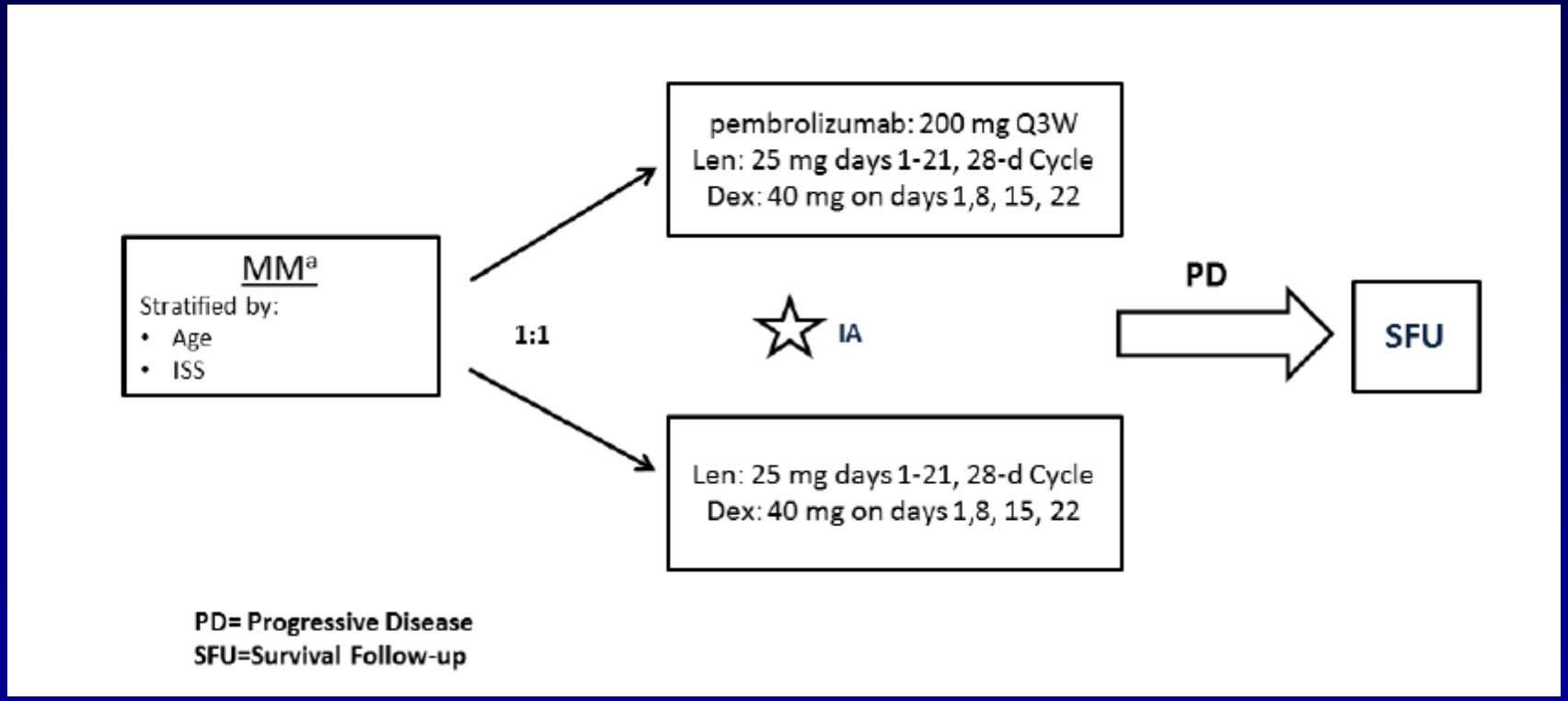
Patient Population:

- **≥ 2 treatment lines of prior therapy and failed their last line of treatment (refractory to last line of treatment).**
- **Prior anti-myeloma treatments must have included an IMiD AND proteasome inhibitor alone or in combination and must have failed therapy with an IMiD OR proteasome inhibitor (refractory or relapsed and refractory)**

Endpoints:

- **PFS (primary), OS, ORR, DOR, PFS2, Safety, biomarkers, patient reported outcome.**

KEYNOTE-185: A phase III study of Lenalidomide and low dose Dexamethasone with or without Pembrolizumab (MK3475) in in Newly Diagnosed and Treatment-Naïve Multiple Myeloma. (NCT02579863)



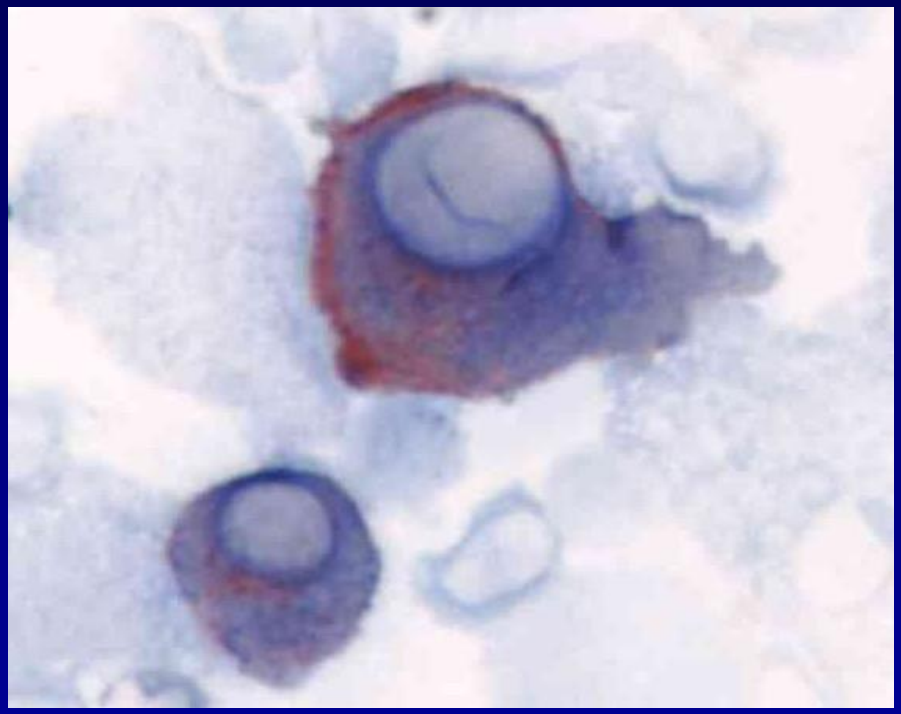
Patient Population:

- Newly diagnosed, treatment naïve, ineligible to receive treatment with ASCT

Endpoints:

- PFS (primary), OS, PFS2, ORR, DCR, DOR, Safety, biomarkers, patient reported outcome.

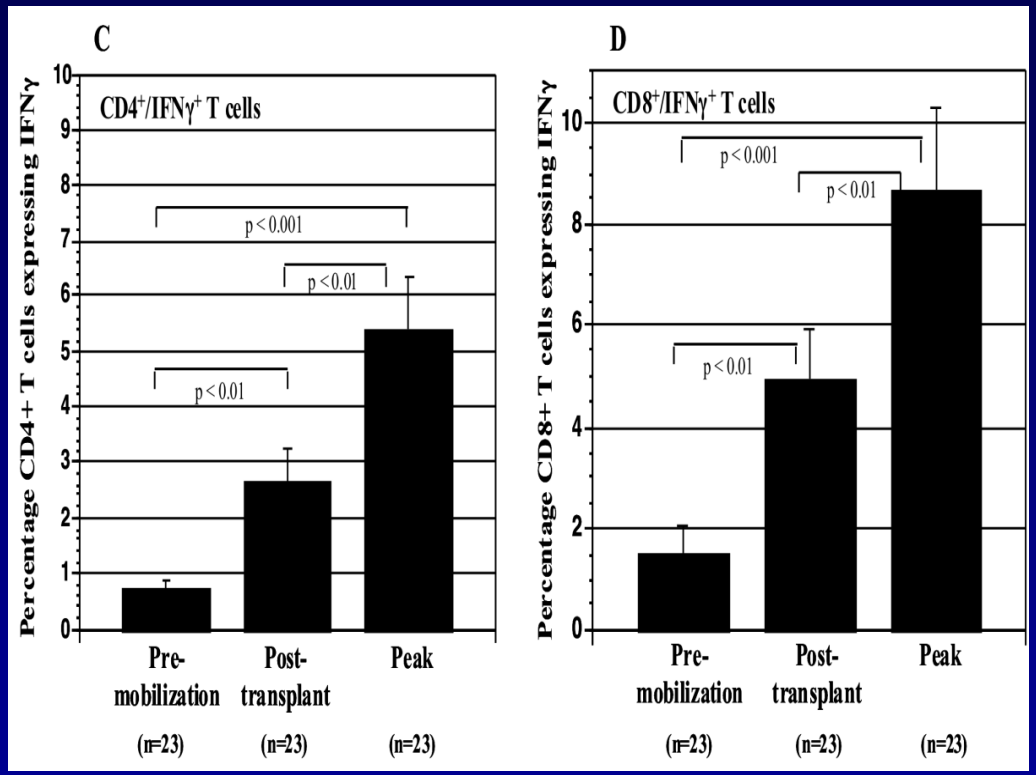
Phase I Trial of Vaccination with DC/MM Fusions in Relapsed Refractory MM

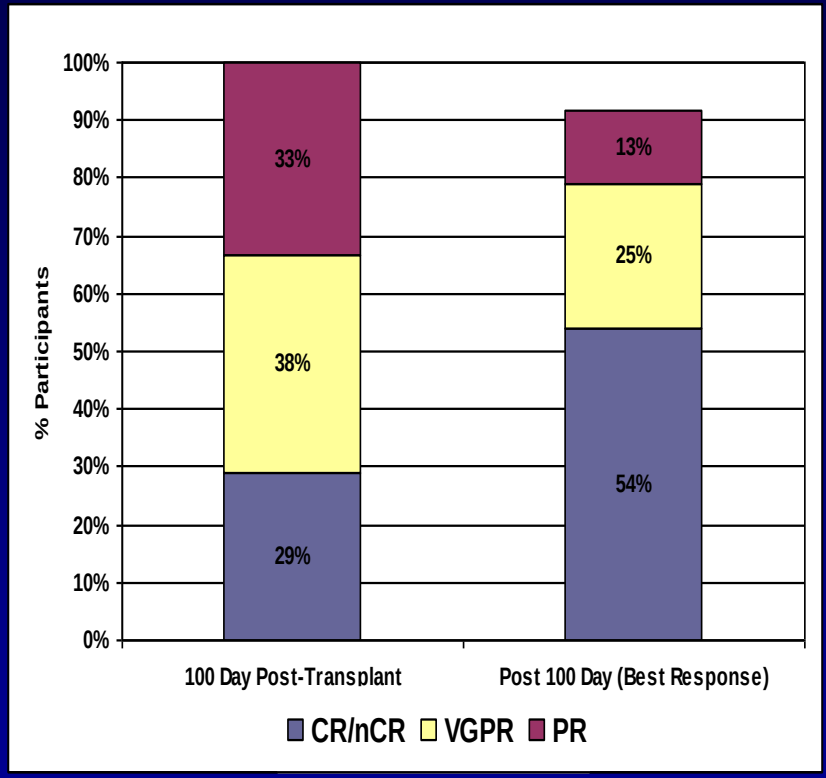


- Well tolerated, no autoimmunity
- Induced tumor reactive lymphocytes in a majority of patients
- Induced humoral responses to novel antigens (SEREX analysis)
- Disease stabilization in 70% of patients
- DC/MM fusions induce anti-MM immunity in vitro and inhibit MM cell growth in vivo in xenograft models

Rosenblatt et al Blood 2011; 117:393-402.
Vasir et al. Brit J Hematol 2005; 129: 687-700

MM/DC Vaccination following Autologous PBSCT for Myeloma





Ongoing CTN Randomized trial of lenalidomide with or without vaccine posttransplant

Rosenblatt et al, CCR 2013; 19: 3640-8.

Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses

Clinical trials:

Immune responses to vaccine in all patients

Lenalidomide with vaccine to augment immune response

Lenalidomide and PDL-1 with vaccine to induce memory Immune response against myeloma

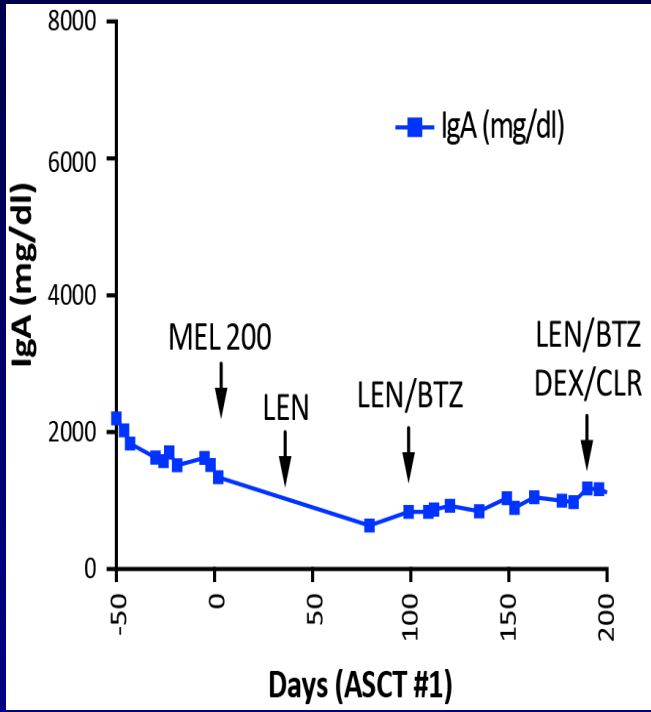
Bae et al, Leukemia 2011; 25:1610-9.
Bae et al, Brit J Hematol 2011; 155: 349-61.
Bae et al, Brit J Hematol 2012; 157: 687-701.
Bae et al, Clin Can Res 2012; 17:4850-60.
Bae et al, Leukemia 2015

Myeloma CAR therapy ASH 2015

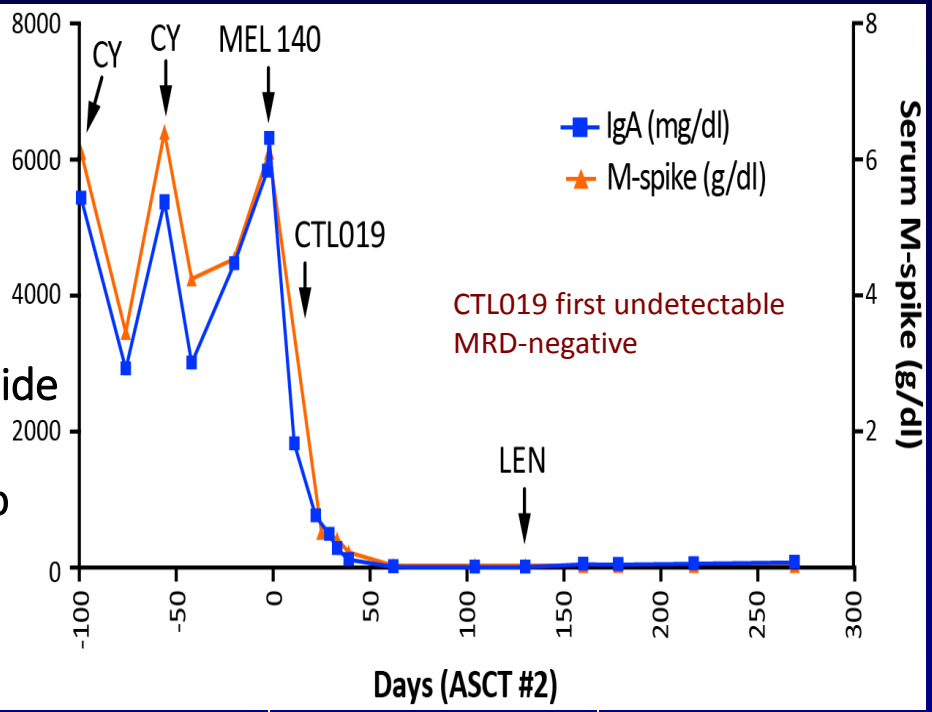
- **Multiple promising targets:**
  - **CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA**
- **Functional CAR T cells can be generated from MM patients**
- **CAR T and NK cells have in vitro and in vivo activity against MM**
- **Clinical trials underway**
  - **Anecdotal prolonged 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**

Stadtmauer et al, NEJM 2015

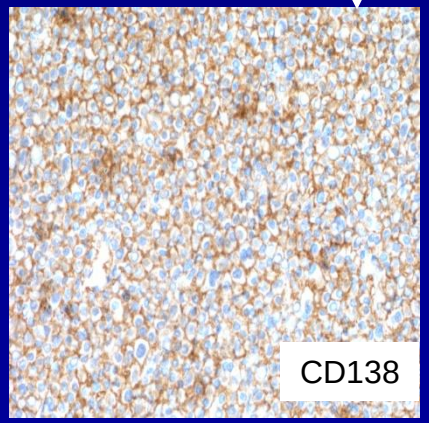
MM Pt #1: Response to CD19 CAR Therapy

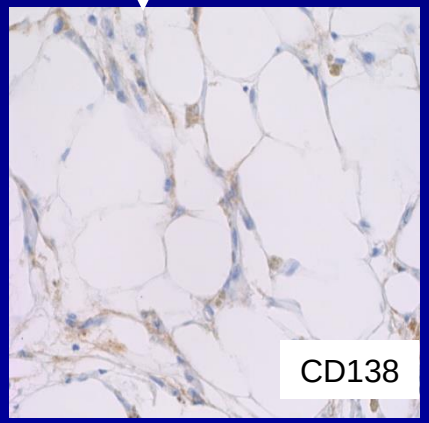


Additional regimens including...
- carfilzomib
- pomalidomide
- vorinostat
- elotuzomab



>> sCR, MRD neg
>> D +307 (per paper)
>> TTP after ASCT #1 D+190
>> Remission inversion
>> Relapsed after 1 yr – now in response to DARA

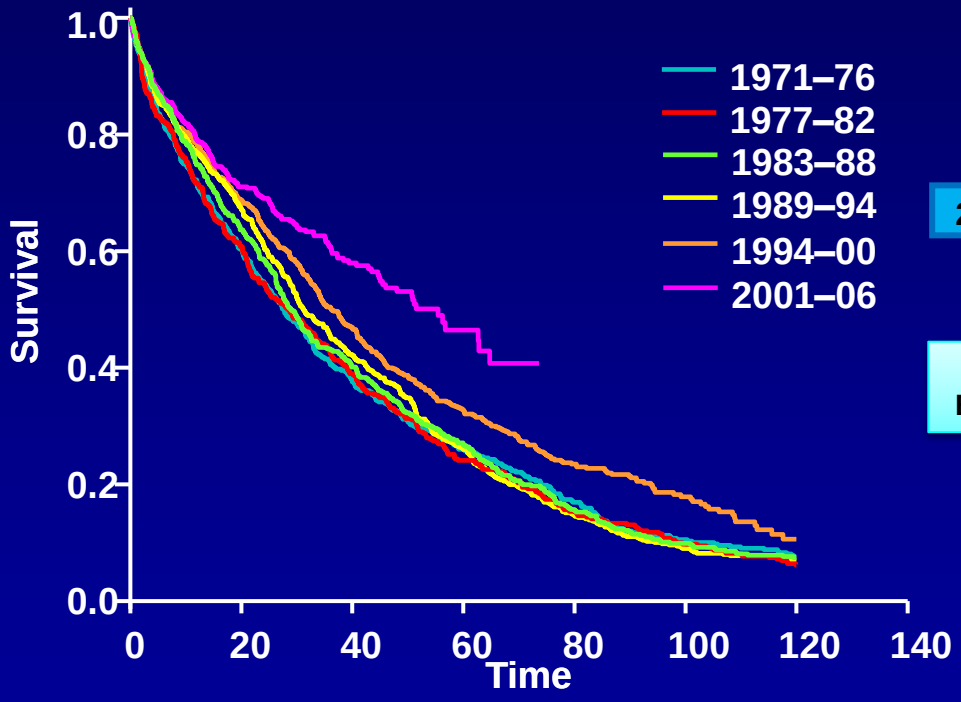




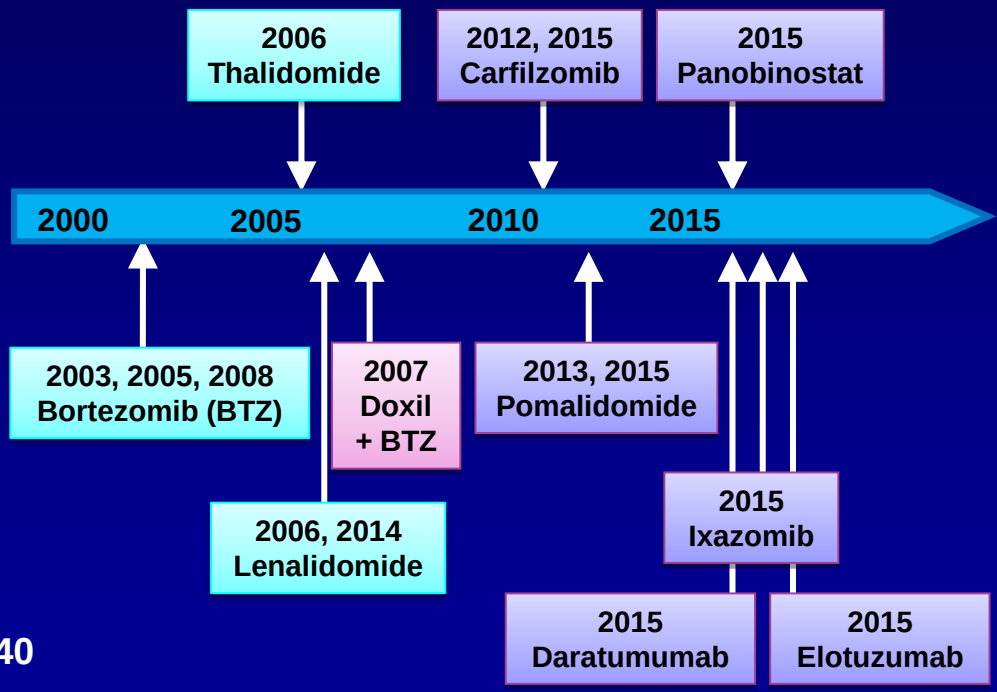
Garfall et al, *NEJM* 2015; 373: 1040-7

Outcomes in Myeloma; Continued Progress and Real Hope

Changes in OS from 1970-2006



FDA Approvals in MM

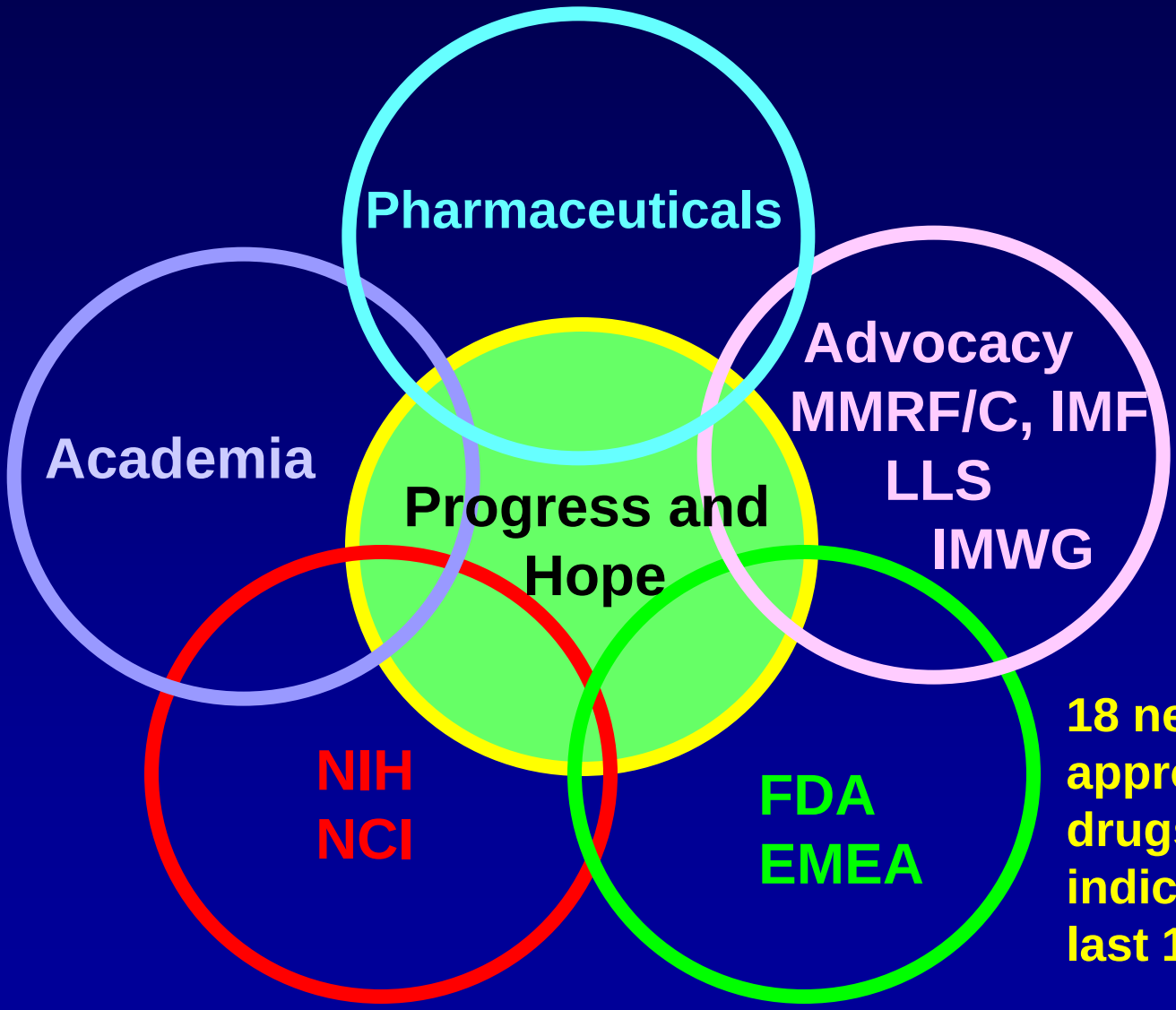


Kumar SK, et al. *Blood.* 2008;111(5):2516-2520
Richardson PG et al, ASH 2015

Integration and Impact of Novel Agents, including Immune Therapies

- Innovations (PIs, IMiDs) to date have produced significant improvements in PFS and OS: recent approvals (e.g. Carfilzomib, Ixazomib) will augment this
- Next wave of therapies….. crucially, agnostic to mutational thrust?
- Baseline immune function appears to also be a key barrier to success but may be targetable (e.g. use of PD1/PDL1 blockade)
- MoAbs (Elo, DARA, ISA) have activity 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. AC 241) are further expanding therapeutic opportunities with combinations
- Numerous other small molecule inhibitors show promise (e.g. HDACi's, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/Myc, DUBs, MEK)
- Further refinement of prognostics and MRD will guide therapy

Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside



18 new FDA-approved drugs/combos/ indications in last 13 yrs