Clonal Evolution in Myeloma: What have We Learned and How Can We Drive Future Treatment Strategies? A Clinical Perspective….

Paul G. Richardson, MD

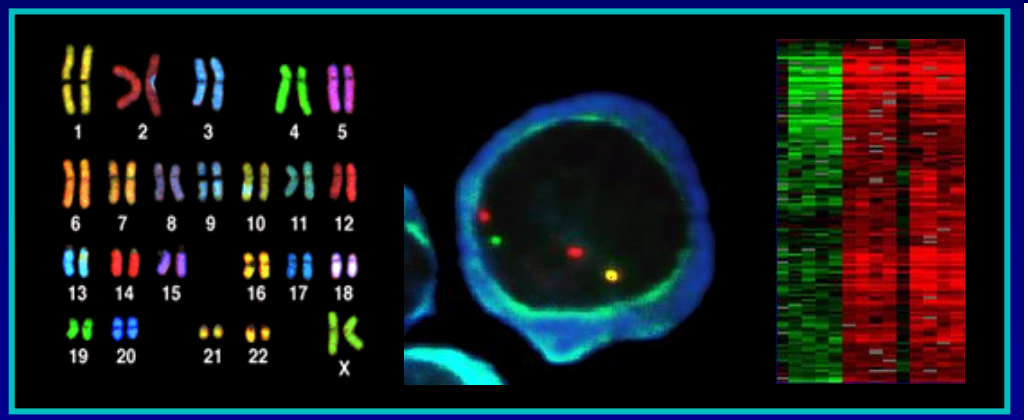
RJ Corman Professor of Medicine,
Harvard Medical School

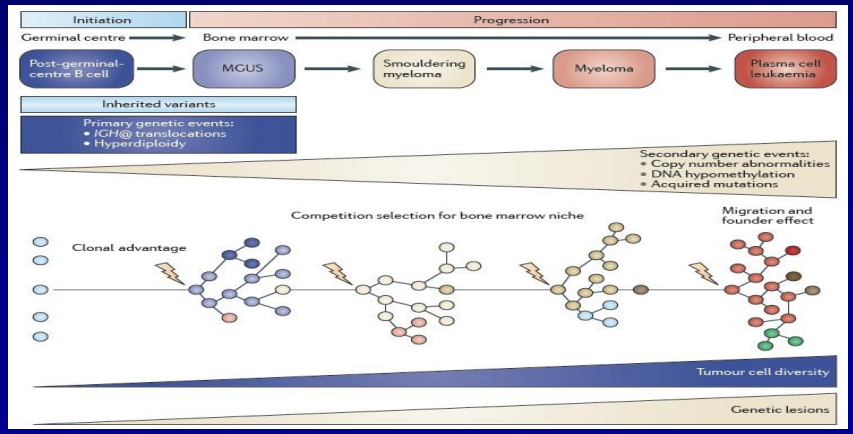
Clinical Program Leader, Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Boston, Massachusetts, USA

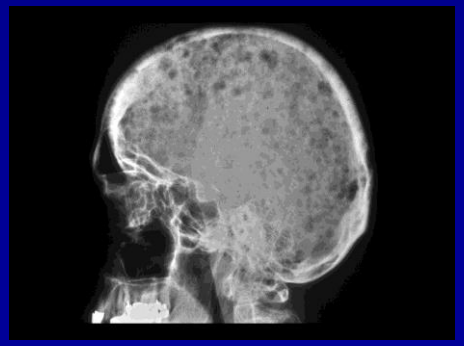
MULTIPLE MYELOMA
…not just one disease!

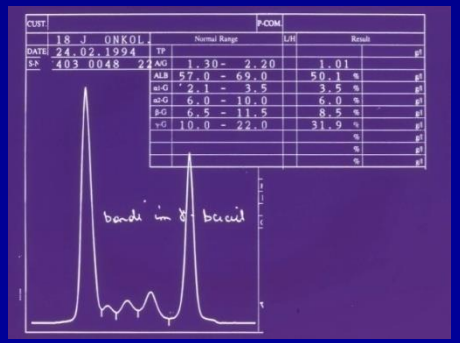
- Risk stratification, recognition of clonal heterogeneity
- Individualization of treatment, advent of novel therapies

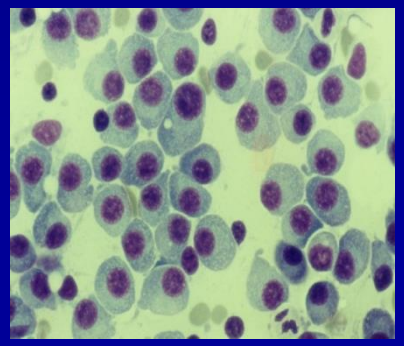
3 decades







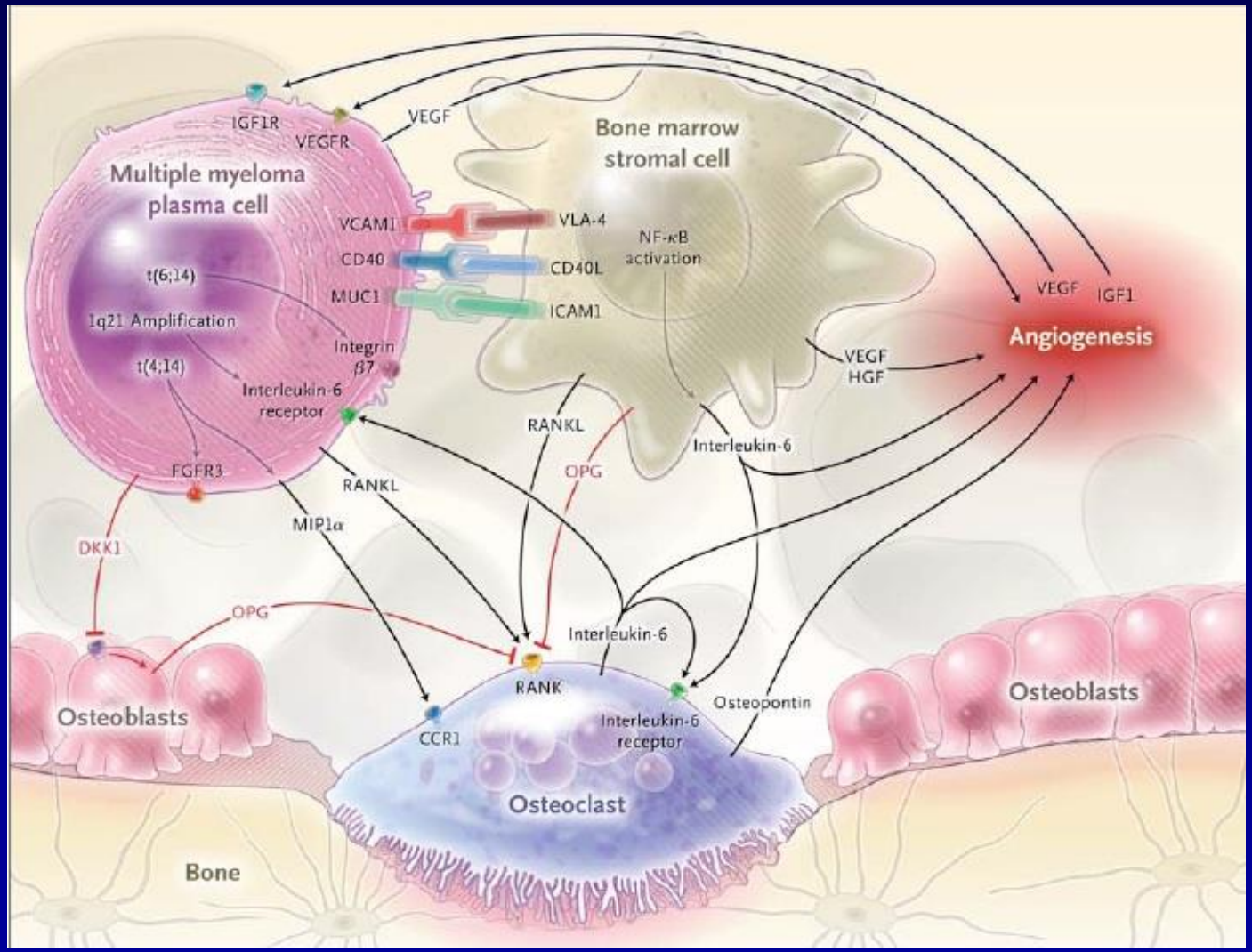




Drach J, ASH 2012

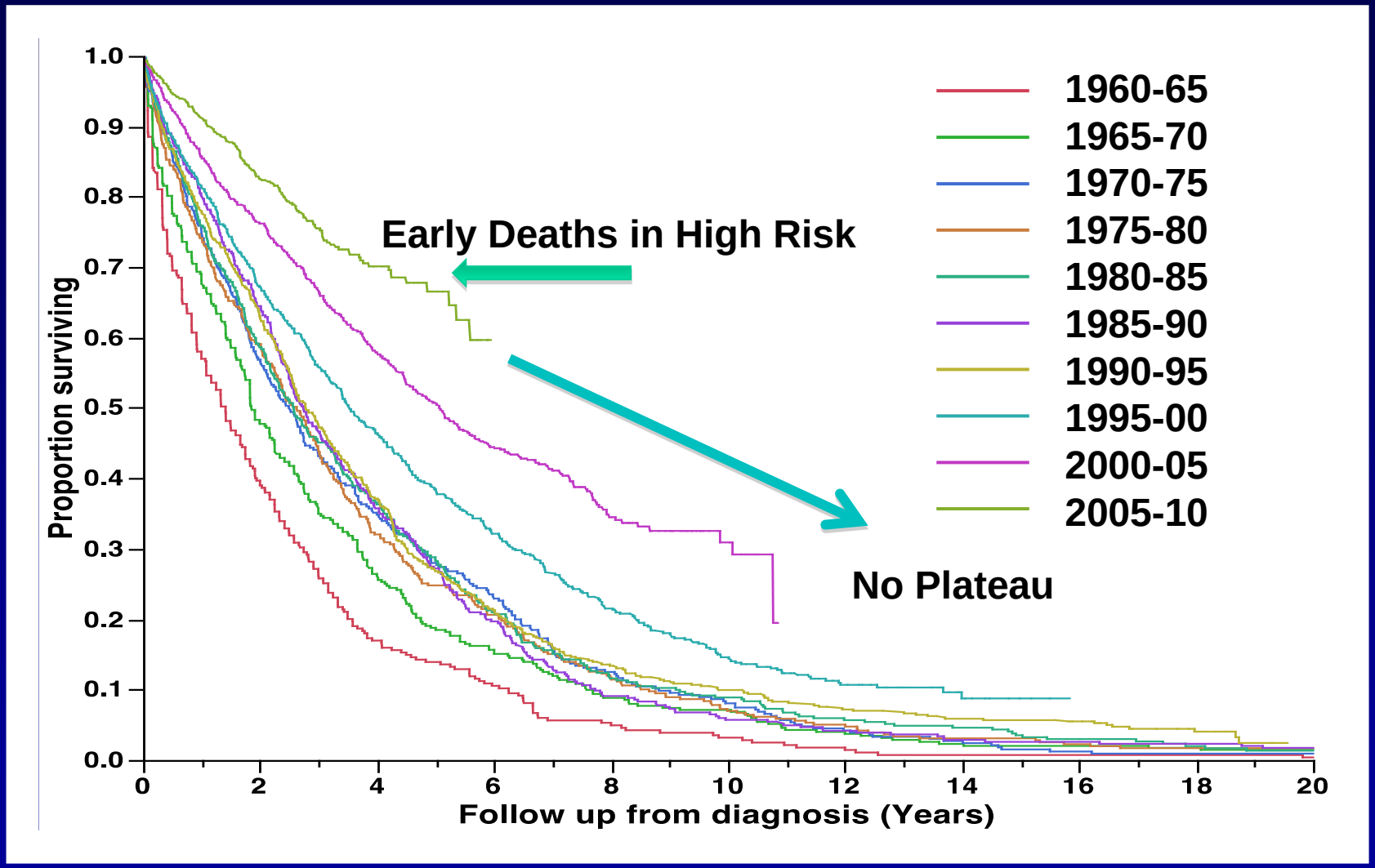
Morgan et al. *Nat Rev Cancer* 2012;12:335-348

Importance of Interaction Between Plasma Cells and Bone Marrow for Development of Myeloma



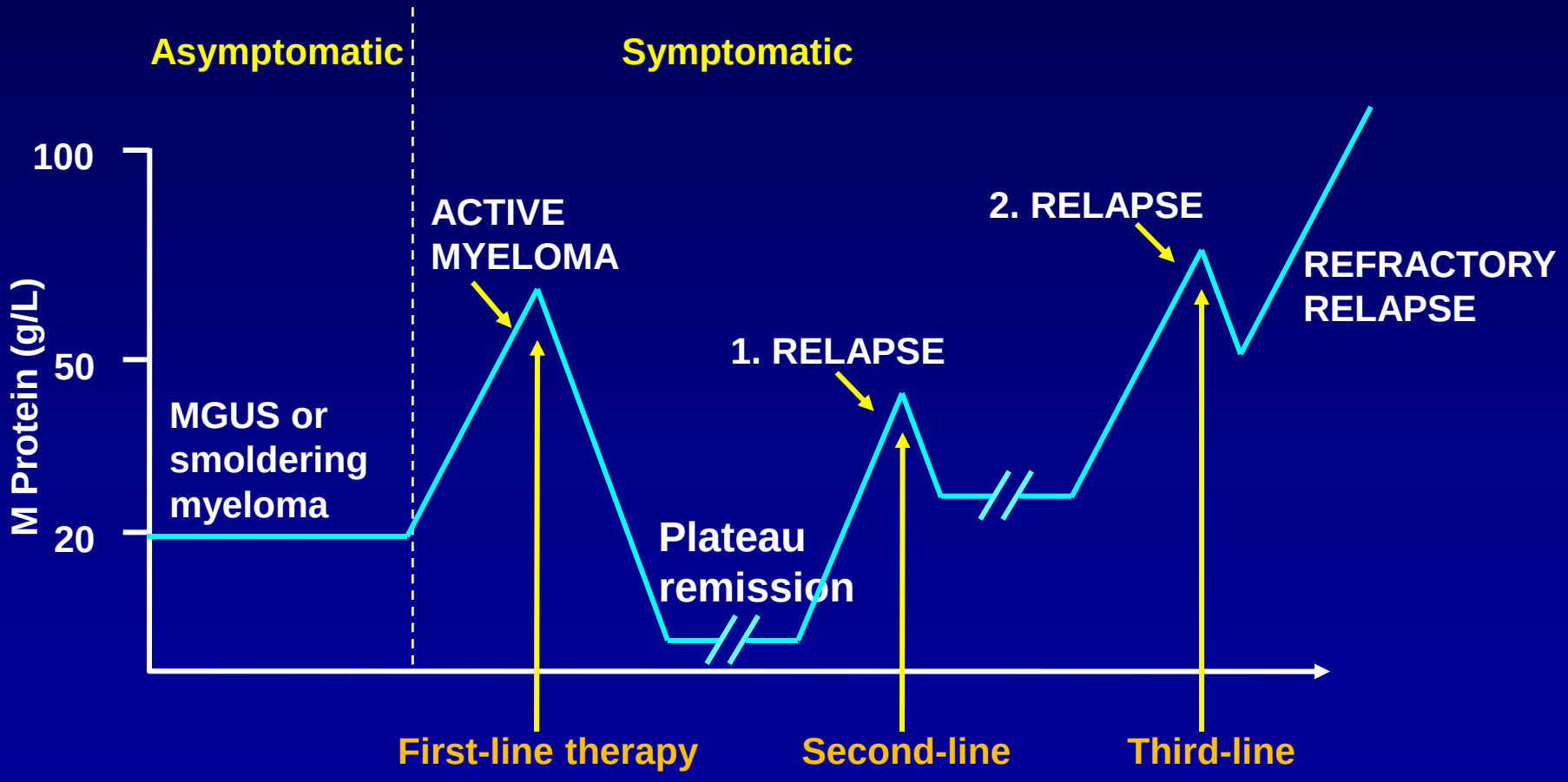
Palumbo A. and Anderson KC. New Engl J Med 2011;364:1046-1060

Multiple Myeloma Survival Improving With New Drugs: But All Pts Still Relapse After IMiD and PI Failure



Adapted from Kumar et al *Leukemia* 2014

Natural History of Multiple Myeloma: All Pts Experience Relapse



Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009
Available from: http://myeloma.org/pdfs/cr08-eng_f1web.pdf

NCCN Guidelines 2016

MYELOMA THERAPY[1-3]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

	Preferred Regimens	Other Regimens
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[4]/dexamethasone • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide[4]/dexamethasone (category 1)	• Carfilzomib[7]/lenalidomide[4]/dexamethasone • Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Thalidomide/dexamethasone (category 2B)
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Lenalidomide/low-dose dexamethasone (category 1)[5] • Melphalan/prednisone/bortezomib (MPB) (category 1) • Melphalan/prednisone/lenalidomide (MPL) (category 1) • Melphalan/prednisone/thalidomide (MPT) (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Melphalan/prednisone (MP) • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide[6] (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[4]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[5]Continuously until progression. Facon T, Dimopoulos MA, Dispenzieri A, et al. Continuous lenalidomide and low-dose dexamethasone demonstrates a significant PFS and OS advantage in transplant ineligible NDMM patients. The FIRST: MM-020/IFM0701 [oral]. Oral presented at: 55th Annual Meeting of the American Society of Hematology (ASH) 2013; December 7-10; New Orleans, LA USA.
[6]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.
[7]Optimal dosing in this regimen has not been defined.

Continued on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines 2016

MYELOMA THERAPY[1,2,3,8]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

	Preferred Regimens	Other Regimens
Therapy for Previously Treated Multiple Myeloma	• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Carfilzomib/dexamethasone • Carfilzomib/lenalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide/dexamethasone[9] (category 1) • Panobinostat/bortezomib/dexamethasone[10] (category 1) • Pomalidomide[11]/dexamethasone[9] (category 1) • Thalidomide/dexamethasone[9]	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/dexamethasone

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[8]Consideration for appropriate regimen is based on the context of clinical relapse.
[9]Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.
[10]Indicated in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.
[11]Indicated for patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Multiple Myeloma: Initiation and Progression

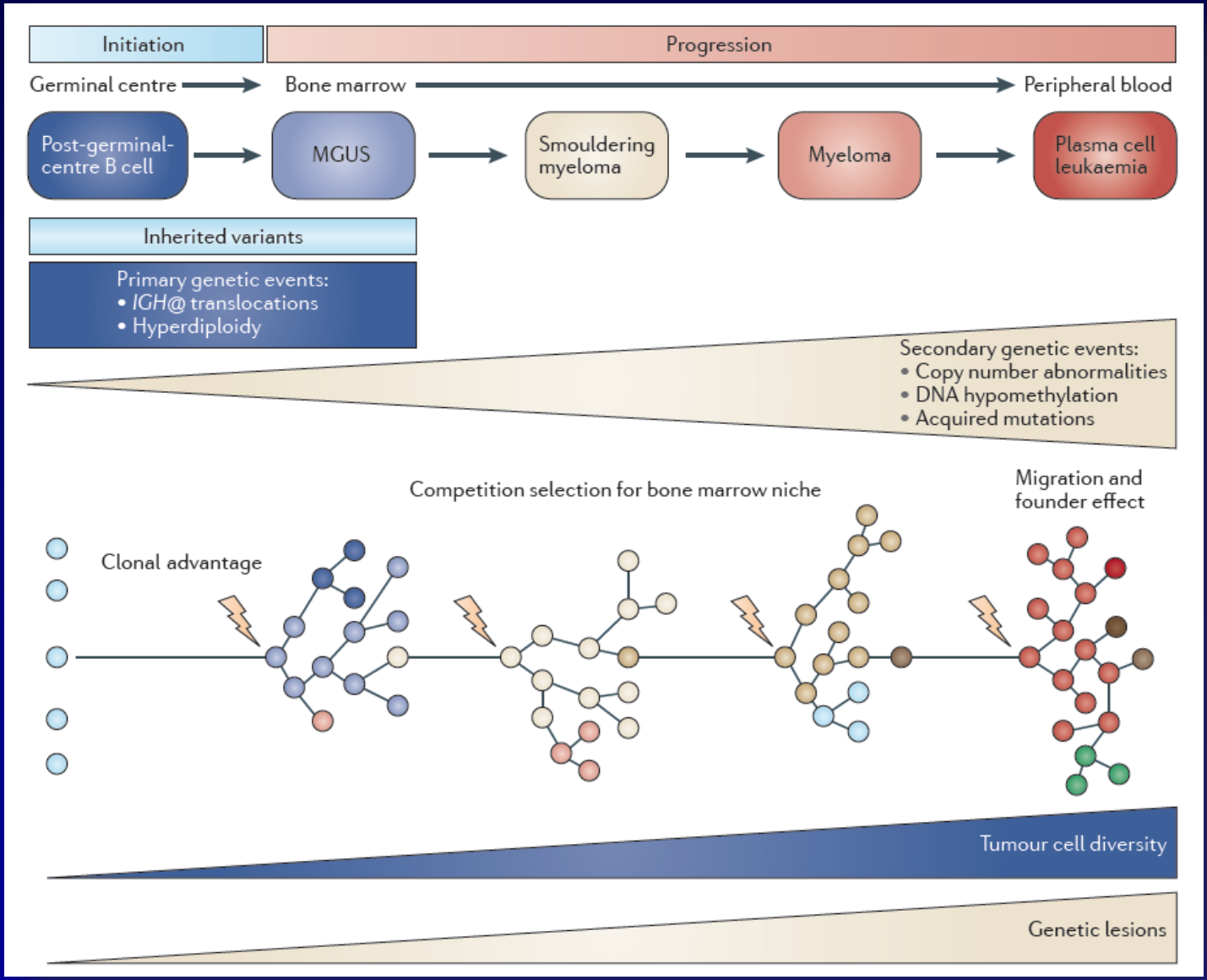


Figure adapted from: Morgan GJ et al. *Nat Rev Cancer* 2012;12:335–48.

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]**

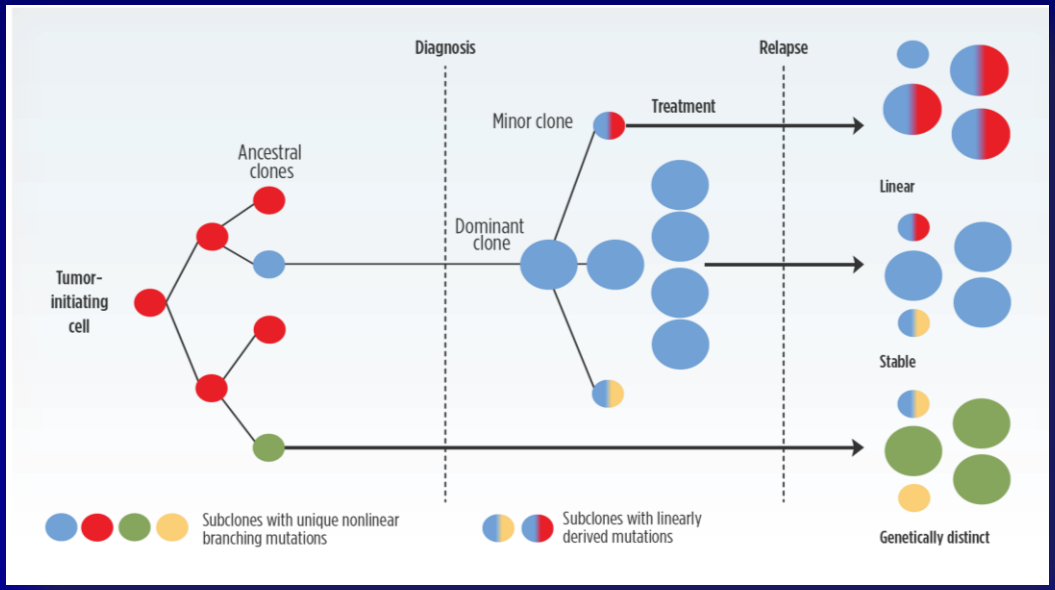


Figure adapted from: Bahlis N et al. *Blood* 2012;120:927–28.[1]

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.

Intra-clonal heterogeneity

Intra-clonal heterogeneity:

the existence of multiple sub-clones, descended from a common progenitor cancer stem cell, which all share a main common feature but also harbor other acquired mutations

Clonal homogeneity **Interclonal heterogeneity** **Intraclonal heterogeneity**

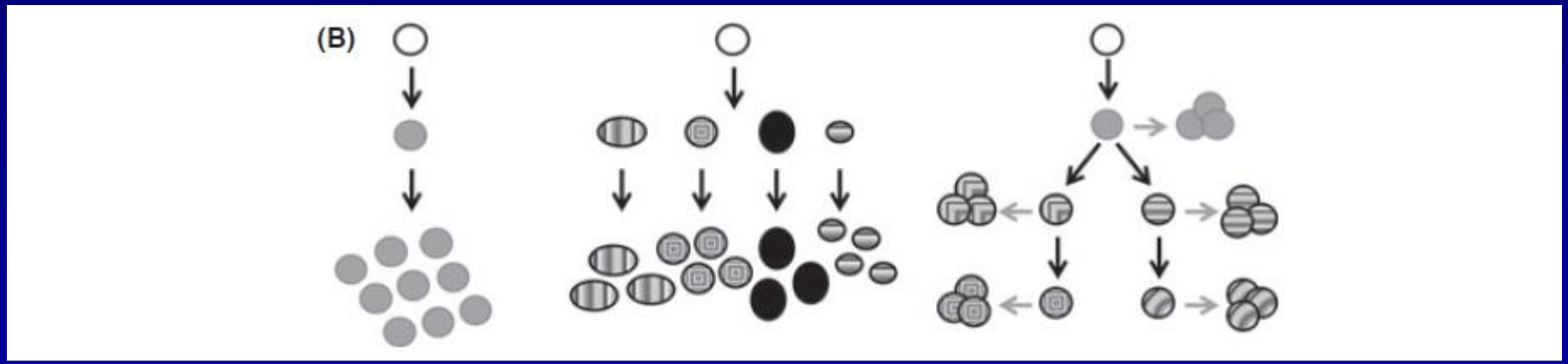
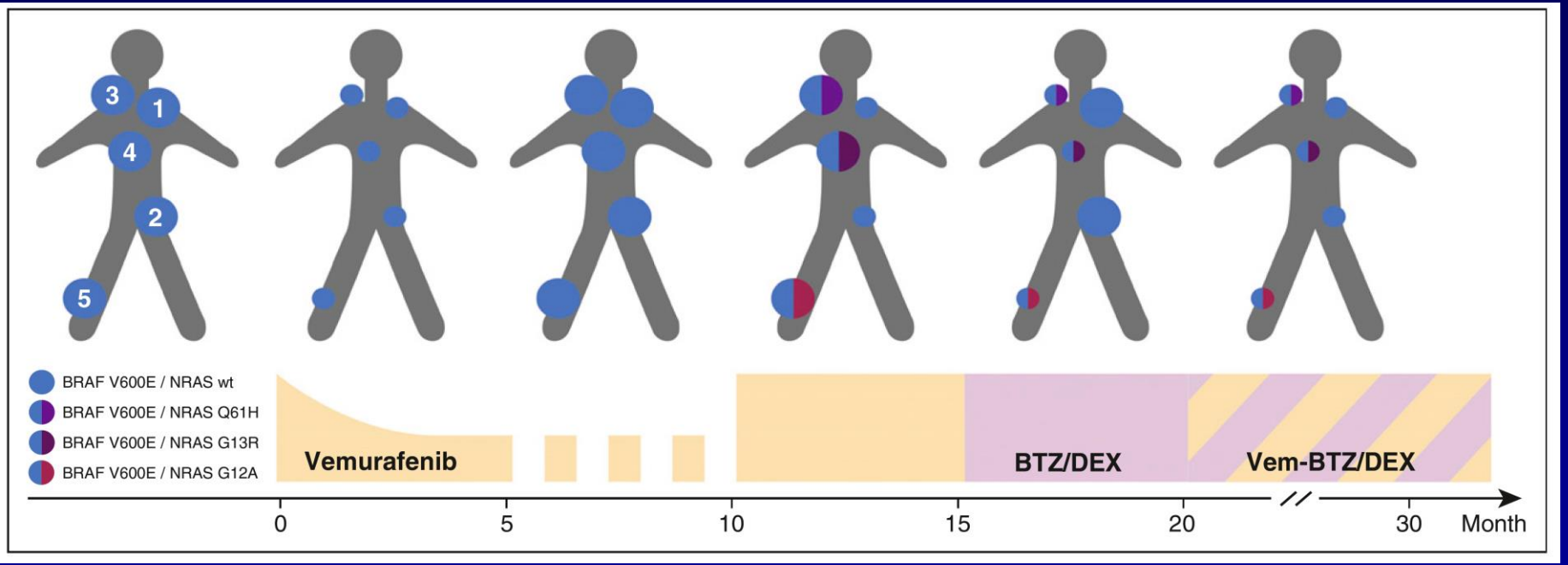


Figure adapted from: Brioli A et al. *Br J Haematol* 2014;165:441–54.

Brioli A et al. *Br J Haematol* 2014;165:441–54.

Spatially divergent clonal evolution in multiple myeloma



BTZ, bortezomib; DEX, dexamethasone; Vem, vemurafenib.

Raab MS et al. *Blood* 2016;127:2155–7.

Targeting genomic abnormalities

Identifying targets

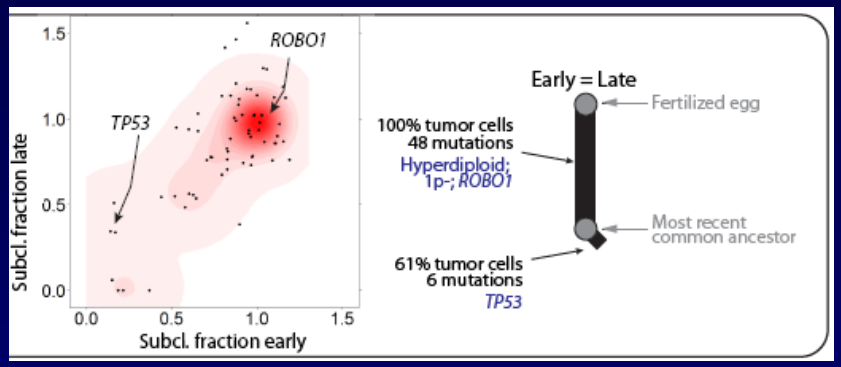
Characterizing changes over time and the impact of treatment (e.g. genotoxic injury)

Deriving rational combination strategies

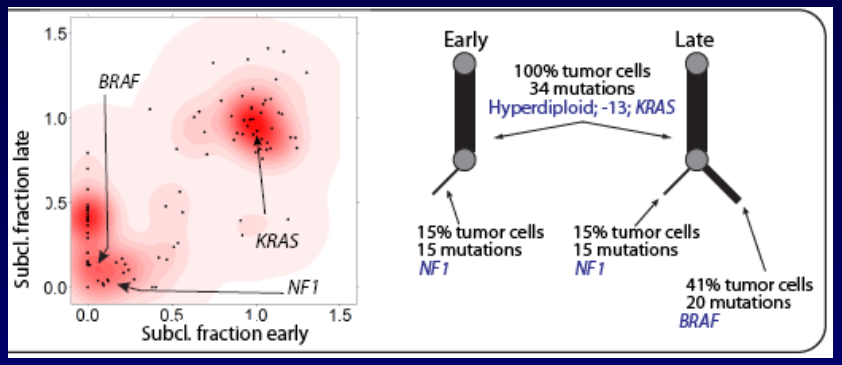
How to best integrate therapeutic strategies, and the role of MRD to tailor therapy?

Genomic Evolution in Myeloma and Patterns of Clonal Change

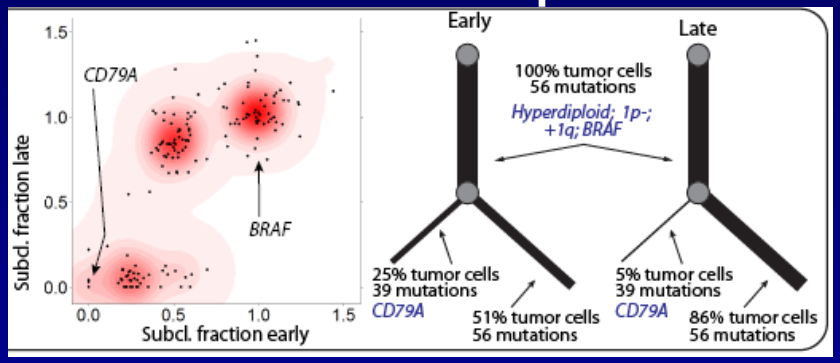
No Change



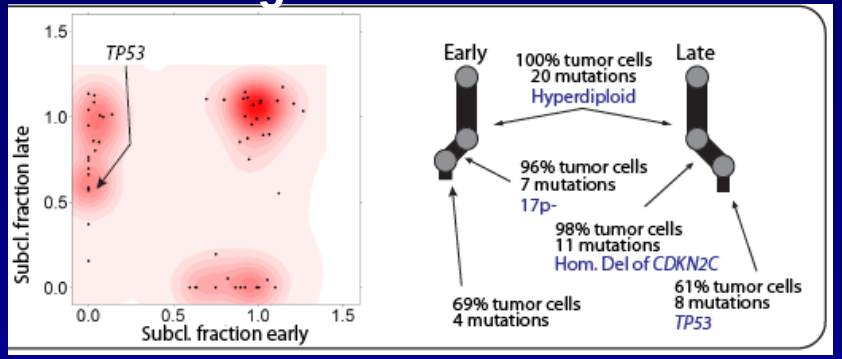
Linear Evolution

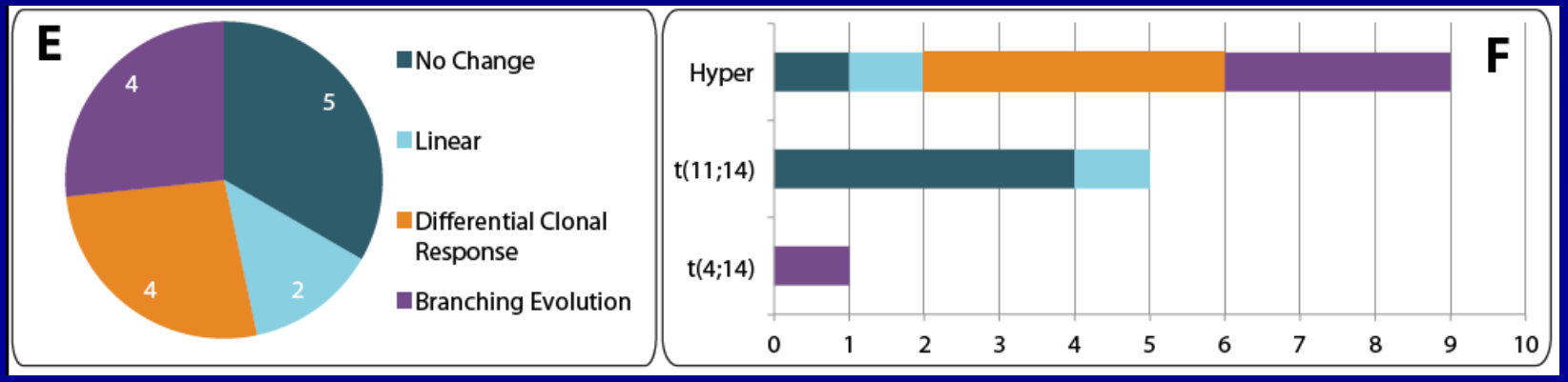


Differential Clonal Response



Branching Evolution

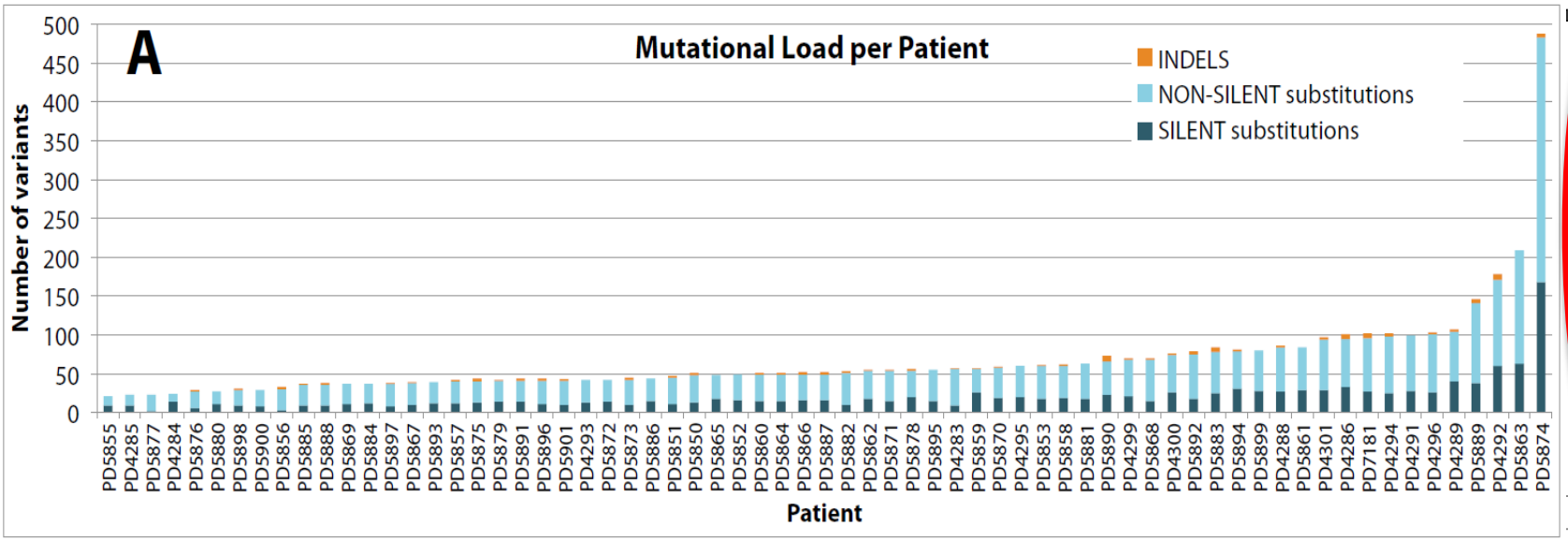


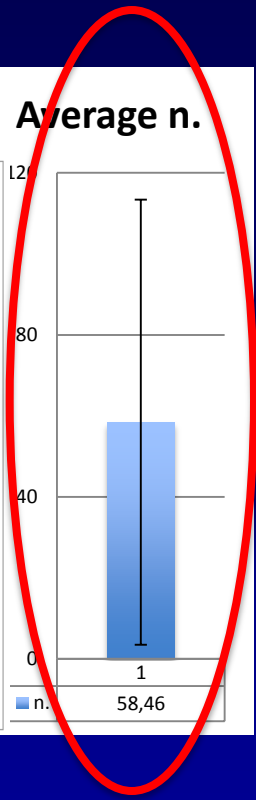


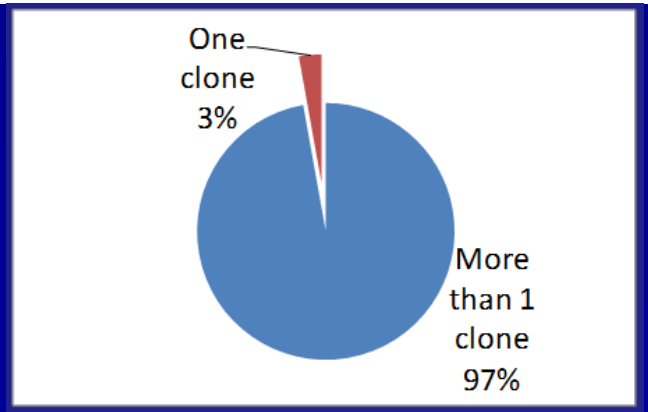
Bolli et al, Nature Comm, 2014

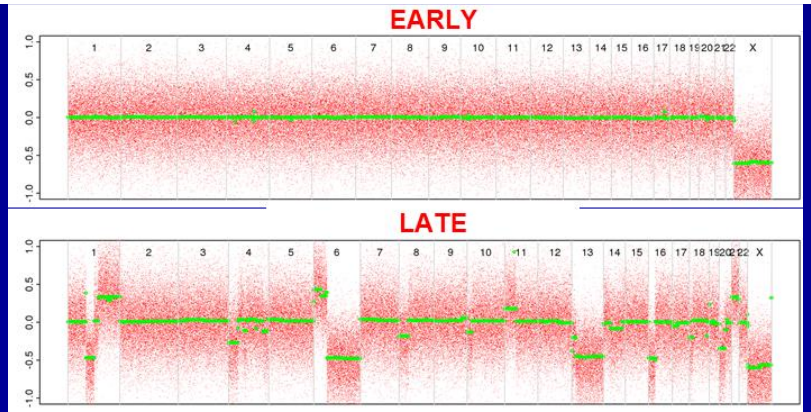
Genomic Heterogeneity in Myeloma: Are We Treating Multiple Diseases at The Same Time?

Whole Genome Sequencing: Somatic variants in Multiple Myeloma



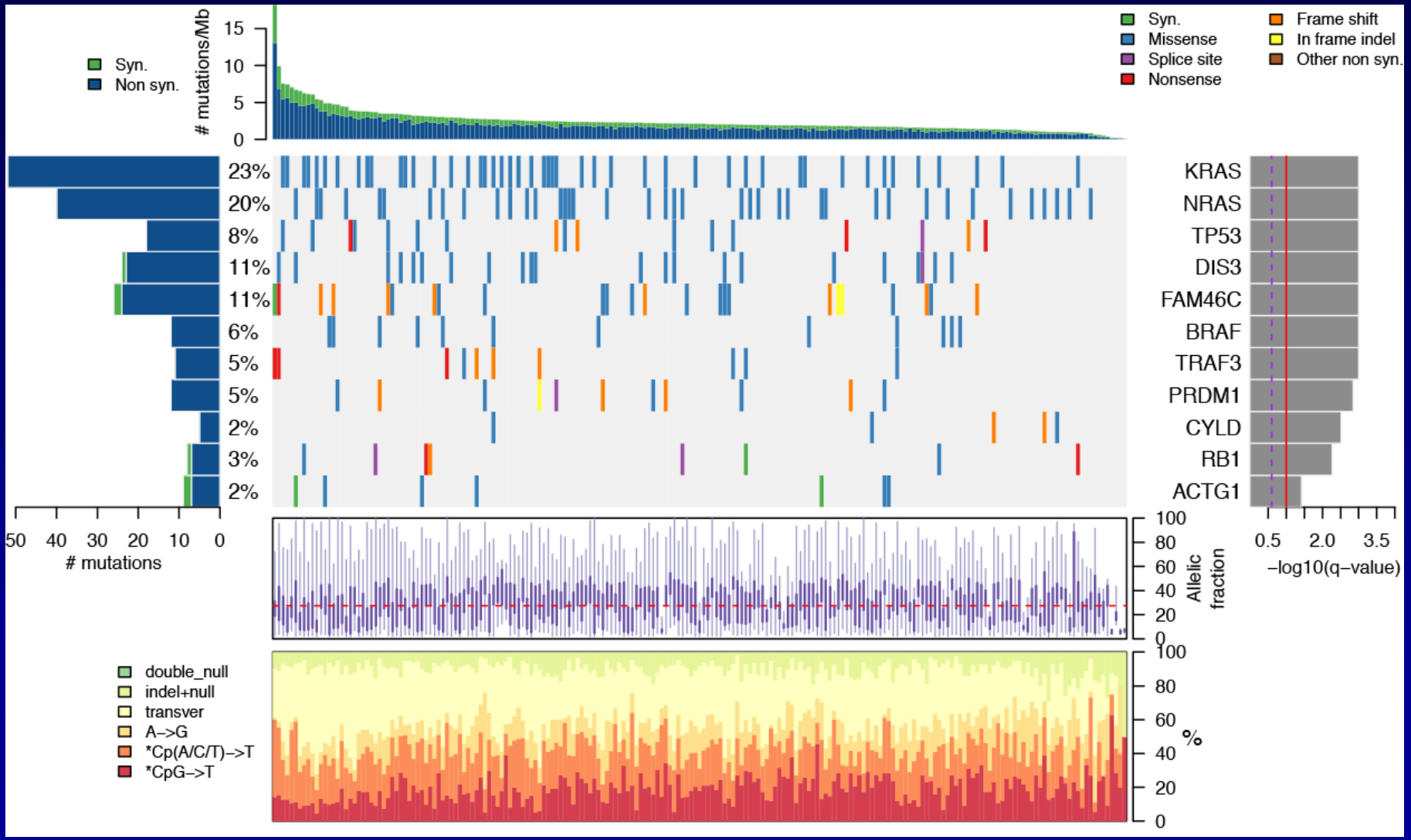




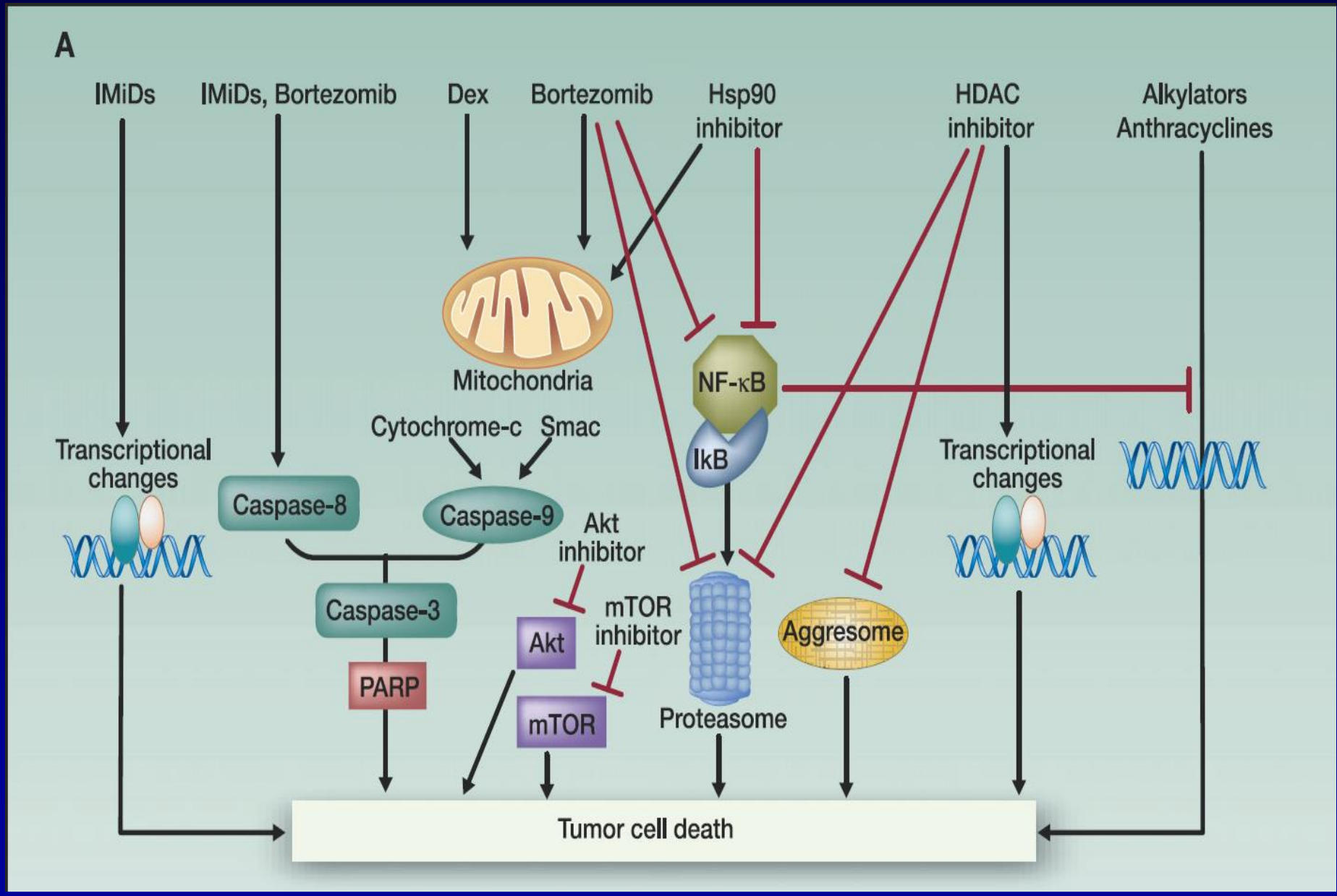


Bolli et al
Nature Comm
2014

MEK/ERK pathway is frequently activated in MM Whole exome/genome sequencing in 203 MM pts (Jens Lohr, DFCI)

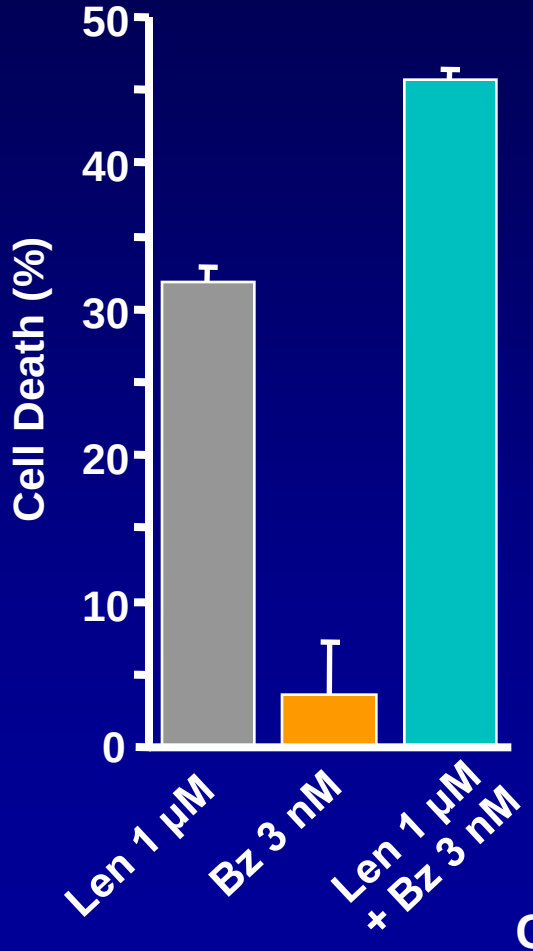


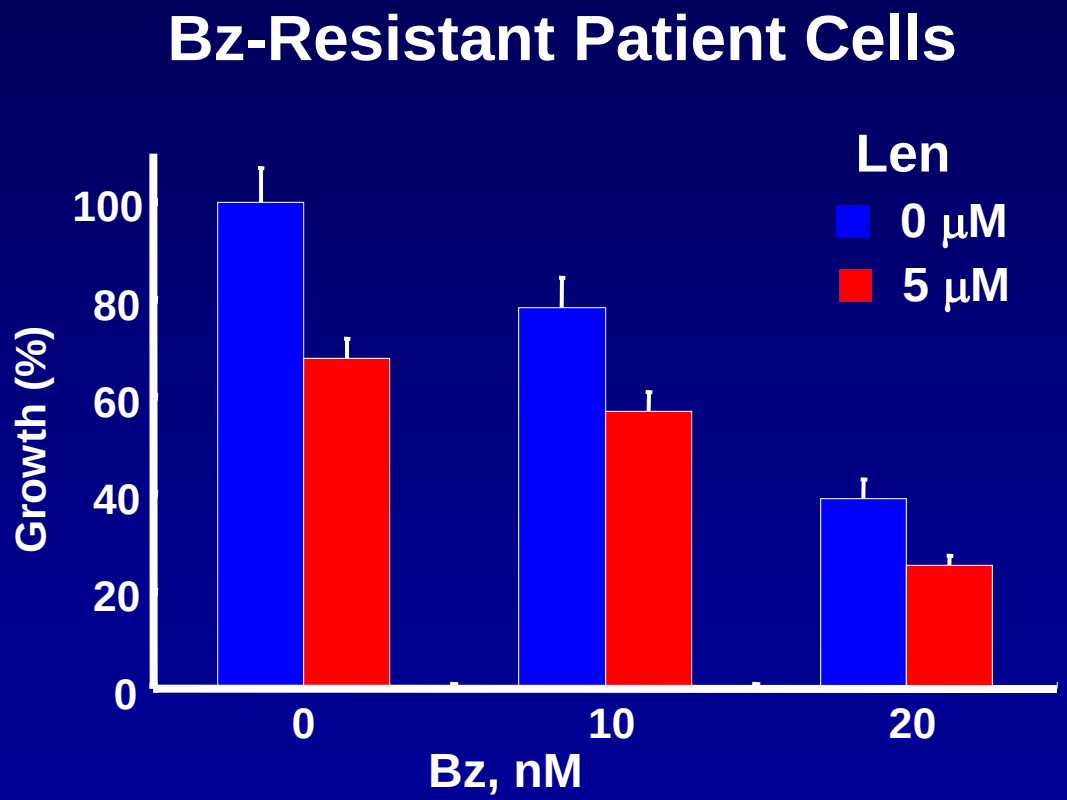
Rational Combination Strategies in Relapsed Refractory MM



Lonial S, Mitsiades CS, Richardson PG. *Clin Cancer Res.* 2011;17(6):1264-1277

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

Bortezomib and Lenalidomide Therapy

- Lenalidomide induces caspase 8–mediated apoptosis of MM cells in BM *in vitro* and *in vivo*; Dex (caspase 9) enhances response.
- Synergistic MM cell toxicity of lenalidomide (caspase 8) with bortezomib (caspase 9 > 8) *in vitro* and *in vivo* (dual apoptotic signaling).
- Phase I trial (RVd) in RRMM shows that majority of pts refractory to either agent alone respond to the combination (ORR 58%, OS >3 years), and manageable toxicity.
- Phase I-II trial in NDMM (n = 66) show 100% response with 74% VGPR or better, 52% CR/nCR when used as initial therapy.
- Phase II study in RRMM (n = 60) confirms high ORR (65%) and favorable OS (~ 3 years), with favorable tolerability.

Richardson PG, et al. *J Clin Oncol.* 2009;27(34):5713-5719
Richardson PG, et al. *Blood.* 2010;116(5):679-686
Richardson PG, et al. *Blood*. 2014;123:1461-1469

RRMM, relapsed/refractory multiple myeloma

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

***J Clin Oncol* 2009 Dec 1;27(34):5713-9.; *Blood* 2010 Aug 5;116(5):679-86.; *Blood* 2014 Mar 6;123(10):1461-9.**

Recent clinical trials of triplet vs doublet regimens

Addition to doublet regimen of:	MoA	Study design	N, patients	Prior lines of therapy	Primary endpoint
Bortezomib VTd vs Td[1]	PI	Randomized, controlled, open-label	269 RRMM	1	TTP
Carfilzomib KRd vs Rd[2]	PI	Randomized, controlled, open-label	792 RRMM	1–3	PFS
Ixazomib IRd vs placebo-Rd[3]	PI	Randomized, double-blind, placebo-controlled	772 RRMM	1–3	PFS
Elotuzumab ERd vs Rd[4]	SLAMF7 stimulator	Randomized, controlled, open-label	646 RRMM	1–3	PFS and ORR
Panobinostat PanVd vs placebo-Vd[5]	PDI	Randomized, double-blind, placebo-controlled	768 RRMM	1–3	PFS
Bortezomib VMP vs MP[6–8]	PI	Randomized, controlled	682 NDMM	0	TTP
Bortezomib VRd vs Rd[9]	PI	Randomized, open-label	473 NDMM	0	PFS

d, dexamethasone; E, elotuzumab; I, ixazomib; K, carfilzomib; M, melphalan; MoA, mechanism of action; NDMM, newly-diagnosed multiple myeloma; ORR, overall response rate; P, prednisone; Pan, Panobinostat; PDI, pan-deacetylase inhibitor; PFS, progression-free survival; PI, proteasome inhibitor; R, lenalidomide; SLAMF7, signaling lymphocytic activation molecule F7; T, thalidomide; TTP, time to progression; V, bortezomib.

1. Garderet L. *JCO* 2012;30:2475–826; 2. Stewart AK et al. *N Engl J Med* 2015;372:142–52; 3. Moreau P et al. *N Engl J Med* 2016;374:1621–34; 4. Lonial S et al. *N Engl J Med* 2015;373:621–31; 5. San Miguel JF. *Lancet Oncol* 2014;15:1195–206; 6. San Miguel JF et al. *N Engl J Med* 2008;359:906–17; 7. Mateos MV. *JCO* 2010;28:2259–66; 8. San Miguel JF et al. *JCO* 2013;31:448–55; 9. Durie B, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5–8, 2015; Orlando, FL. Oral session 653.

Recent clinical trials of triplet vs doublet regimens

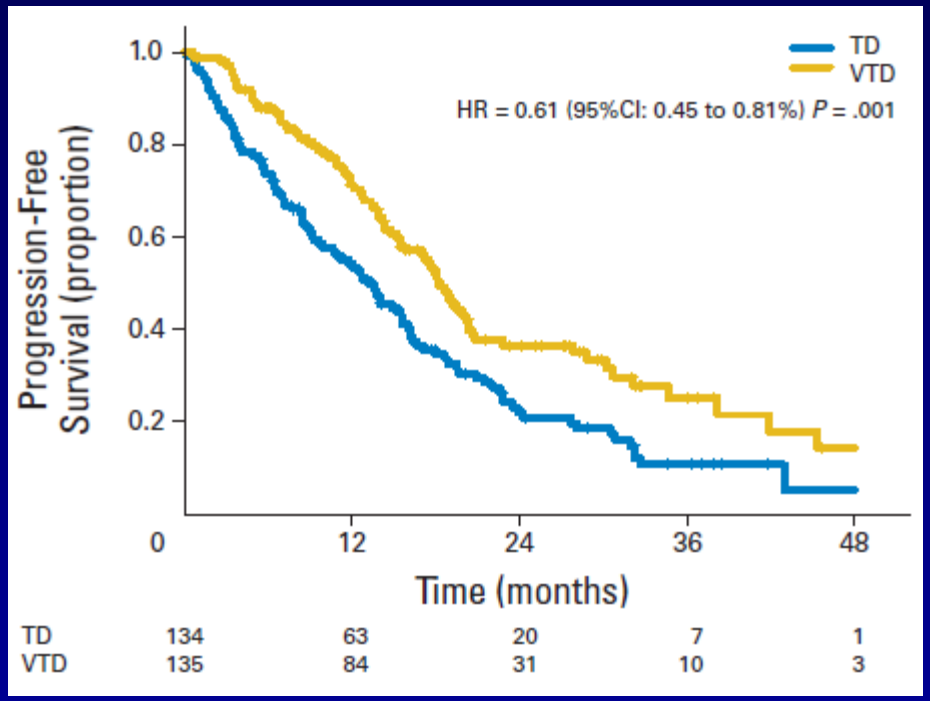
Addition to doublet therapy of:	ORR (≥PR)	≥VGPR	CR	Median PFS/TTP (months)	Median OS (months)	Response rate in high-risk cytogenetic groups
Bortezomib VTd vs Td[1]	87 vs 72% P=0.003	56 vs 35% P=0.001	28 vs 13% P=0.004	PFS: 18.3 vs 13.6 HR=0.61, P=0.001	NR	NA
Carfilzomib KRd vs Rd[2]	87 vs 67% P<0.001	70 vs 40% P<0.001	18 vs 5%	PFS: 26.3 vs 17.6 HR=0.69, P=0.0001	NR	NA
Ixazomib IRd vs placebo-Rd[3,4]	78 vs 72% P=0.04	48 vs 39% P=0.01	12 vs 7% P=0.02	PFS: 20.6 vs14.7 HR=0.74, P=0.01	NR	PFS: 21.4 vs 9.7 mo (HR=0.54, P=0.02) CR=12 vs 2% ORR=79 vs 60%
Elotuzumab ERd vs Rd[5]	79 vs 66% P<0.001	33 vs 28%	4 vs 7%†	PFS: 19.4 vs 14.9 HR=0.70, P<0.001	NR	NA
Panobinostat PanVd vs placebo-Vd[6]	61 vs 55% P=0.09	NA	11 vs 6%	PFS: 11.99 vs 8.08 HR=0.63, P<0.0001	34 vs 30‡ HR=0.87, P=0.26	NA
Bortezomib VMP vs MP[7,8*]	74 vs 39% P<0.001	41 vs 8%	33 vs 31%	TTP: 24.0 vs 16.6 HR=0.48	56.4 vs 43.1	CR=28 vs 28% [inc. t(4;14), t(14;16) or 17p del]
Bortezomib VRd vs Rd[9]	82 vs 72%	NA	16 vs 8%	PFS: 43 vs30 HR=0.71, P=0.0018	75 vs 64 HR=0.71, P=0.025	NA

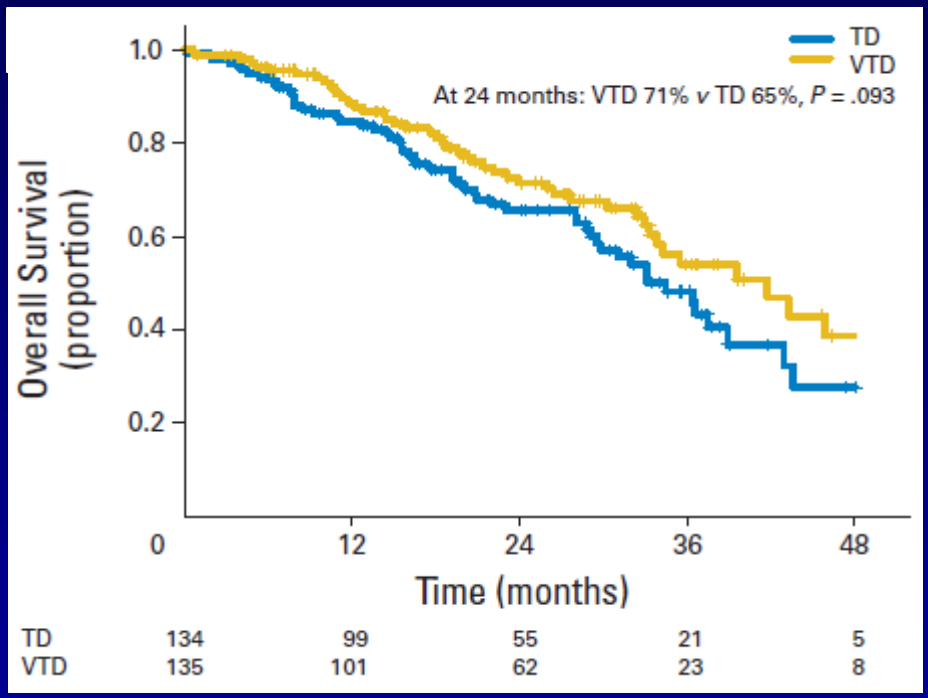
*Responses defined according to the International Uniform Response Criteria. †E CR may be underestimated. ‡OS data not mature. CR, complete response; d, dexamethasone; E, elotuzumab; I, ixazomib; K, carfilzomib; M, melphalan; mo, months; NA, not available; NR, not reached; ORR, overall response rate; P, prednisone; Pan, panobinostat; PFS, progression-free survival; PR, partial response; R, lenalidomide; T, thalidomide; TTP, time to progression; V, bortezomib; VGPR, very good partial response.

1. Garderet L et al. *JCO* 2012;30:2475–826; 2. Stewart AK et al. *N Engl J Med* 2015;372:142–52; 3. Moreau P et al. *N Engl J Med* 2016;374:1621–34; 4. Moreau P et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5–8, 2015; Orlando, FL. Oral session 653; 5. Lonial S et al. *N Engl J Med* 2015;373:621–31; 6. San Miguel JF et al. *Lancet Oncol* 2014;15:1195–206; 7. San Miguel JF et al. *N Engl J Med* 2008;359:906–17; 8. San Miguel JF et al. *JCO* 2013;31:448–55; 9. Durie B, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5–8, 2015; Orlando, FL. Oral session 653.

Addition of bortezomib to thalidomide + dexamethasone

- Significantly longer median PFS with VTD vs TD (18.3 vs 13.6 months)





- Higher incidence of Grade 3 neurotoxicity with VTD vs TD; dose adjustments are prudent

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TD, thalidomide-dexamethasone; TTP, time to progression; VTD, bortezomib-thalidomide-dexamethasone.

Garderet L et al. *JCO* 2012;30:2475–82.

VISTA Phase III Trial 2004-2006 (NEJM 2008)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

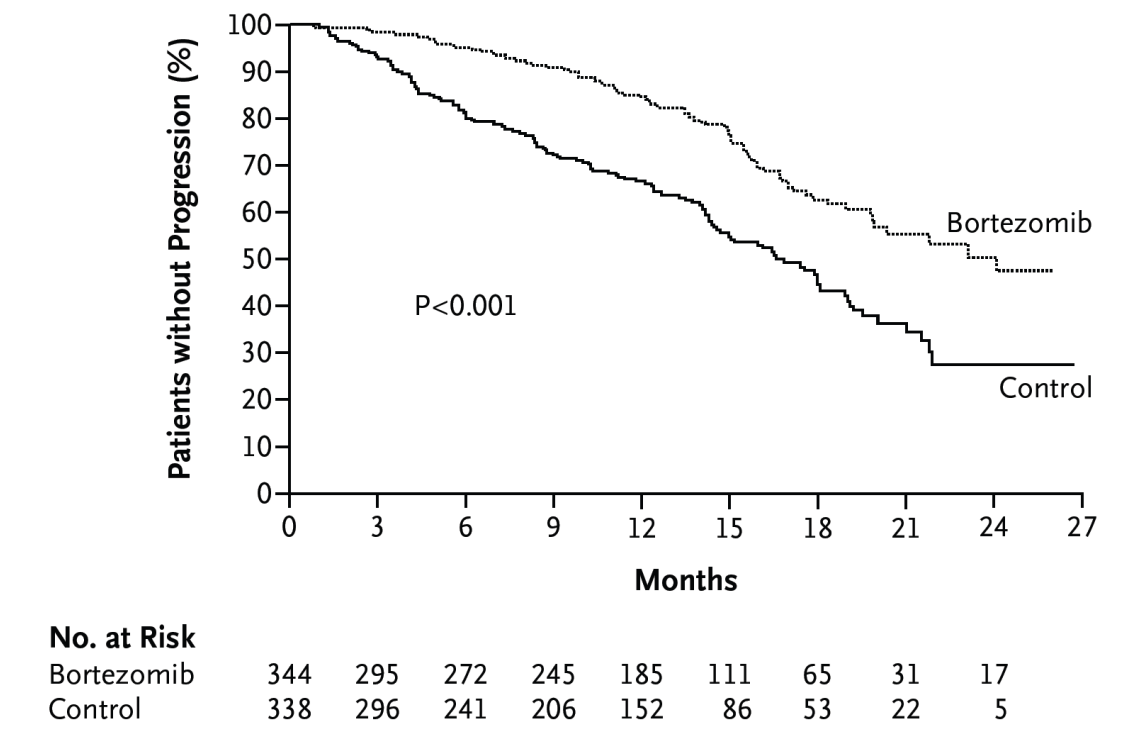
Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D.,
Nuriet K. Khuageva, M.D., Ph.D., Meletios A. Dimopoulos, M.D.,
Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D.,
Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D.,
Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D.,
Rik Schots, M.D., Ph.D., Bin Jiang, M.D., Maria-Victoria Mateos, M.D., Ph.D.,
Kenneth C. Anderson, M.D., Dixie L. Esseltine, M.D., Kevin Liu, Ph.D.,
Andrew Cakana, M.D., Helgi van de Velde, M.D., Ph.D., and Paul G. Richardson, M.D.,
for the VISTA Trial Investigators*

San Miguel JF, et al. *N Engl J Med*. 2008;359(9):906-917.

Addition of bortezomib to melphalan-prednisone

- **Significantly longer median TTP with VMP vs MP (24.0 vs 16.6 months; P < 0.001)**



- **Though hematologic effects were similar in both groups, peripheral neuropathy and all Grade 3 and 4 gastrointestinal symptoms were more frequent in the VMP group compared with the MP group**

MP, melphalan-prednisone; TTP, time to progression; VMP, bortezomib, melphalan-prednisone.

San Miguel JF et al. *N Engl J Med* 2008;359:906–17.

ASPIRE Phase III Trial 2010-2012 (NEJM 2015)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

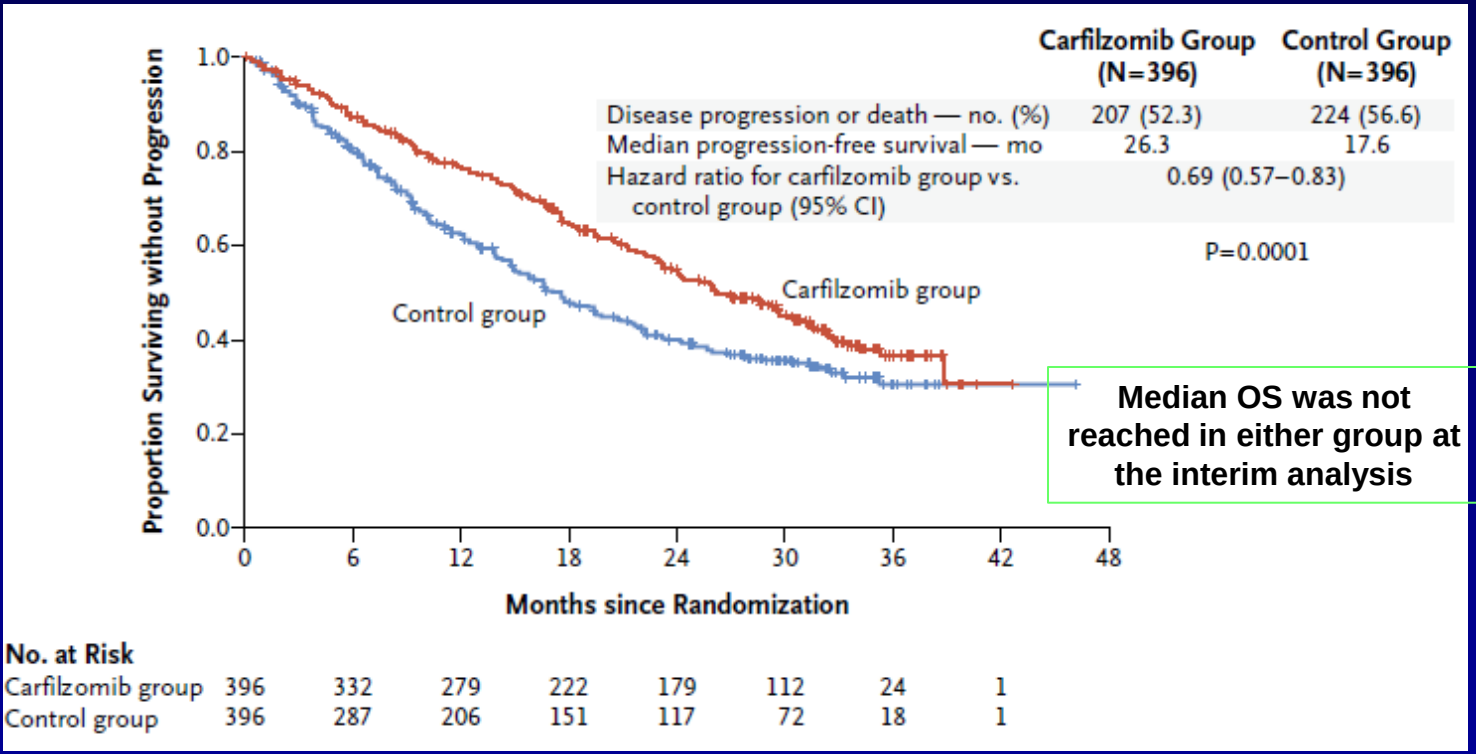
Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma

A. Keith Stewart, M.B., Ch.B., S. Vincent Rajkumar, M.D., Meletios A. Dimopoulos, M.D., Tamás Masszi, M.D., Ph.D., Ivan Špička, M.D., Ph.D., Albert Oriol, M.D., Roman Hájek, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., David S. Siegel, M.D., Ph.D., Georgi G. Mihaylov, M.D., Ph.D., Vesselina Goranova-Marinova, M.D., Ph.D., Péter Rajnics, M.D., Ph.D., Aleksandr Suvorov, M.D., Ruben Niesvizky, M.D., Andrzej J. Jakubowiak, M.D., Ph.D., Jesus F. San-Miguel, M.D., Ph.D., Heinz Ludwig, M.D., Michael Wang, M.D., Vladimír Maisnar, M.D., Ph.D., Jiri Minarik, M.D., Ph.D., William I. Bensinger, M.D., Maria-Victoria Mateos, M.D., Ph.D., Dina Ben-Yehuda, M.D., Vishal Kukreti, M.D., Naseem Zojwalla, M.D., Margaret E. Tonda, Pharm.D., Xinqun Yang, Ph.D., Biao Xing, Ph.D., Philippe Moreau, M.D., and Antonio Palumbo, M.D., for the ASPIRE Investigators*

N Engl J Med. 2015 Jan 8;372(2):142-52.

Addition of carfilzomib to lenalidomide + dexamethasone

- **Significantly longer median PFS in the carfilzomib vs the control group (26.3 vs 17.6 months; P = 0.0001)**



Median OS was not reached in either group at the interim analysis

- **AEs of any grade, occurring more frequently in the carfilzomib vs the control group by ≥5%, included hypokalemia, cough, upper respiratory tract infection, diarrhea, pyrexia, hypertension, thrombocytopenia, nasopharyngitis and muscle spasms**

Carfilzomib group: carfilzomib, lenolidamide + dexamethasone; control group: lenolidamide + dexamethasone. Aes, adverse events; CI, confidence interval; mo, months; OS, overall survival; PFS, progression-free survival.

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

TOURMALINE-MM1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

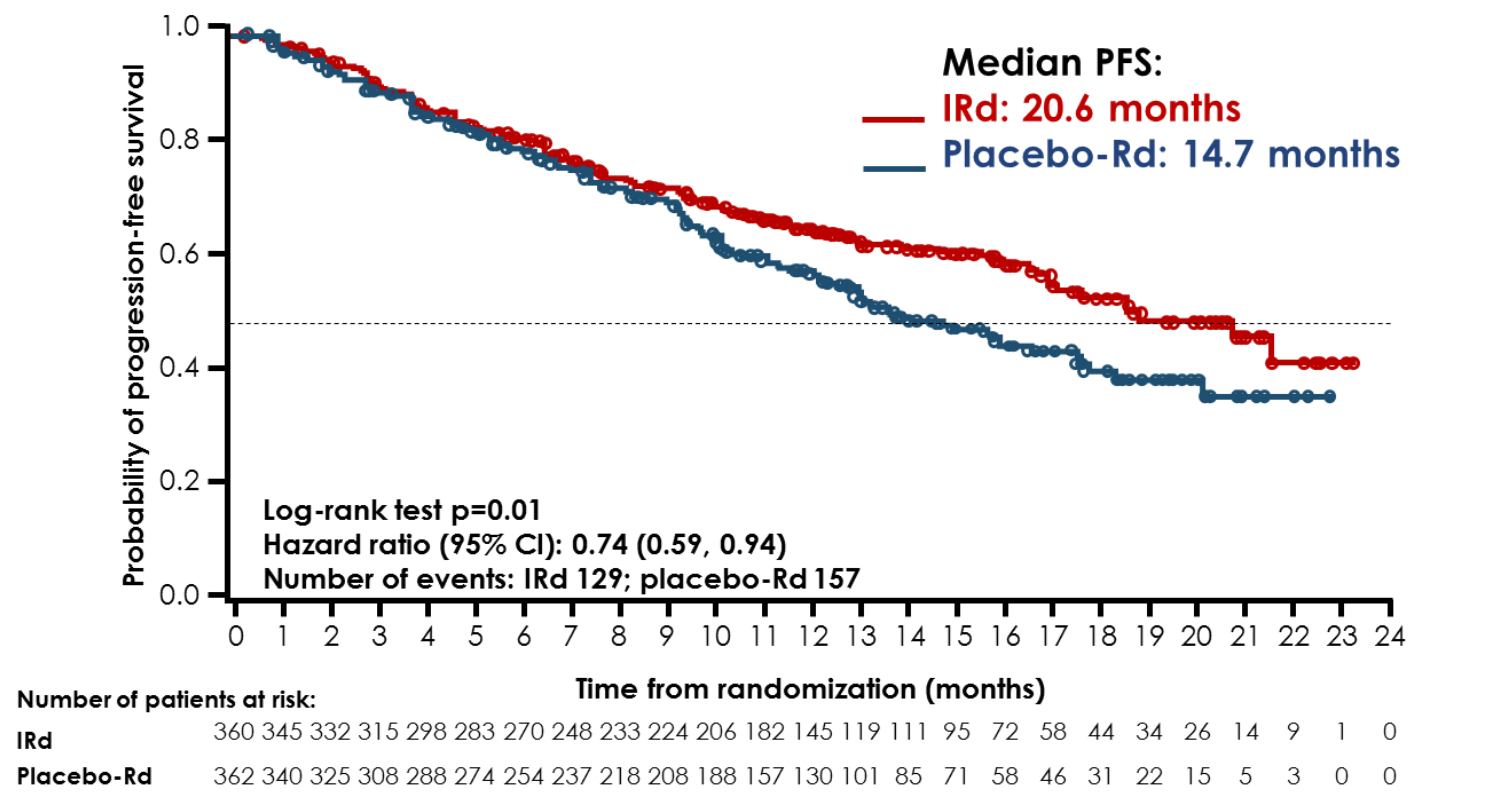
Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

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*

N Engl J Med 2016 374;17

Addition of ixazomib to lenalidomide + dexamethasone

- Significantly longer median PFS with IRd vs placebo-Rd (20.6 vs 14.7 months; P = 0.01)



- The IRd regimen did not add significant toxicity vs Rd

CI, confidence interval; IRd, ixazomib-lenalidomide-dexamethasone; PFS, progression-free survival; Rd, lenalidomide-dexamethasone.

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

blood®
2013 122: 2331-2337
doi:10.1182/blood-2013-01-481325 originally published online August 15, 2013

PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma

Paul G. Richardson, Robert L. Schlossman, Melissa Alsina, Donna M. Weber, Steven E. Coutre, Cristina Gasparetto, Sutapa Mukhopadhyay, Michael S. Ondovik, Mahmudul Khan, Carole S. Paley and Sagar Lonial

THE LANCET Oncology

Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial

Jesús F San-Miguel, Vânia T M Hungria, Sung-Soo Yoon, Meral Beksac, Meletios Athanasios Dimopoulos, Ashraf Elghandour, Wieslaw Wiktor Jedrzejczak, Andreas Günther, Thanyaphong Na Nakorn, Noppadol Siritanaratkul, Paolo Corradini, Suporn Chuncharunee, Je-Jung Lee, Robert L Schlossman, Tatiana Shelekhova, Kwee Yong, Daryl Tan, Tontanai Numbenjapon, Jamie D Cavenagh, Jian Hou, Richard LeBlanc, Hareth Nahi, Lugui Qiu, Hans Salwender, Stefano Pulini, Philippe Moreau, Krzysztof Warzocha, Darrell White, Joan Bladé, WenMing Chen, Javier de la Rubia, Peter Gimsing, Sagar Lonial, Jonathan L Kaufman, Enrique M Ocio, Ljupco Veskovski, Sang Kyun Sohn, Ming-Chung Wang, Jae Hoon Lee, Hermann Einsele, Monika Sopala, Claudia Corrado, Bourras-Rezki Bengoudifa, Florence Binlich, Paul G Richardson

blood®
2016 127: 713-721
doi:10.1182/blood-2015-09-665018 originally published online December 2, 2015

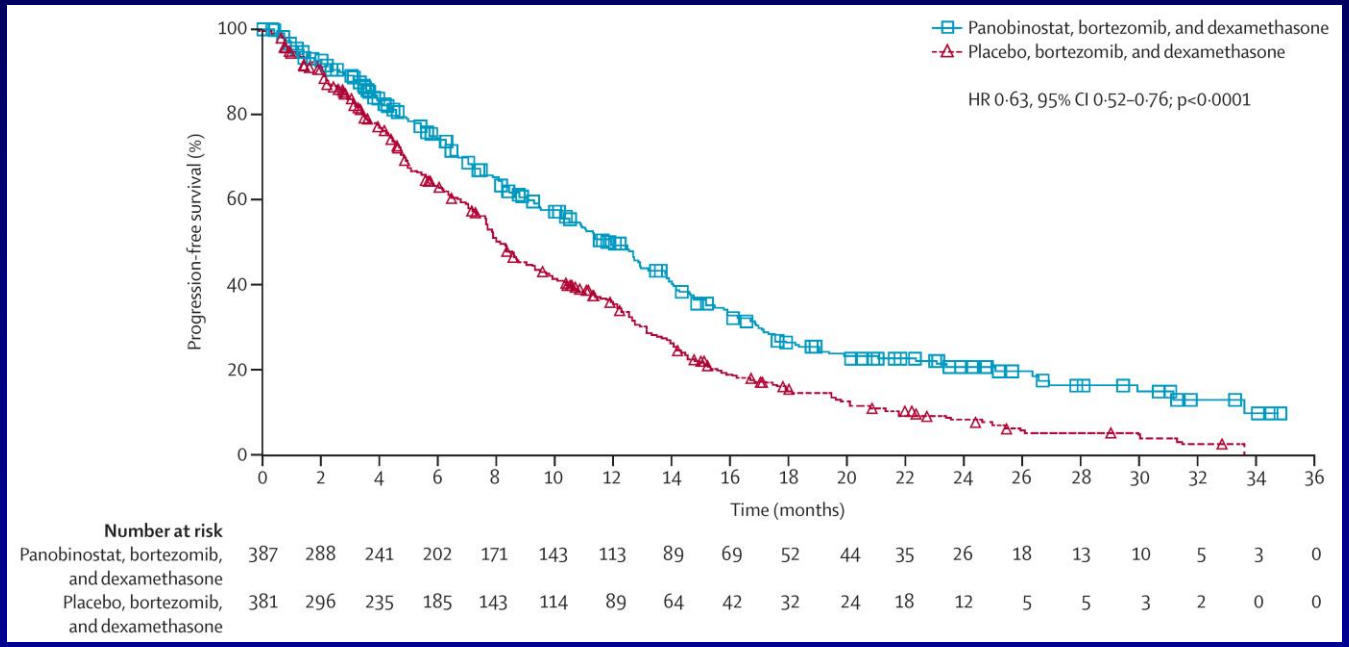
Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment

Paul G. Richardson, Vânia T. M. Hungria, Sung-Soo Yoon, Meral Beksac, Meletios Athanasios Dimopoulos, Ashraf Elghandour, Wieslaw W. Jedrzejczak, Andreas Guenther, Thanyaphong Na Nakorn, Noppadol Siritanaratkul, Robert L. Schlossman, Jian Hou, Philippe Moreau, Sagar Lonial, Jae Hoon Lee, Hermann Einsele, Monika Sopala, Bourras-Rezki Bengoudifa, Claudia Corrado, Florence Binlich and Jesús F. San-Miguel

***Blood* 2013 Oct 3;122(14):2331-7; *Lancet Oncol* 2014 Oct;15(11):1195-206; *Blood* 2016 Feb 11;127(6):713-21.**

Addition of panobinostat to bortezomib-dexamethasone

- Significantly longer median PFS in the panobinostat vs the placebo group (11.99 months vs 8.08 months; P < 0.0001)



- Common Grade 3-4 AEs which were more common in the panobinostat vs placebo group included diarrhea, asthenia/fatigue, peripheral neuropathy, thrombocytopenia, lymphopenia and neutropenia

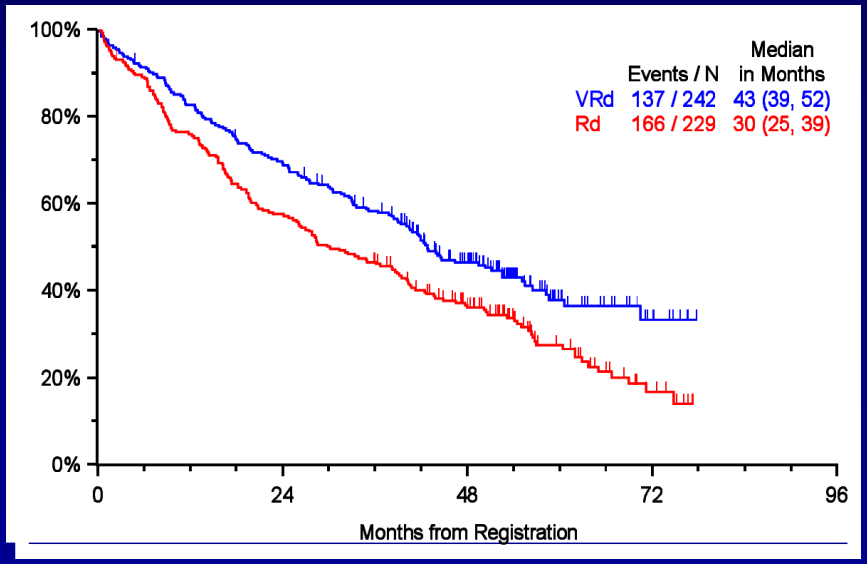
AEs, adverse events; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

San Miguel JF et al. *Lancet Oncol* 2014;15:1195–206.

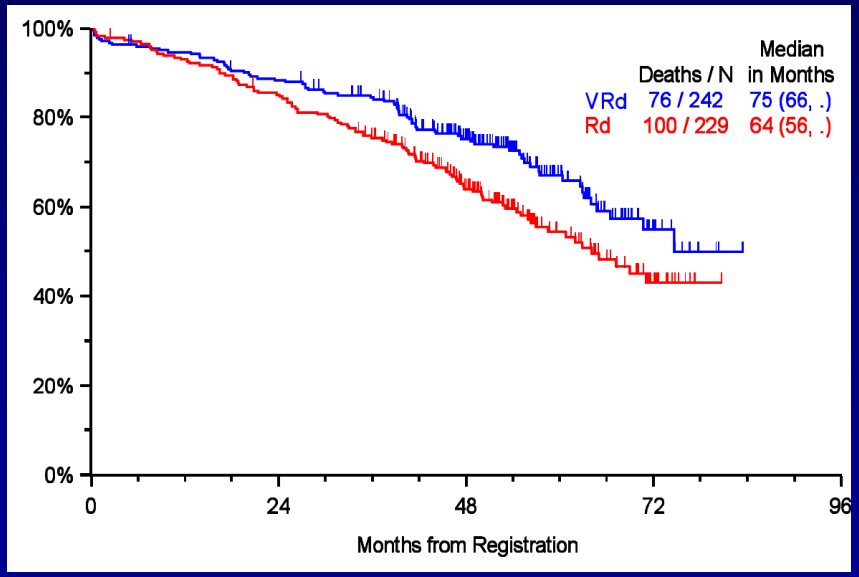
Addition of bortezomib to lenalidomide + dexamethasone: SWOG S0777

- Median PFS was significantly longer with VRd compared with Rd (43 months vs 30 months; P = 0.0018, respectively)

Progression-free survival



Overall survival



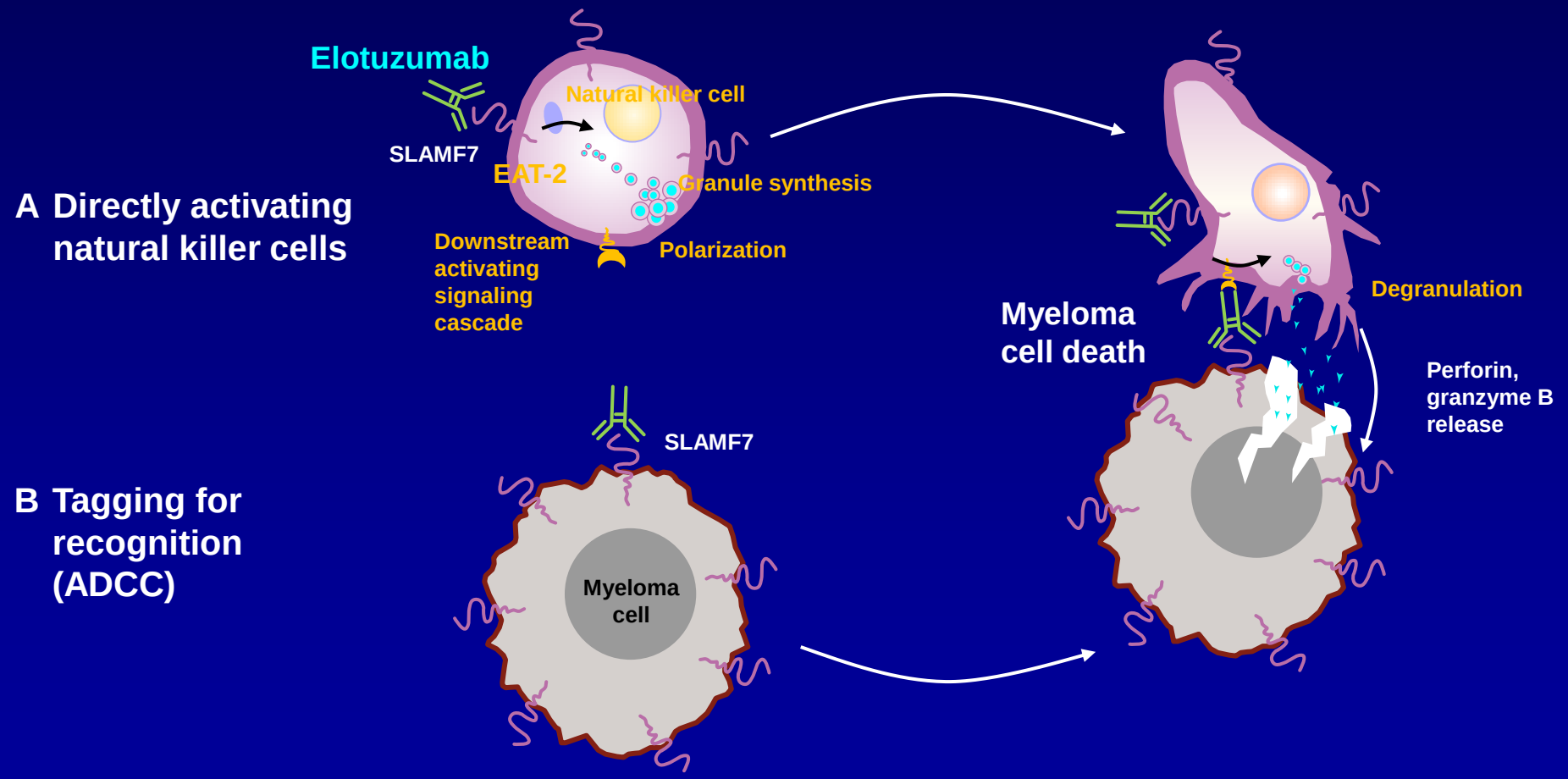
- As expected, ≥ Grade 3 neuropathy was more frequent with VRd vs Rd (24% vs 5%; P < 0.0001)

PFS, progression-free survival; Rd, lenalidomide-dexamethasone; VRd, bortezomib-lenalidomide-dexamethasone.

Durie B et al. ASH 2015; Orlando, FL. Oral session 653.

Elotuzumab: Immunostimulatory Mechanism of Action

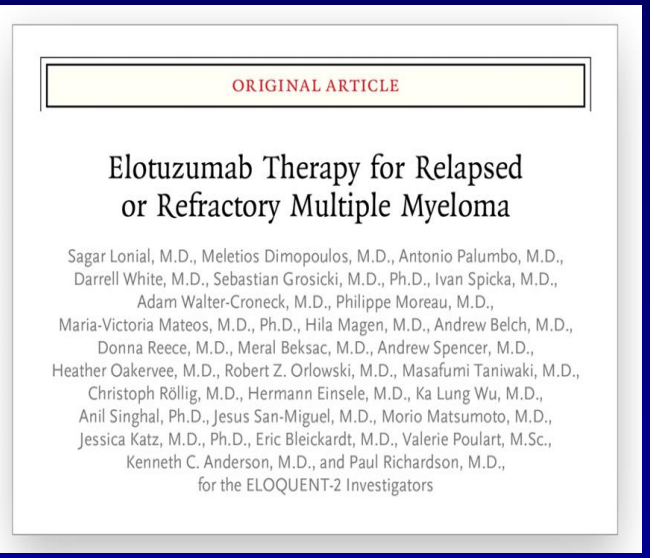
- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7, a protein highly expressed by myeloma and natural killer cells[1]
- Elotuzumab causes myeloma cell death via a dual mechanism of action[2]



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

Addition of elotuzumab to lenalidomide + dexamethasone

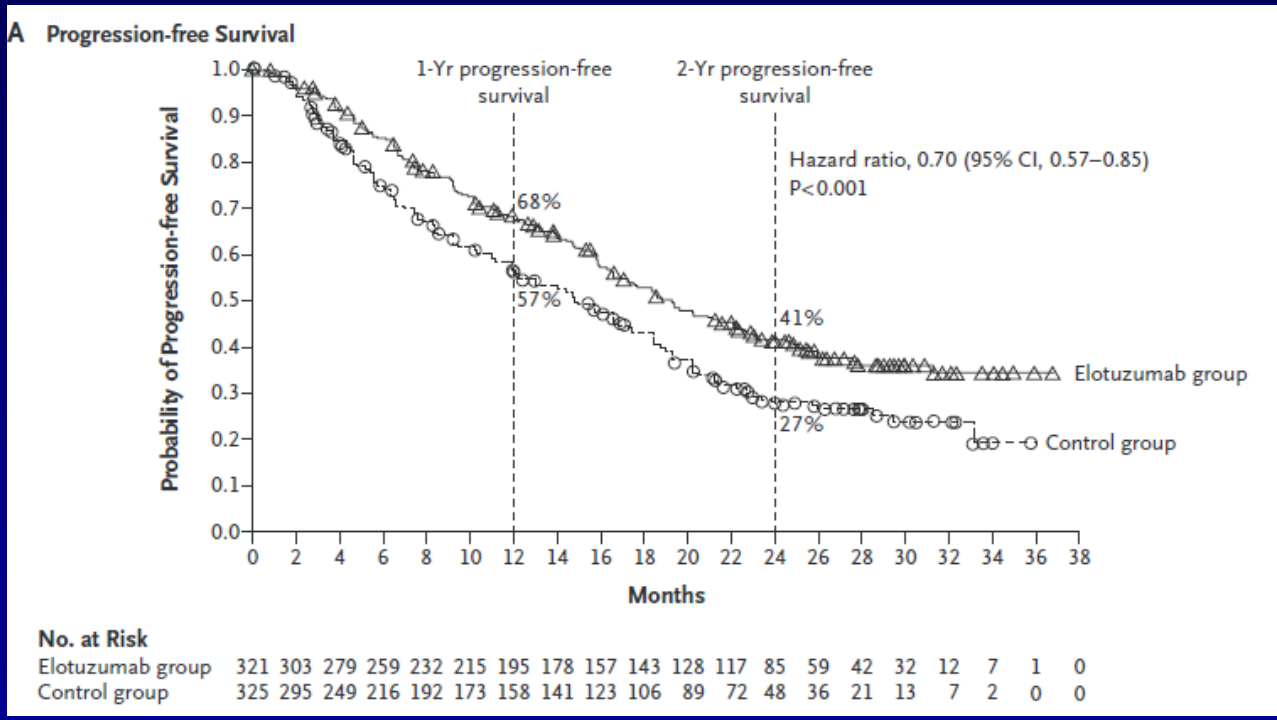
- **Significantly longer median PFS in the elotuzumab group vs control group (19.4 vs 14.9 mos, respectively; P < 0.001)**



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



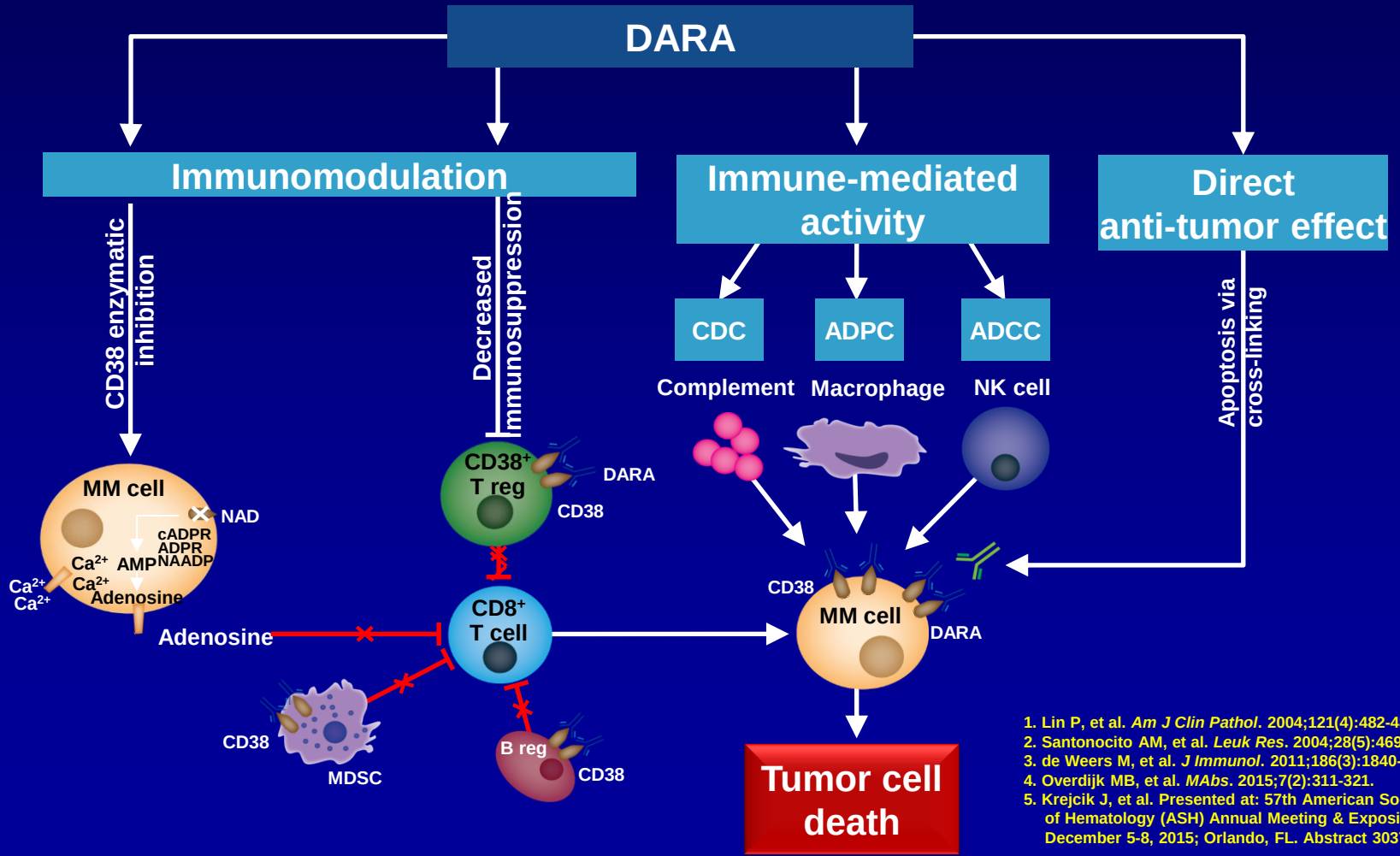
- **Elotuzumab-Rd resulted in a modest increase in AEs vs. the control group in a population where >50% of pts were ≥ 65 yrs old**

Control group: lenolidamide + dexamethasone; Elotuzumab group: elotuzumab, lenolidamide + dexamethasone.
AEs, adverse events; CI, confidence interval; PFS, progression-free survival; Rd, lenolidamide and dexamethasone.

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

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. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 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

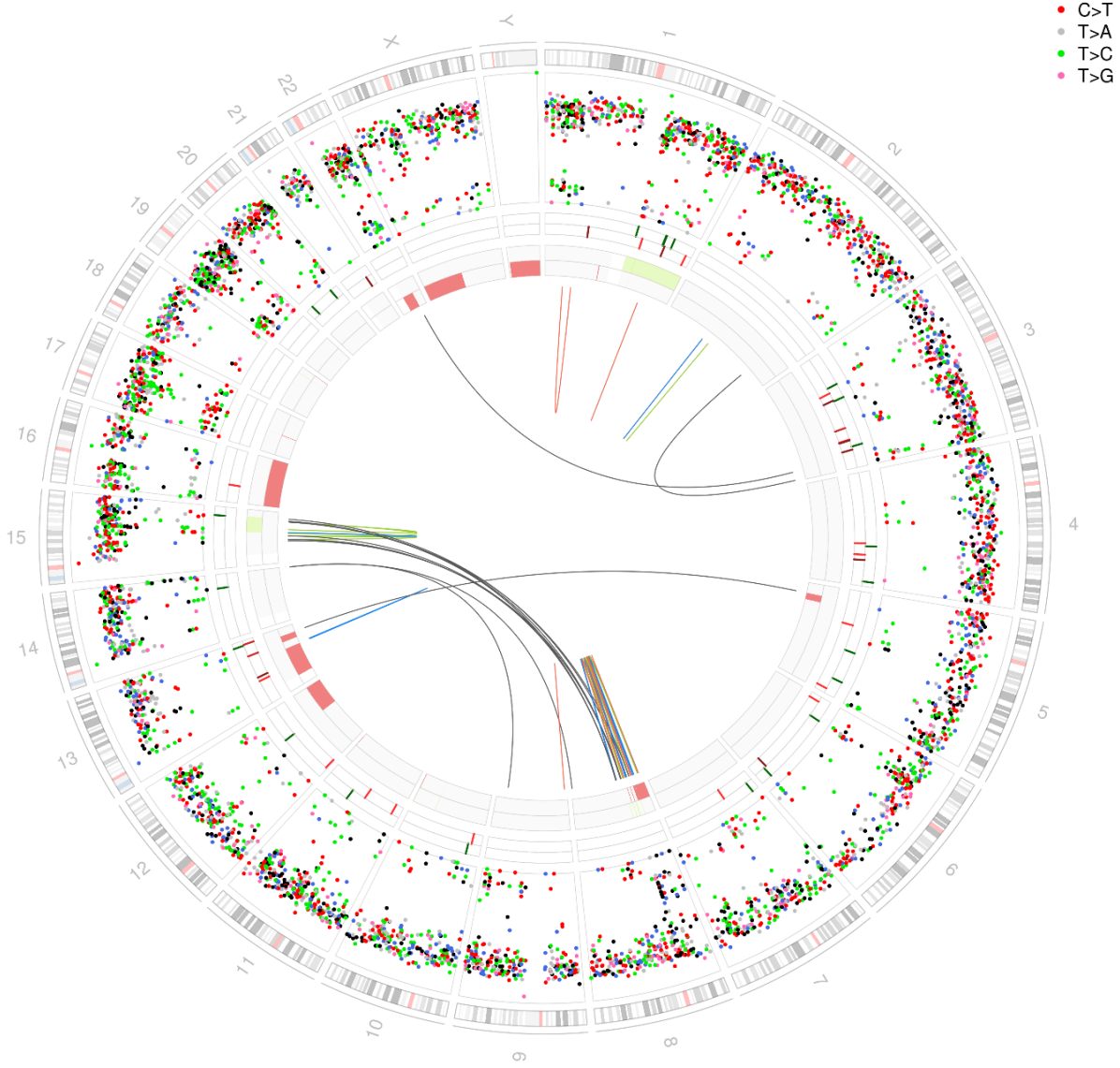
Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial

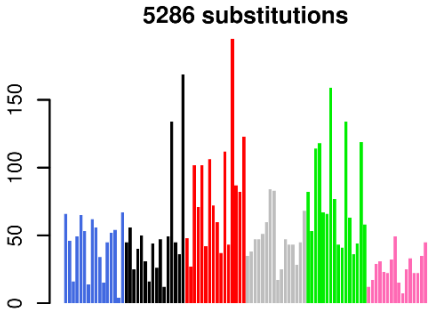
Sagar Lonial, Brendan M Weiss, Saad Z Usmani, Seema Singhal, Ajai Chari, Nizar J Bahlis, Andrew Belch, Amrita Krishnan, Robert A Vescio, Maria Victoria Mateos, Amitabha Mazumder, Robert Z Orlowski, Heather J Sutherland, Joan Bladé, Emma C Scott, Albert Oriol, Jesus Berdeja, Mecide Gharibo, Don A Stevens, 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

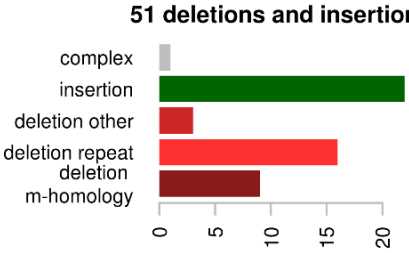
***N Engl J Med* 2015 Sep 24;373(13):1207-19; *Lancet* 2016 Apr 9;387(10027):1551-60.**

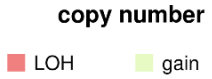
PD26419c

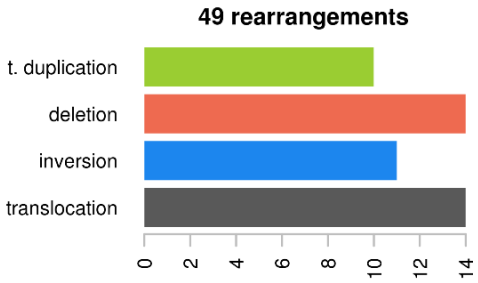
WGS at diagnosis





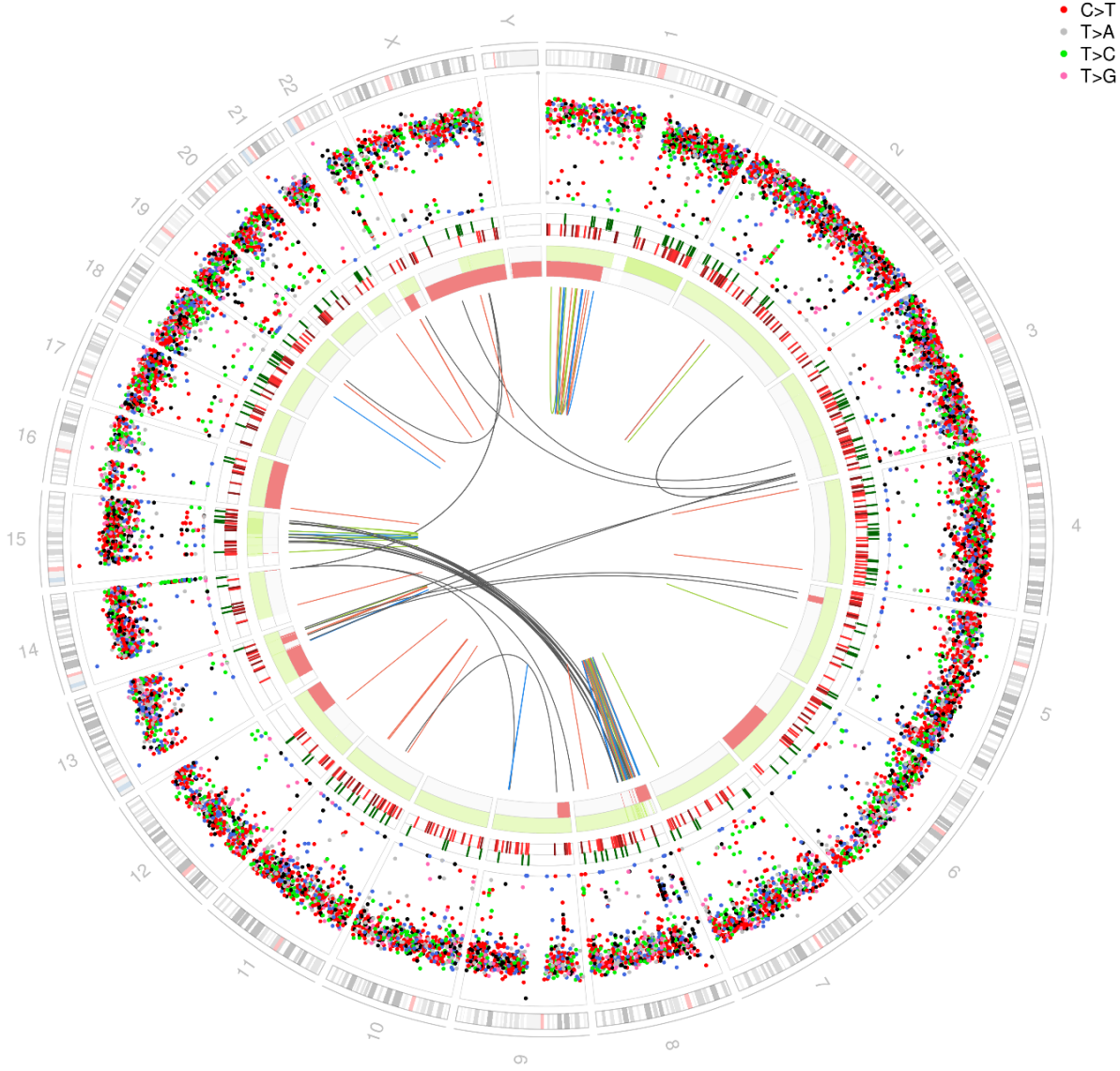


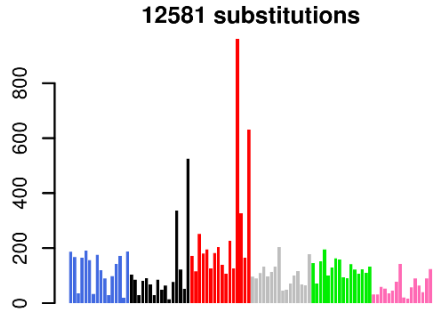


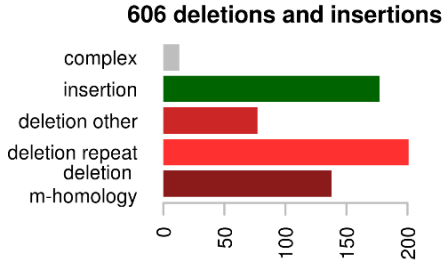


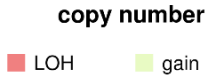
WGS at relapse

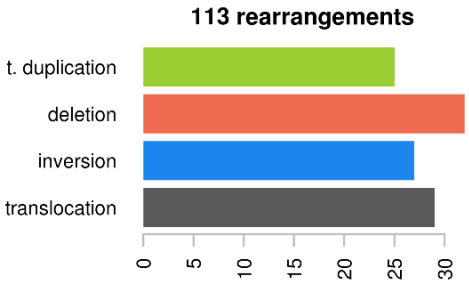
PD26419d



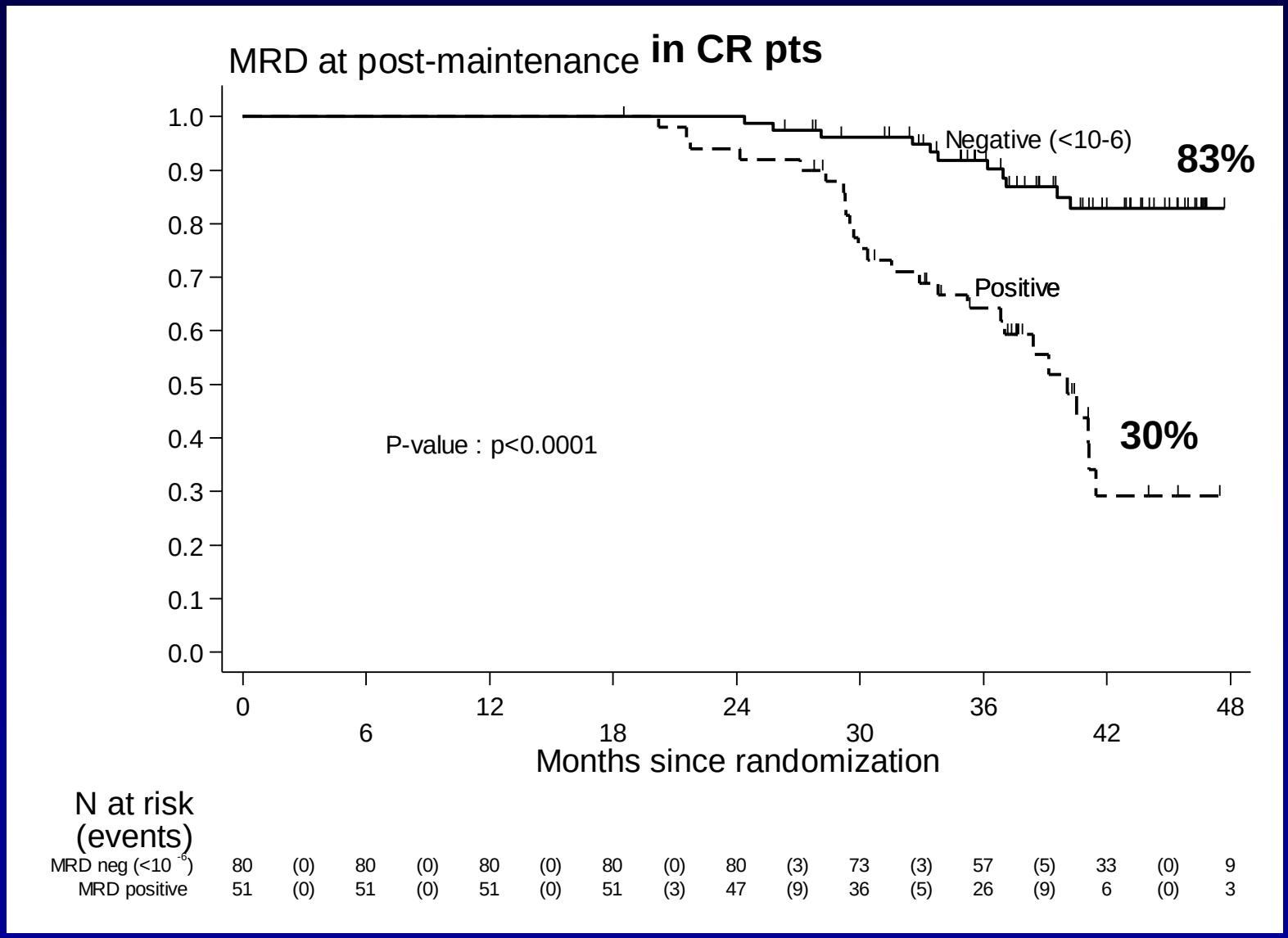








IFM DFCI 2009 update - 375 CR/sCR, 131 MRD pts



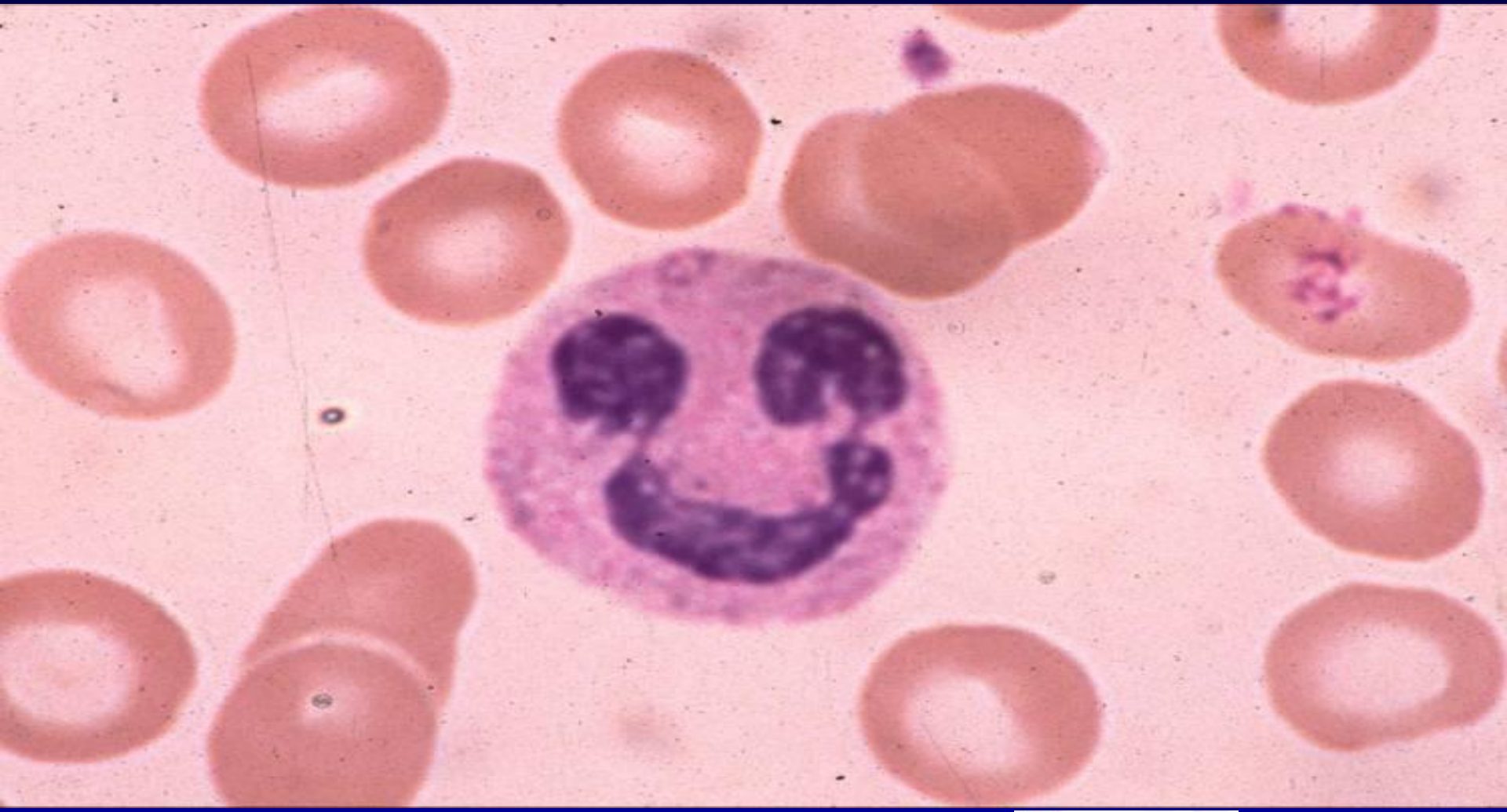
Avet-Loiseau et al, ASH 2015

Integration and Impact of Novel Agents

- Innovations (PIs, IMiDs) to date have produced significant improvements in PFS and OS: recent approvals (e.g. Ixazomib) will augment this
- Next wave of therapies ~ mutation-driven, as well as plasma cell biology-related - Daratumumab and Elotuzumab: first in class MoAbs, and paradigm agents; further refinement of prognostics and MRD will guide therapy
- Baseline immune function appears to also be a key barrier to success but may be targetable (e.g. use of PD1/PDL1 blockade)
- MoAbs 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. panobinostat, AC 241) are further expanding therapeutic opportunities with combinations
- Numerous other small molecule inhibitors show promise (e.g. HDAC, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/Myc, DUBs, MEK)

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Thank YOU!!



Slide Courtesy of Phil McCarthy MD

DANA-FARBER CANCER INSTITUTE

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Alliance for Clinical Trials in Oncology

Alliance for Clinical Trials in Oncology FOUNDATION

I F M

VE RI TAS