terapia del mieloma multiplo refrattario

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Refractory mieloma

Refractory

non responsive while on primary or salvage therapy or progresses within 60 days of last therapy

relapsed-and-refractory myeloma

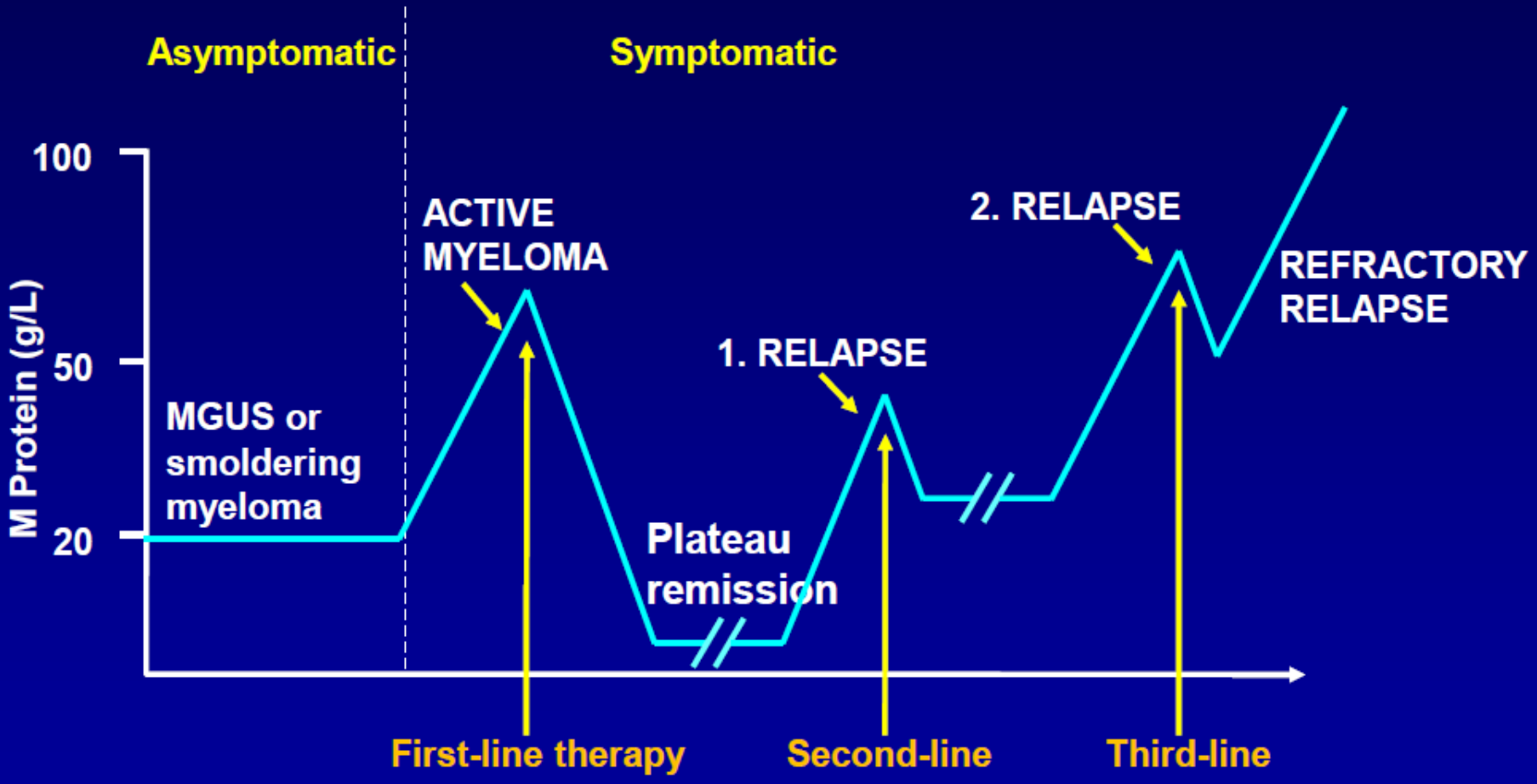
disease that is non responsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course

primary refractory myeloma

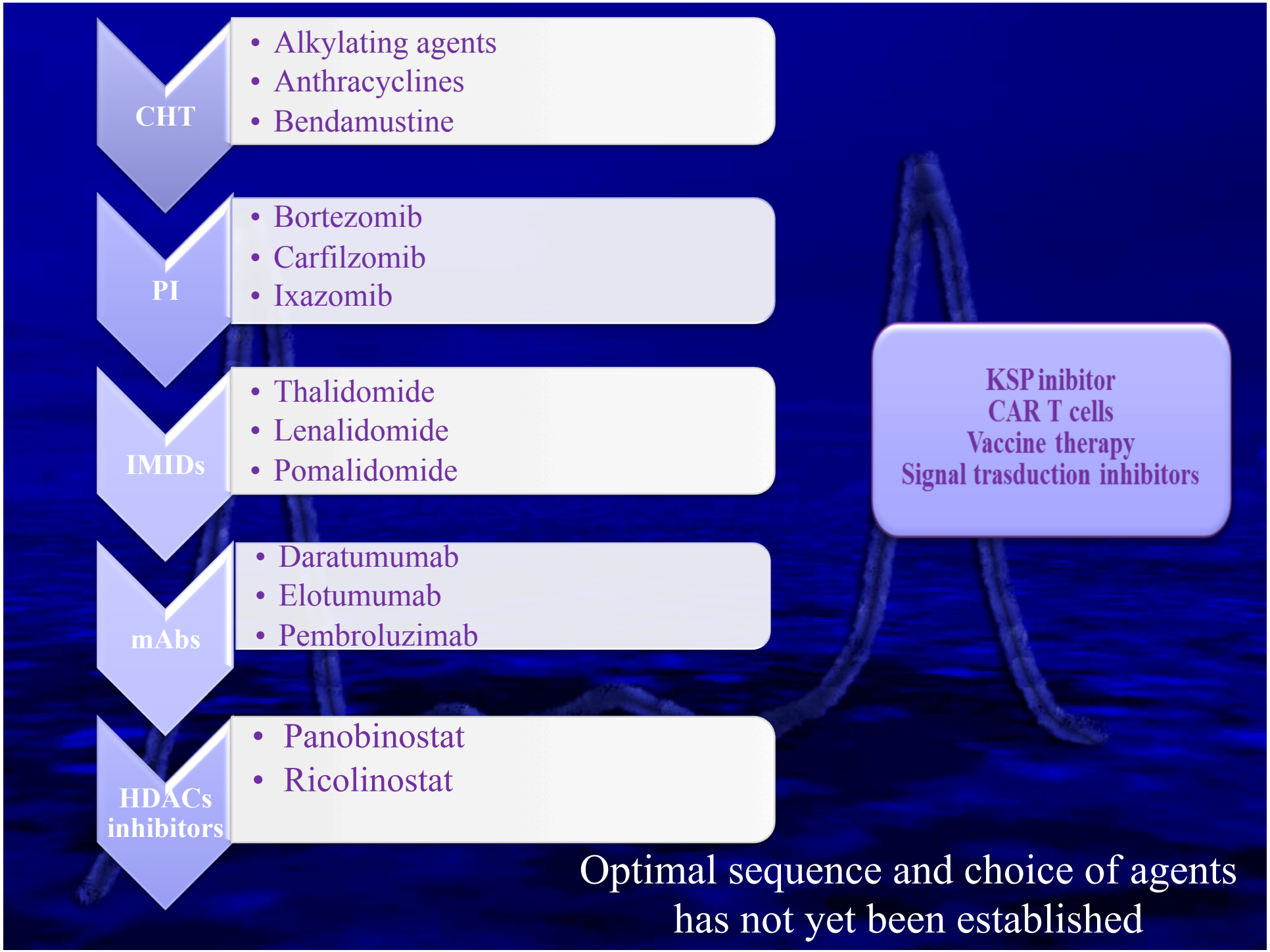
disease that is non responsive in patients who have never achieved a minimal response or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression as well as primary refractory, PD where patients meet criteria for true PD.

Rajkumar et al. Blood 2011

Natural History of Multiple Myeloma: All Pts Experience Relapse



Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009


CHT
• Alkylating agents
• Anthracyclines
• Bendamustine
PI
• Bortezomib
• Carfilzomib
• Ixazomib
IMIDs
• Thalidomide
• Lenalidomide
• Pomalidomide
mAbs
• Daratumumab
• Elotumumab
• Pembroluzimab
HDACs inhibitors
• Panobinostat
• Ricolinostat
KSP inibitor
CAR T cells
Vaccine therapy
Signal trasduction inhibitors
Optimal sequence and choice of agents has not yet been established

NCCN 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.

Chemotherapy

- High tumor burden
- Extramedullary disease
- Secondary plasma cell leukemia

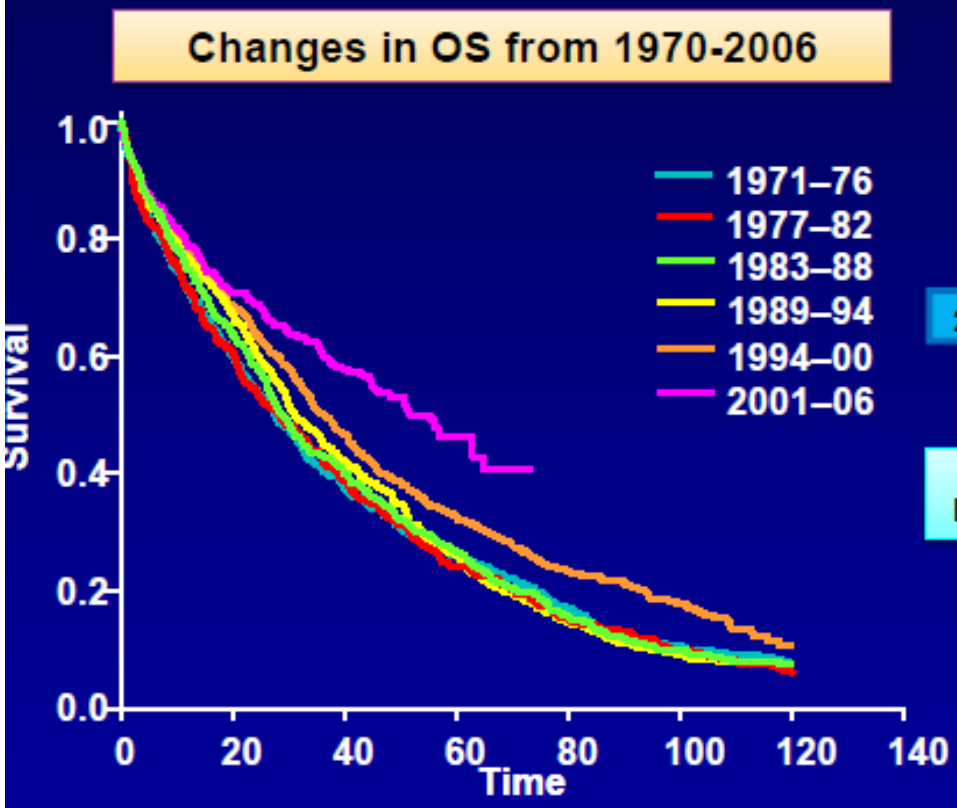
- ❖DT-PACE (Cy, VP16, CDDP, DEX DOXO)
- ❖VTD-PACE,
- ❖DCEP (Cy, VP16, CDDP, DEX)

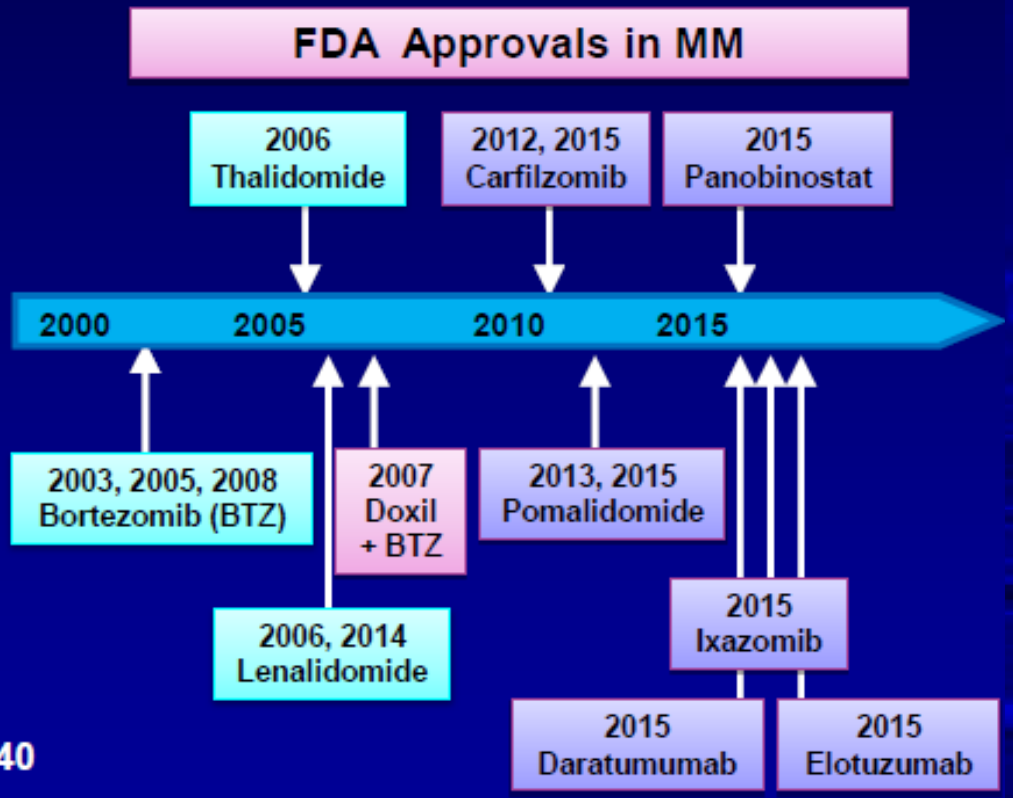
Bendamustine + Ld
RRMM Phase I/II

38 pz	
32% refractory 68% relapsed exposed at Imids ed PI	❖ORR 47% ❖PFS 10 mo median follow-up of 22 mo

Pozzi et al. Leukemia Limphoma 2016

Outcomes in Myeloma; Continued Progress and Real Hope





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

Overview of Phase III Trials with Len and Bortezomib in Relapsed/Refractory MM

Regimen	Trial	ORR, %	CR or nCR, %	≥ VGPR, %	DOR, Mos	TTP or PFS, Mos	Median OS, Mos
Len + dex	MM-009[1]	61	24	NE	16	11	35[5]
Len + dex	MM-010[2]	60	25	NE	17	11	
Bortezomib	APEX[3]	43	16	NE	8	6	30
Vdox	MMY-3001[4]	44	13	27	10	9	NE

1. Weber DM, et al. N Engl J Med. 2007;357:2133-2142. 2. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-2132. 3. Richardson PG, et al. Blood. 2007;110:3557-3560. 4. Orlowski RZ, et al. J Clin Oncol. 2007;25:3892-3901. 5. Weber D, et al. Blood. 2007;110:Abstract 412.

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

64 Pz

- relapsed 58%
- relapsed and refractory MM 42%

- bortezomib 53%
- thalidomide 75%
- lenalidomide 6%

partial response or better 64%;

median follow-up 44 mo

median duration of response 8.7 mo

Median OS 30 mo

Median PFS 9.5 mo

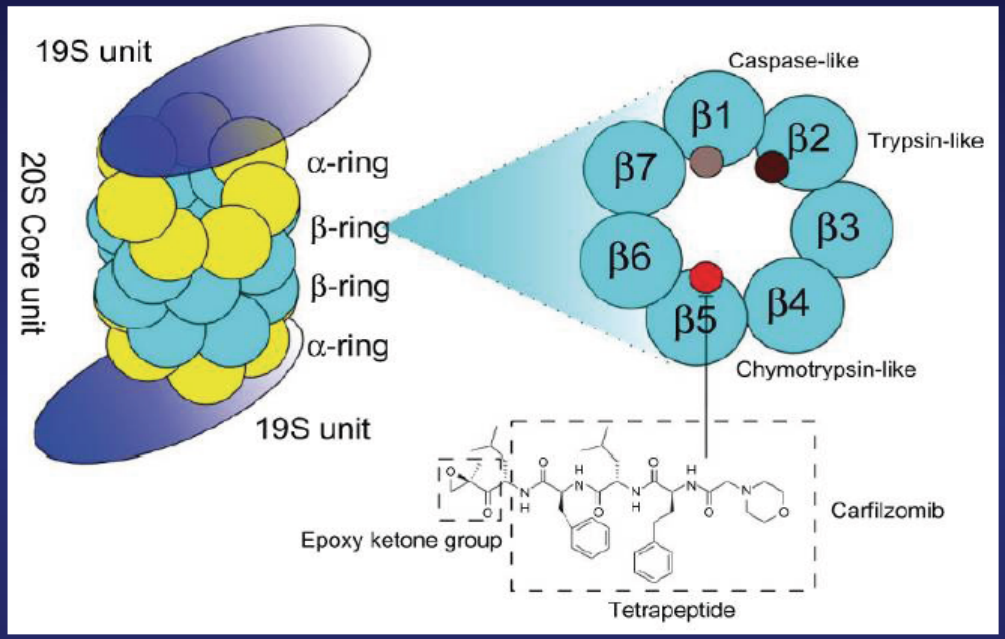
FDA Approvals for MM Since 2012

Initial US Approval	Drug	Drug Type	Indication(s)
2012	Carfilzomib	PI	With Dex or Len/Dex for patients who have received 1 to 3 lines of therapy or as a single agent for patients who have received at least 1 line of therapy
2013	Pomalidomide	Immunomodulatory agent	With Dex for patients who have received ≥2 prior therapies including Len and a PI; disease progression on or within 60 days of last therapy
2015	Daratumumab	CD38-targeted mAb	For patients who have received ≥3 prior lines of therapy including a PI and an immunomodulatory drug or who are double refractory
2015	Elotuzumab	SLAMF7-targeted mAb	In combination with Len/Dex for patients who have received 1 to 3 prior therapies
2015	Ixazomib	Oral PI	In combination with Len/Dex in patients who have received ≥1 prior therapy
2015	Panobinostat	HDAC inhibitor	In combination with Bor/Dex in patients who have received ≥2 prior regimens, including Bor and an immunomodulatory drug

Nooka AK, et al. *Blood*. 2015;125:3085-3099. Thertulien R. Citizen Times website.

SECOND-GENERATION PROTEASOME INHIBITORS

CARFILZOMIB: MECHANISM OF ACTION



Carfilzomib irreversibly and selectively inhibits the chymotripsin-like activity of the 20S proteasome, necessitating de novo protein synthetis to restore activity.

In preclinical studies it demonstrates more potent proteasome inhibition and minimal off-target activity.

Carfilzomib demonstrates significantly less cross-reactivity with nonproteasomal proteases compared to bortezomib, which has been shown to correlate with a lack of neurotoxicity in preclinical study.

Consecutive-day dosing of carfilzomib was well-tolerated and led to prolonged irreversible proteasome inhibition.

CARFILZOMIB

2012
FDA

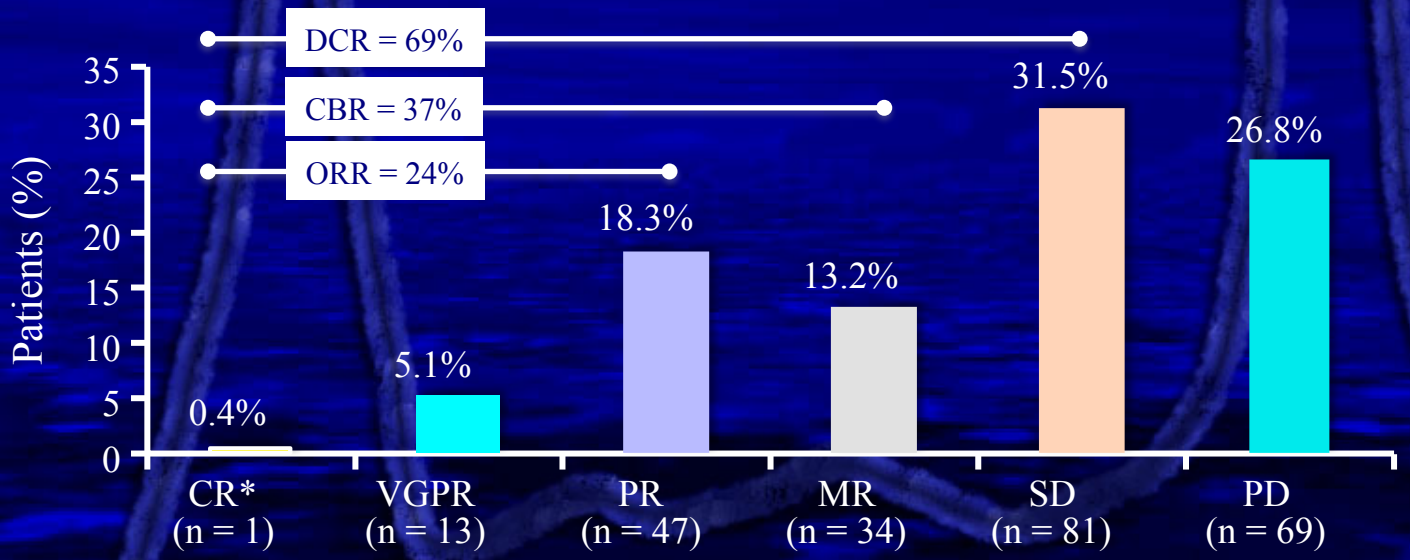
- Approval in monotherapy for patients exposed to at least two prior therapies including bortezomib and an IMiDs and whose disease progressed within 60 days of their last therapy

2015
FDA- EMA

- Approval in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

Carfilzomib in Relapsed/Refractory MM
003-A1 Single-Arm Pivotal Study (N = 266)

- Progressive disease required (>2 lines of therapy)
- Median 5.4 years from diagnosis (range, 0.5-22.3)
- 99.6% prior bortezomib
- 80% refractory or intolerant to bortezomib and lenalidomide



- Well tolerated
- Very low rate of neuropathy
  - G1/2 11.3%
  - G3/4 1.1%

Median OS 15.6 months

Responses not affected by prior treatment or cytogenetics

Abbreviations: CBR, clinical benefit rate; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; SD, stable disease.

Siegel DS, et al. Blood. 2012;120:2817-2825. Slide courtesy of Dr. Lonial.

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd)

Randomization

N=792

Stratification:

- β_2-microglobulin
- Prior bortezomib
- Prior lenalidomide

28-day cycles

KRd

Carfilzomib 27 mg/m^2 IV (10 min)

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

Rd

Lenalidomide 25 mg *Days 1–21*

Dexamethasone 40 mg *Days 1, 8, 15, 22*

Primary endpoint: PFS

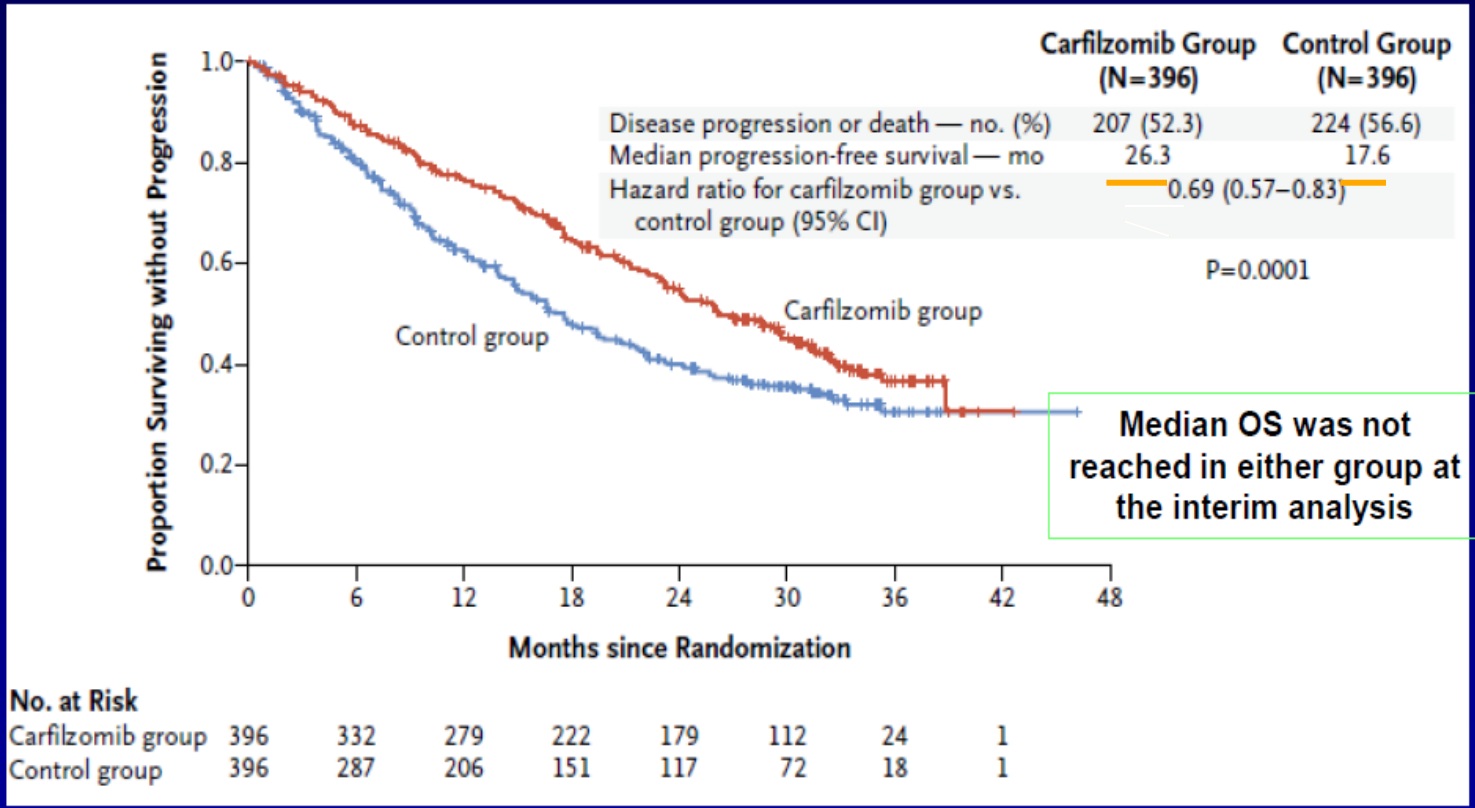
Stewart K et al, NEJM 2015

- 1–3 prior treatments, not lena refractory, no PD on bort

(20% lena exposed, 15% bort refractory)

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)



- 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.

ENDEAVOR: Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd)

Randomization 1:1

N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

Kd

Carfilzomib 56 mg/m^2 IV

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg

Days 1, 2, 8, 9, 15, 16, 22, 23

28-day cycles until PD or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m^2 (IV bolus or subcutaneous injection)

Days 1, 4, 8, 11

Dexamethasone 20 mg

Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles until PD or unacceptable toxicity

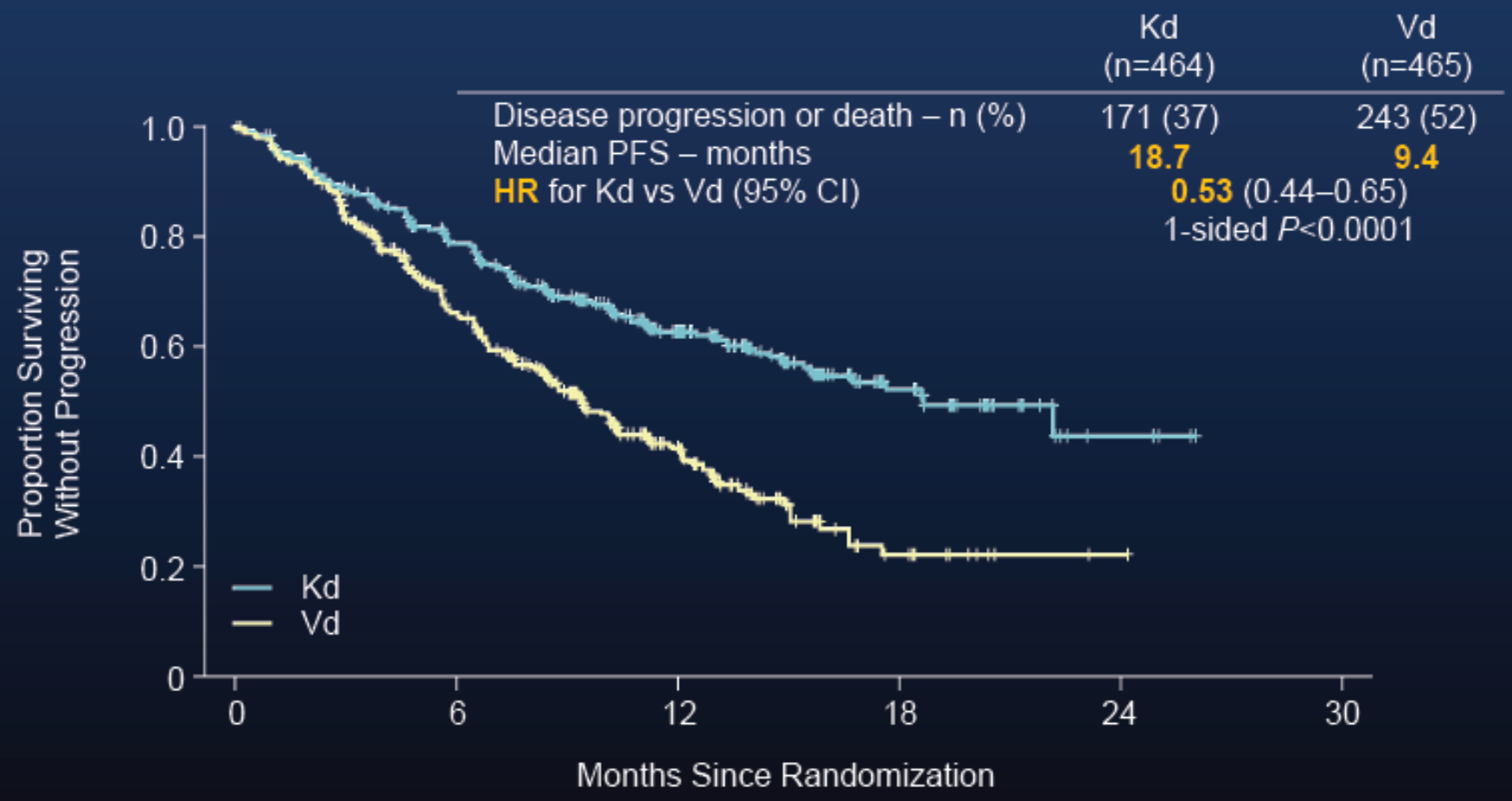
Primary endpoint: PFS

- 1–3 prior treatments, not Carf or Bort refractory

(54% bort exposed, 38% lena exposed)

Dimopoulos D et al, Lancet Oncology 2016

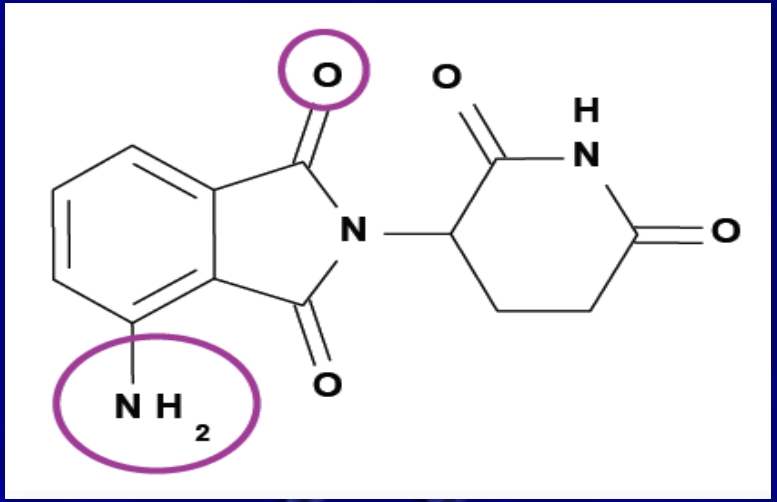
Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)



- **Median follow-up: 11.2 months**

Dimopoulos D et al, Lancet Oncology 2016

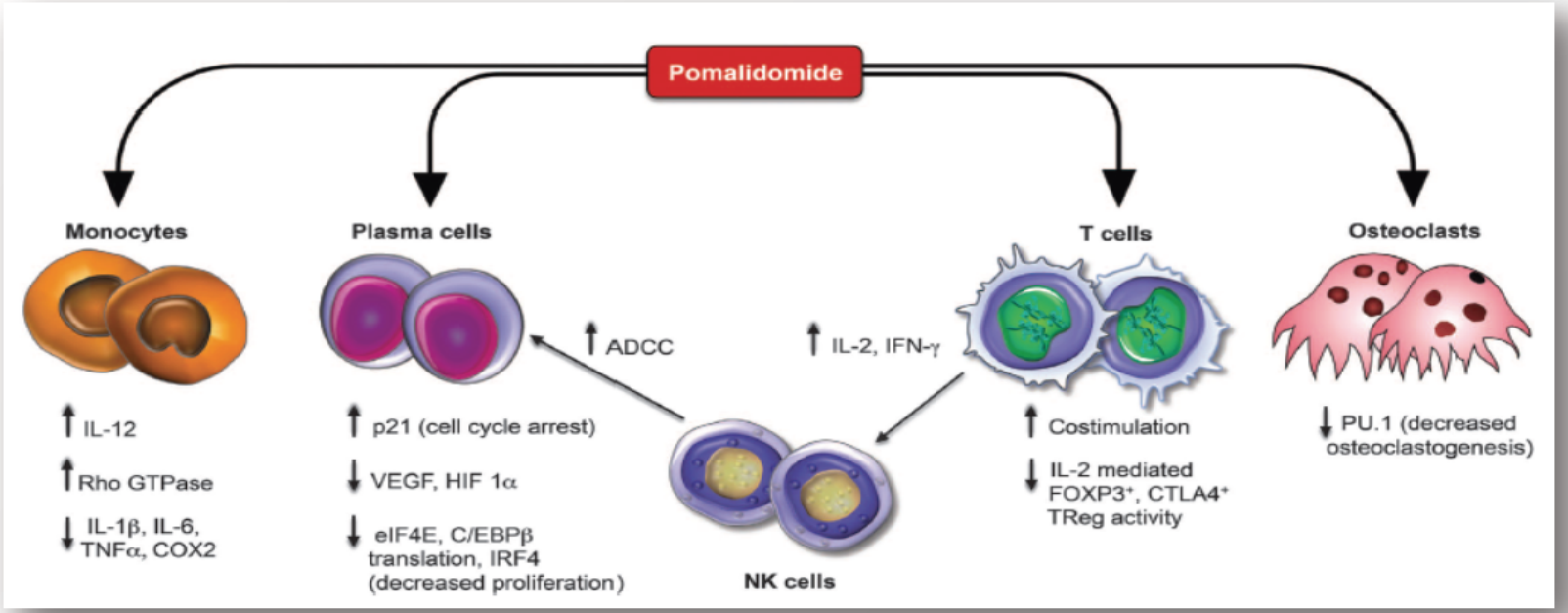
Pomalidomide (CC-4047)
is the newest IMiD, derived from thalidomide with a modified chemical structure, with improved potency and activity demonstrated *in vitro*



Pomalidomide in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy

FDA and EMA APPROVAL IN 2013

Pomalidomide: mechanisms of action



- anti-angiogenic effect
- anti-proliferative activity (by blocking signaling through NFkB)
- pro-apoptotic activity (induction of caspase 8 pathway)
- immunomodulatory properties (downregulation of inflammatory cytokines, stimulation of cytotoxic T-cell)

Chanan-Khan et al, Blood Cancer J 2013

Phase III MM-003 Trial Design

Eligibility (n = 455)

- Advanced relapsed MM or RRMM
- ≥2 prior lines of therapy
- Failure of Len and Btz
- No resistance to HiDEX in last line of therapy
- No Grade ≥2 PN

PN = peripheral neuropathy

R

28-d cycles until PD

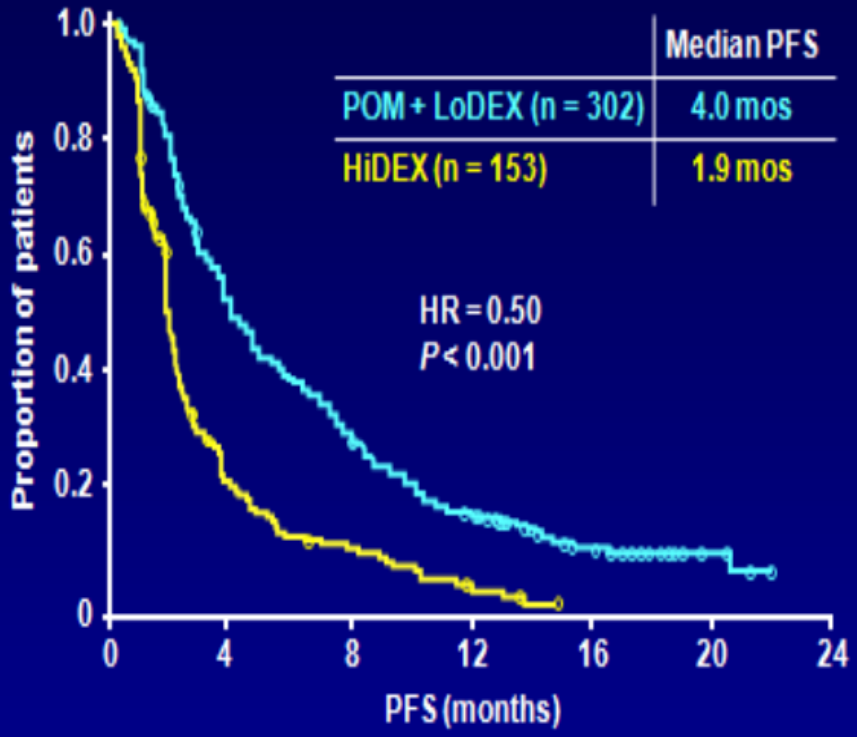
POM + LoDEX (n = 302)
POM: 4 mg, d1-21
LoDEX: 20 mg or 40 mg*, d1,8,15,22

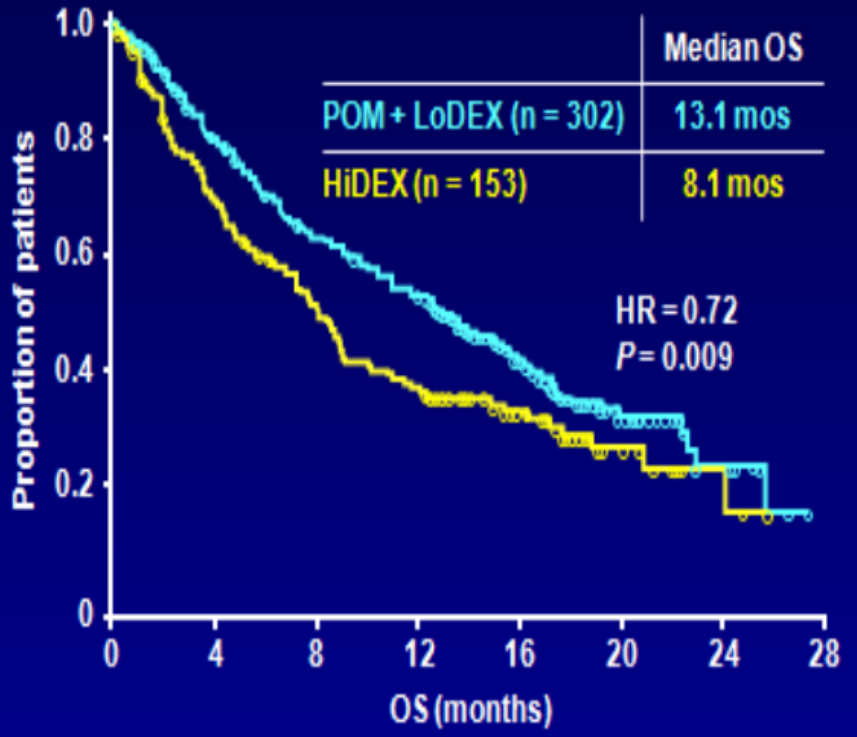
HiDEX (n = 153)
HiDEX: 20 mg or 40 mg*, d1-4, 9-12, 17-20

LoDEX or HiDEX: 20 mg (>75 years) or 40 mg (≤75 years)

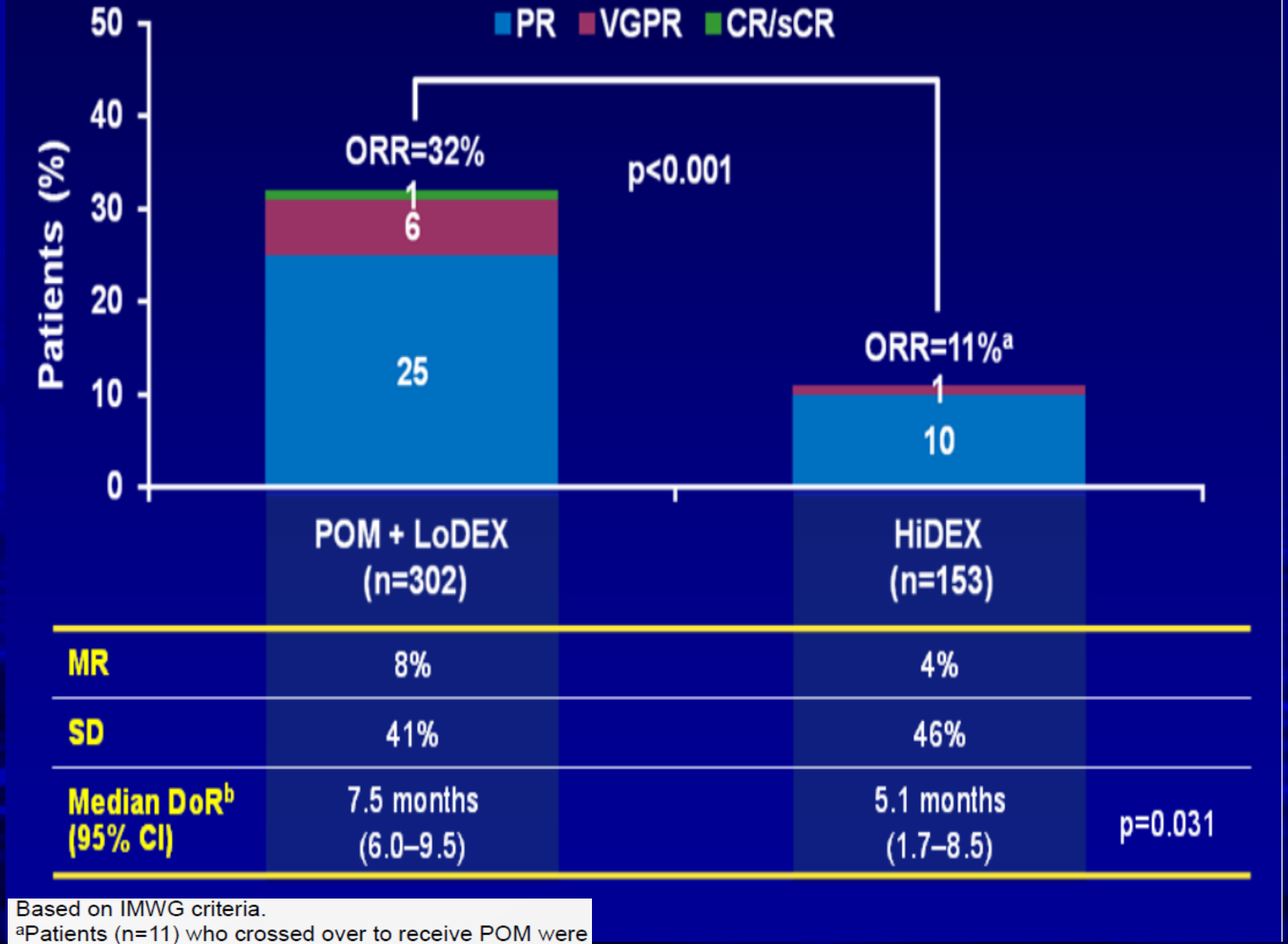
- Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin or equivalent was required for all patients receiving POM and those at high risk of thromboembolic events
- Primary endpoint: Progression-free survival (PFS)

San Miguel JF et al. *Proc EHA* 2013;Abstract S1151; *Proc ASCO* 2013;Abstract 8510





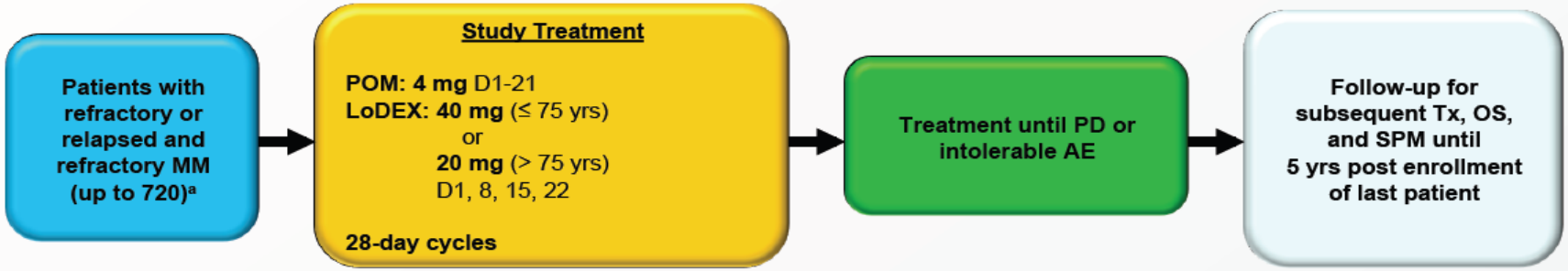
- Compared with HiDEX, POM + LoDEX significantly improved PFS (4.0 vs 1.9 months; P < 0.001) and OS (13.1 vs 8.1 months; *P* = 0.009)
- 85 patients (56%) in the HiDEX arm received subsequent POM



Based on IMWG criteria.
[a]Patients (n=11) who crossed over to receive POM were analysed per original randomised arm.
[b]Kaplan–Meier estimate; patients with ≥PR.

San Miguel et al., Lancet Oncol 2013;14:1055-66
Dimopoulos et al, Blood 2013 (suppl abstr 408)

MM-010 trial (STRATUS)



Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin, or equivalent was required for all pts

RRMM, refractory to last therapy, at least 2 prior therapies, all pts must have failed BORT and LEN
(Pts progressed on or within 60 days, Pts with PR must have progressed within 6 months, Intolerant to BORT)

	STRATUS (MM-010) (n=604)	MM-003 Pom-LoDex arm (n=302)
ORR, %	35	32
PFS, mo	4.2	4.0
OS, mo	11.9	13.1

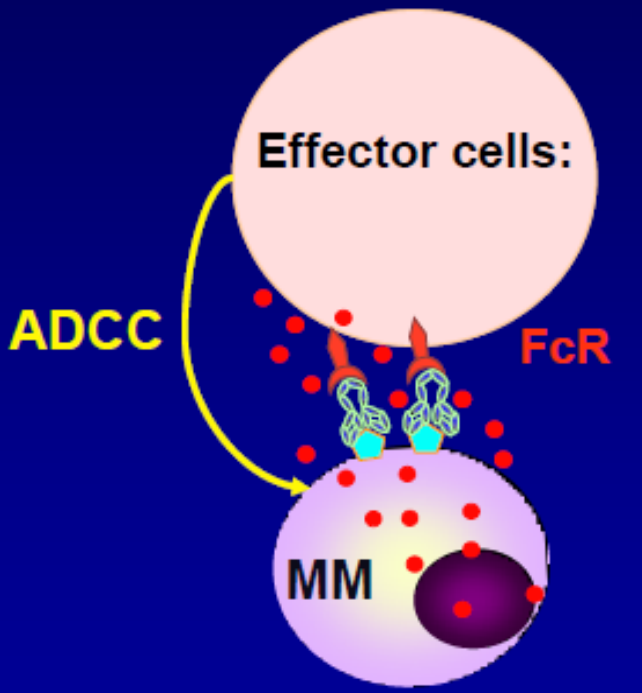
Grade 3-4 AEs, %	
Neutropenia	42
Febrile neutropenia	5
Anemia	29
Thrombocytopenia	22
Infections	30
Pneumonia	11
Fatigue	5
VTE	1
PN	1
Discont. due to AE	5

San Miguel et al. Lancet Oncol 2013;14(11):1055-66
Dimopoulos et al. ASH 2013 (Abstract 408), oral presentation

Dimopoulos et al. ASH 2014

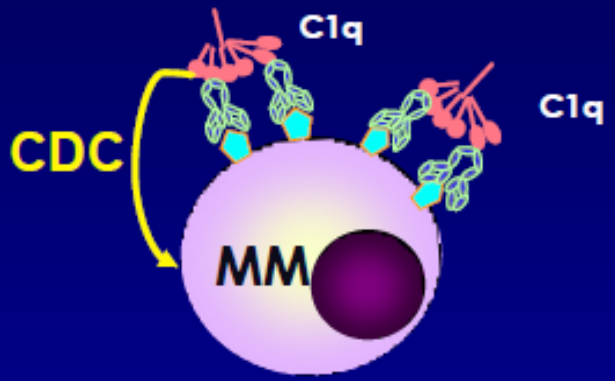
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)



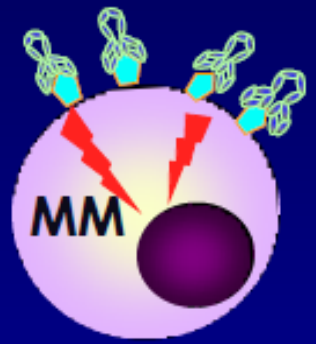
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1; SLAMF7)
- Daratumumab, SAR650984 (CD38)
- XmAb®5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)



- Daratumumab
- SAR650984 (CD38)

Apoptosis/growth arrest via targeting signaling pathways

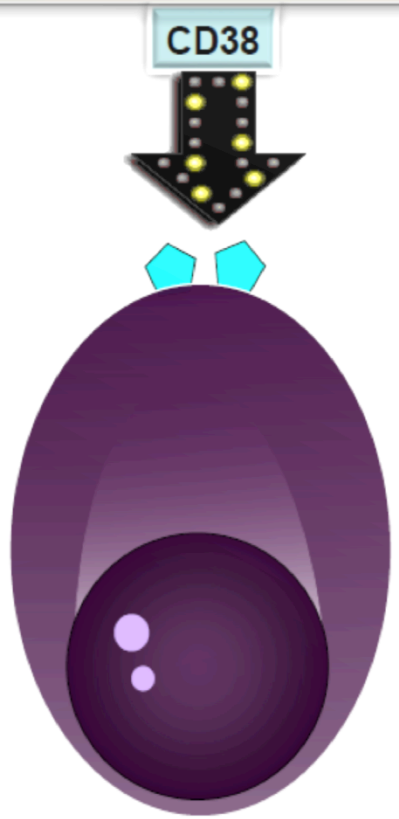


- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- Siltuximab (1339) (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab, SAR650984 (CD38)

Adapted from Tai & Anderson Bone Marrow Research 2011

Daratumumab is an IV human IgG manufactured antibody

It is a targeted immunotherapy which binds to CD38

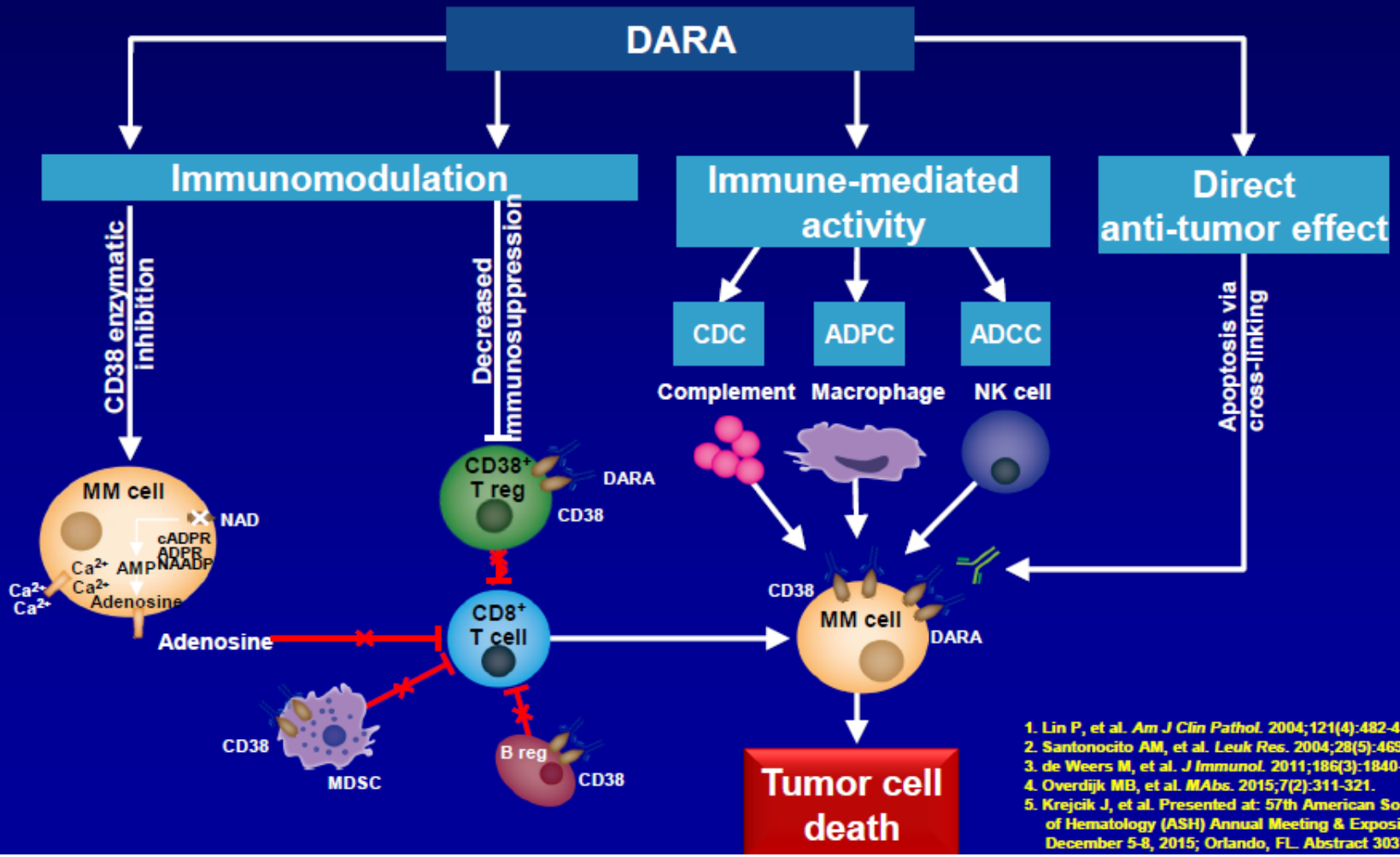


Daratumumab as monotherapy
is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

2015 approval by FDA
May 2016 approval by EMA

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.

SIRIUS Trial

Refractory to, n (%)	n = 106
Last prior therapy	103 (97)
PI and IMiD	101 (95)
BORT	95 (90)
CARF	51 (48)
LEN	93 (88)
POM	67 (63)
Alkylating agent	82 (77)
BORT+LEN	87 (82)
BORT+LEN+CARF	42 (40)
BORT+LEN+POM	57 (54)
BORT+LEN+CARF+POM	33 (31)
BORT+LEN+CARF+POM+THAL	12 (11)

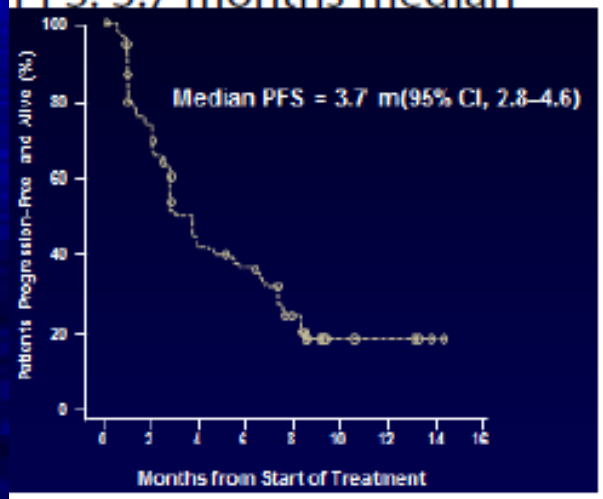
- Patients were heavily pretreated and most patients were refractory to multiple lines of PI and IMiD treatment
  - 97% refractory to their last line of therapy
  - 95% double refractory
  - 66% refractory to 3 of 4 therapies (bortezomib, lenalidomide, carfilzomib, and pomalidomide)
  - 63% refractory to pomalidomide
  - 48% refractory to carfilzomib

Lonial et al Lancet 2016 *Lonial et al: ASCO 2015*

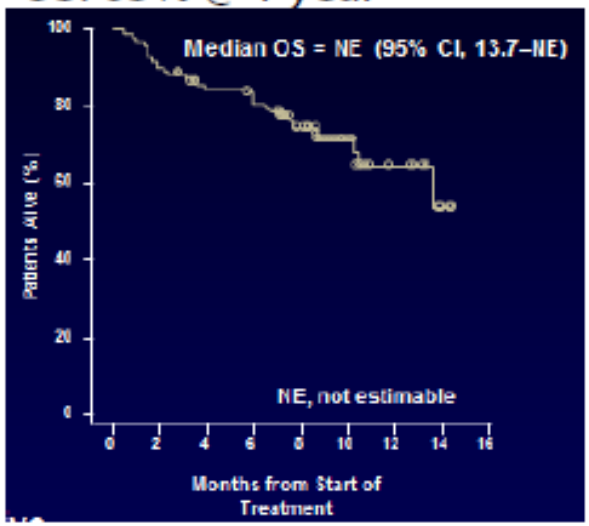
Daratumumab Single-Agent: Efficacy

Sirius Trial	• ORR: 29% ➢ 9% VGPR ➢ 3% sCR

PFS: 3.7 months median

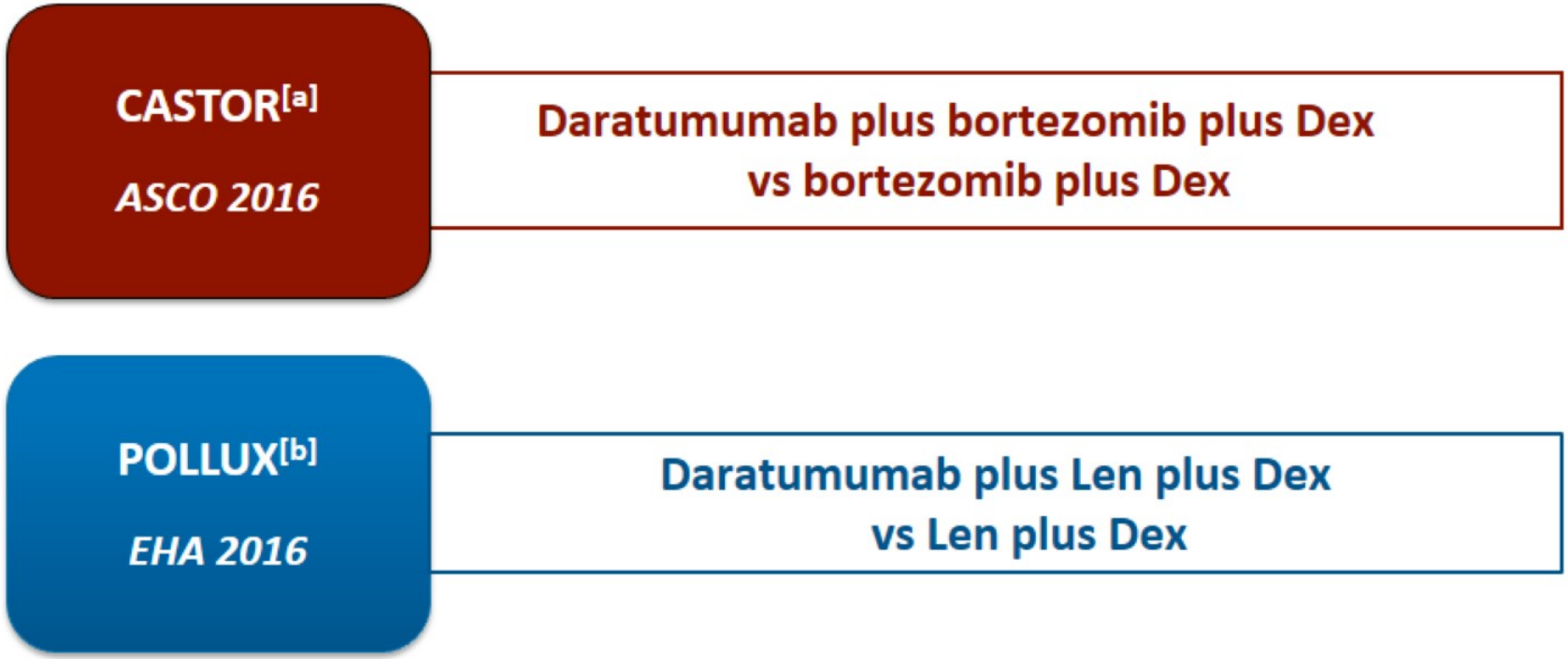


OS: 65% @ 1 year



Two Large Randomized Studies of Daratumumab Reported in 2016

For MM patients with first-line therapy after relapse



a. Palumbo, et al. NEJM 2016
b. Dimopoulos, et al. NEJM 2016

CASTOR Study
Efficacy Endpoints

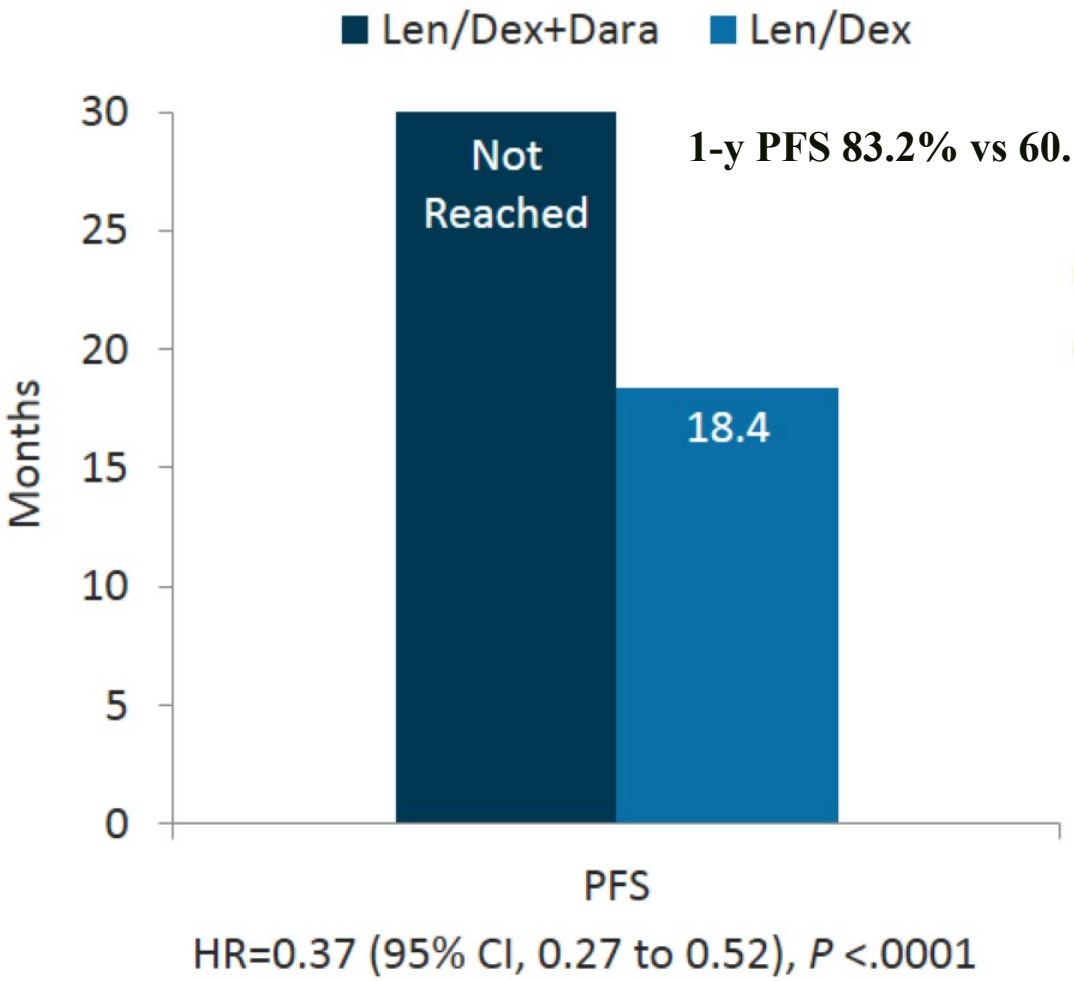
	Dara+Bor/Dex	Bor/Dex	HR (95% CI) *P*
Median PFS, mo *Primary endpoint*	Not reached	7.2	0.39 (0.28-0.53) <.0001
1-y PFS, %	60.7	26.9	
Time to progression, mo	Not reached	7.3	0.30 (0.21-0.43) <.0001
1-y time to progression, %	65.4	28.8	

61.4% reduction in the risk of progression

Median Follow-Up 7.4 mo
Range 0-14.9 mo

Palumbo, et al. NEJM 2016

POLLUX
PFS Primary Endpoint



1-y PFS 83.2% vs 60.1%

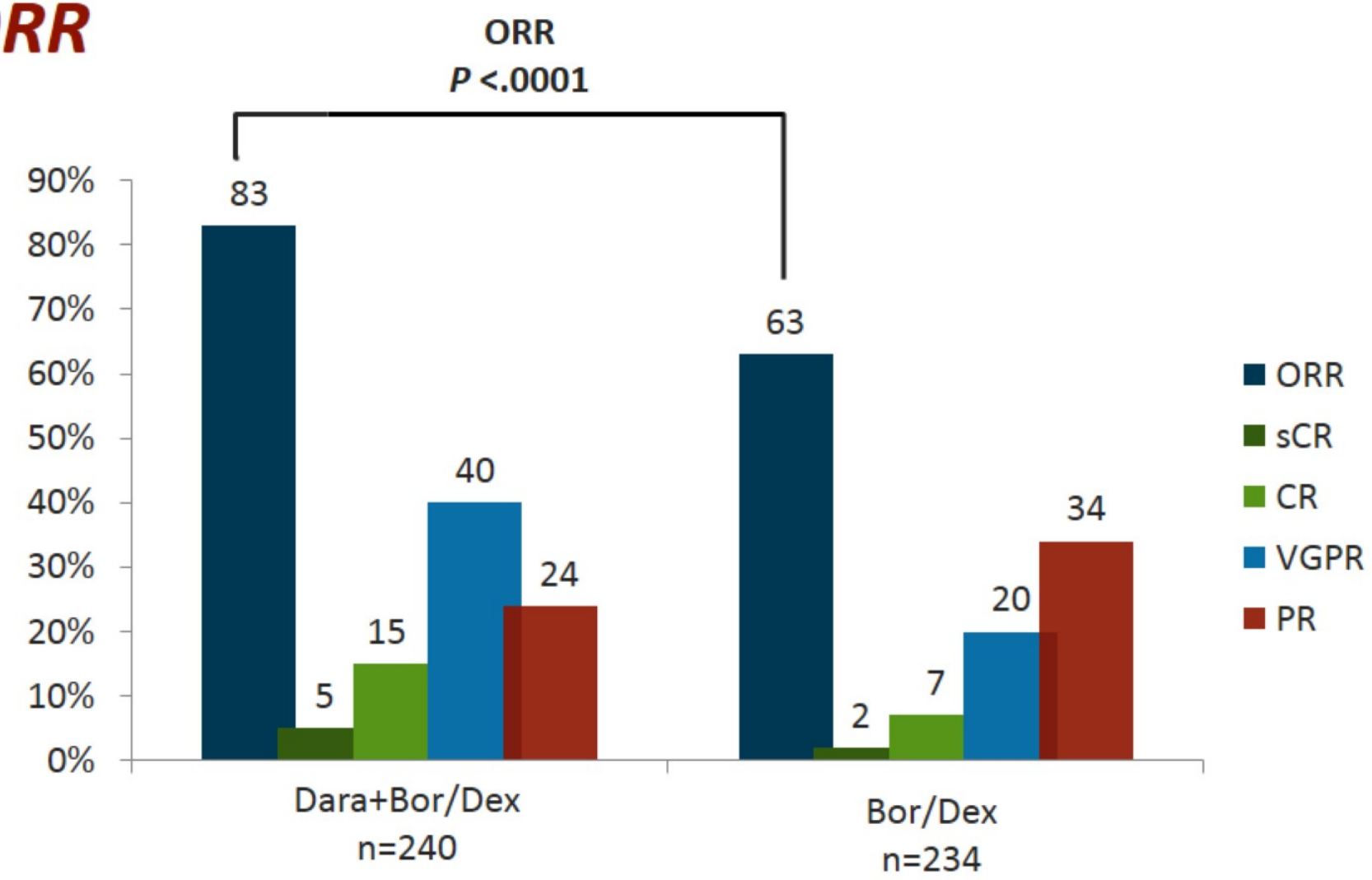
63% reduction in the risk of progression

- PFS benefit consistent among all prespecified subgroups

Dimopoulos, et al. NEJM 2016

CASTOR Study

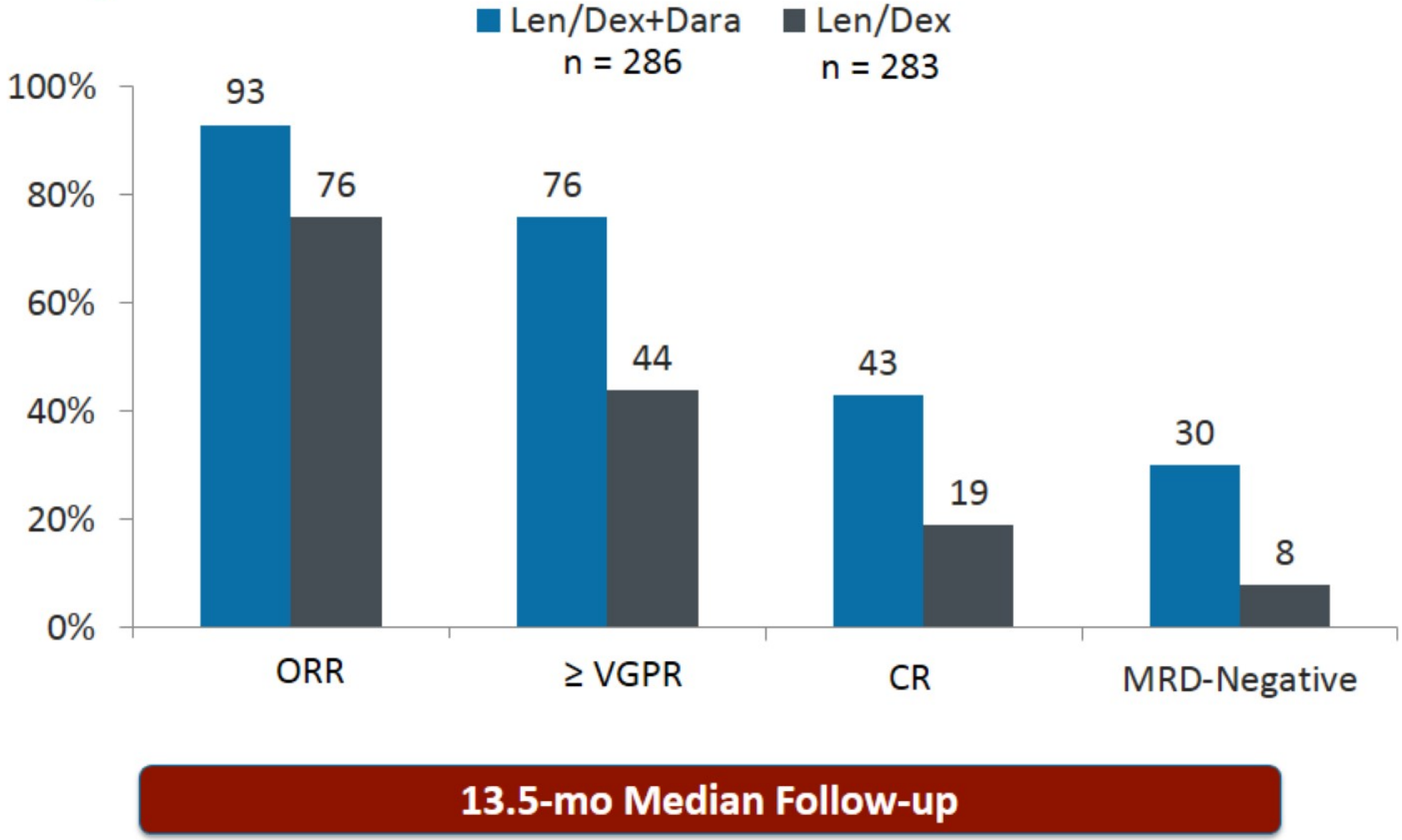
ORR



Palumbo, et al. NEJM 2016

POLLUX

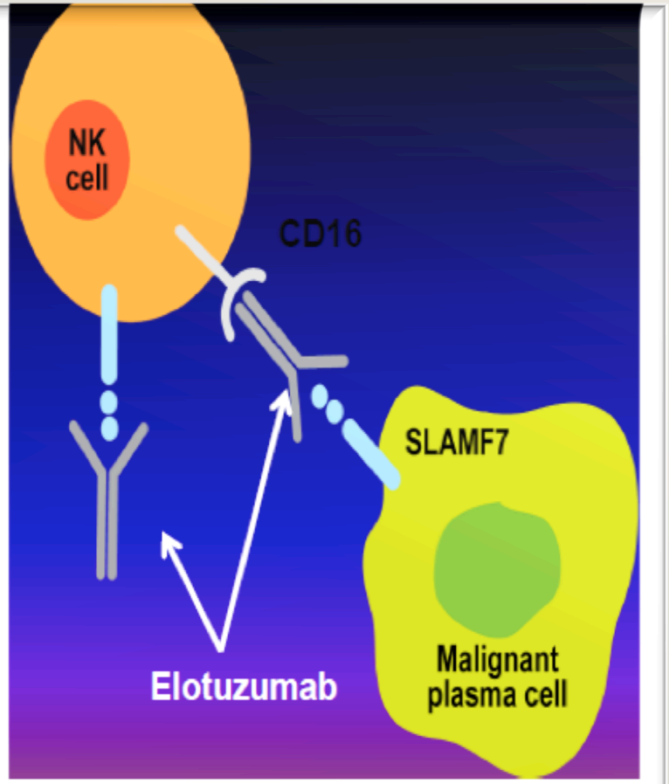
Response Rates



13.5-mo Median Follow-up

Dimopoulos, et al. NEJM 2016

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



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

Elotuzumab is indicated in combination

with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

2015 approval by FDA
May 2016 approval by EMA

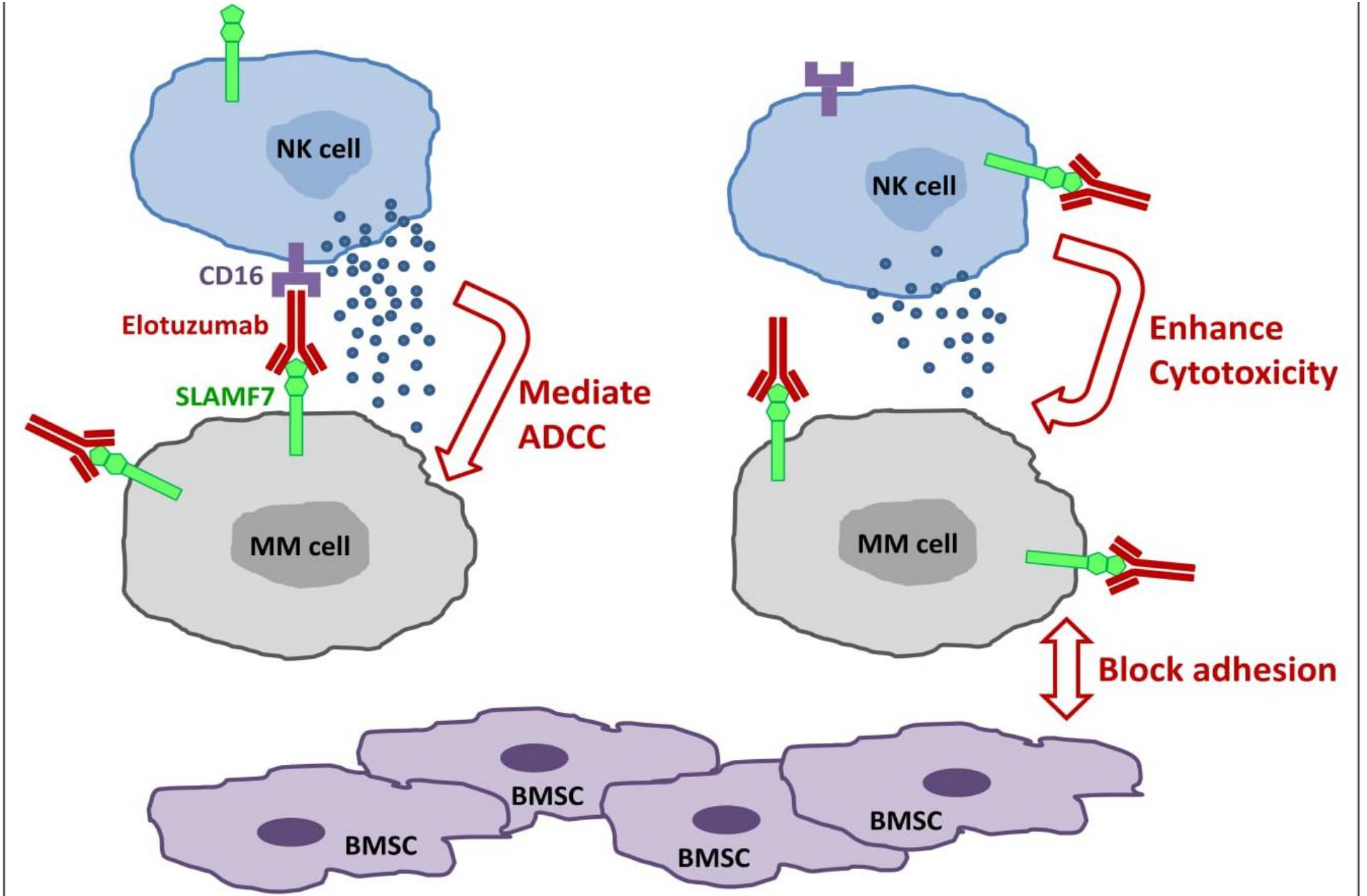
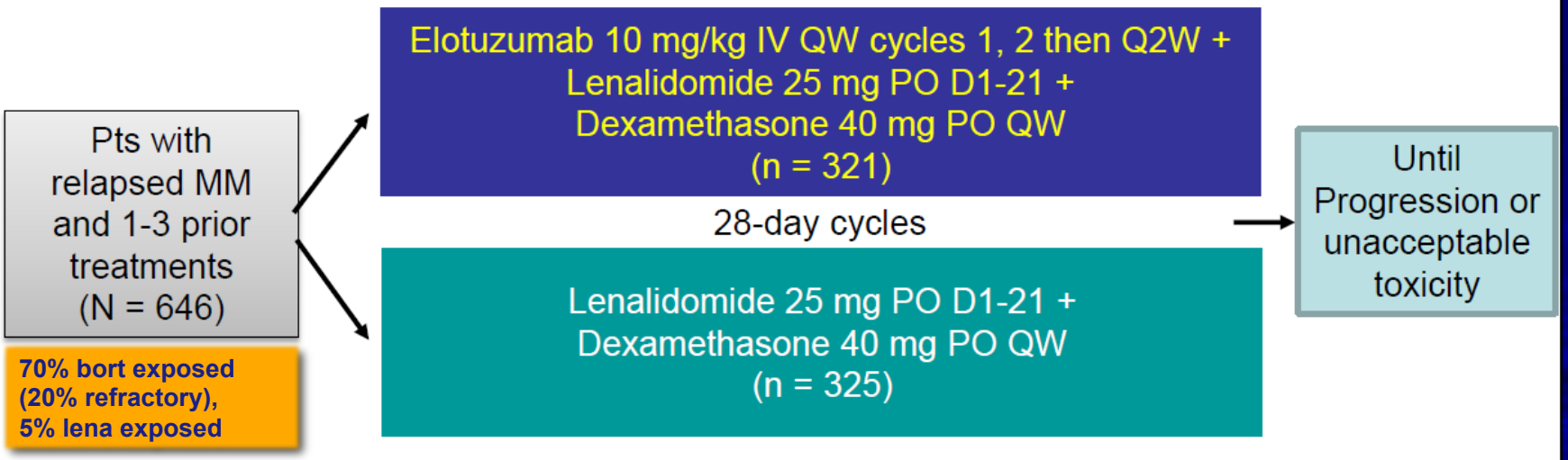


Fig. 1 The mechanisms of action of elotuzumab. *Upper left*, elotuzumab binds SLAMF7 on MM cells, and its Fc fragment is then bound by CD16 on NK cells, mediating ADCC. *Upper right*, elotuzumab binds SLAMF7 on NK cells, directly enhancing its cytotoxicity. *Bottom right*, elotuzumab binds SLAMF7 on MM cells, inhibiting its interaction with BMSCs. *NK cell* natural killer cell; *MM cell* multiple myeloma cell; *BMSC* bone marrow stromal cell; *ADCC* antibody-dependent cellular cytotoxicity

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

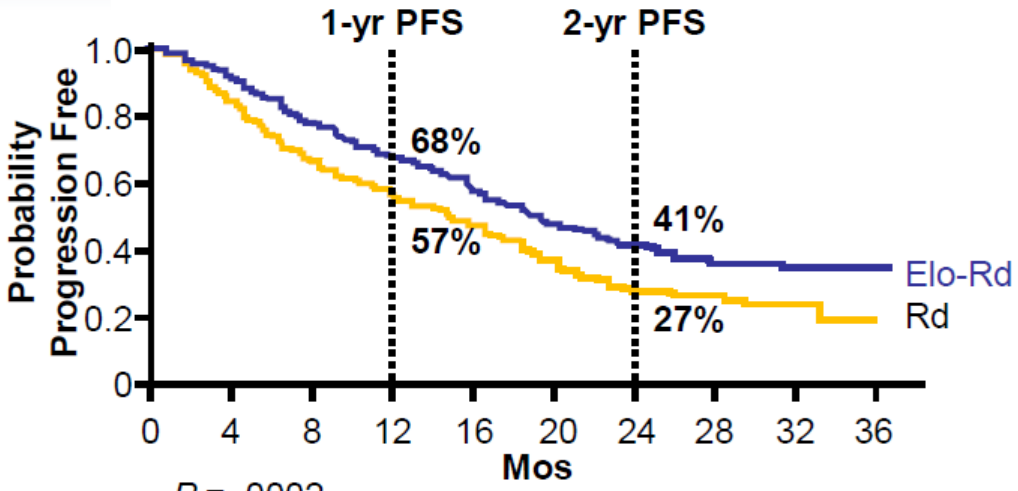
- Randomized, open-label, multicenter phase III trial



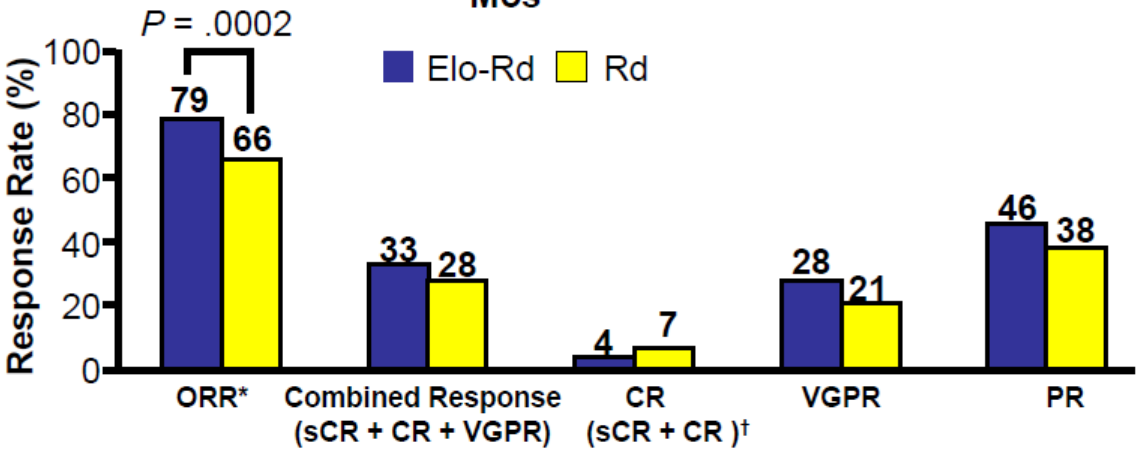
- Primary endpoints: Progression Free time (PFS), Overall Response
- Secondary endpoints: Overall Survival, safety, health-related Quality of Life

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

ELOQUENT-2: Progression Free and Overall Response



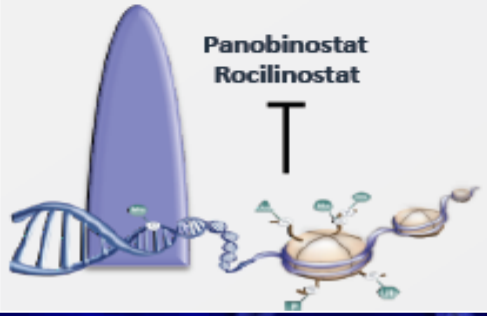
	Elo-Rd	Rd
Median PFS, mos (95% CI)	19.4 (16.6-22.2)	14.9 (12.1-17.2)



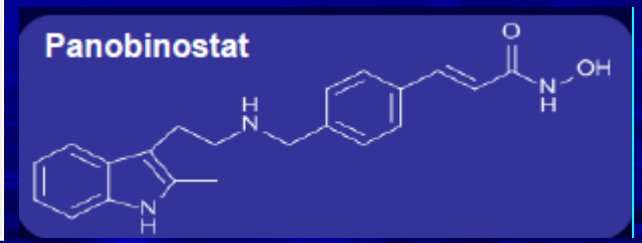
Lonial S, et al. N Engl J Med 2015; 373:621-631

HDAC inhibitors

- Histone deacetylases (HDACs) are present in all eukaryotic cells and impact gene **expression, cell signaling, the cell cycle, and apoptosis** through the regulation of protein acetylation
- Small molecule HDAC inhibitors, such as **panobinostat** and **rocilinostat,** have demonstrated synergistic activity with proteasome inhibitors and induce myeloma cell death through inhibition of the proteasome and aggresome pathways



Panobinostat: pan HDAC inhibitor

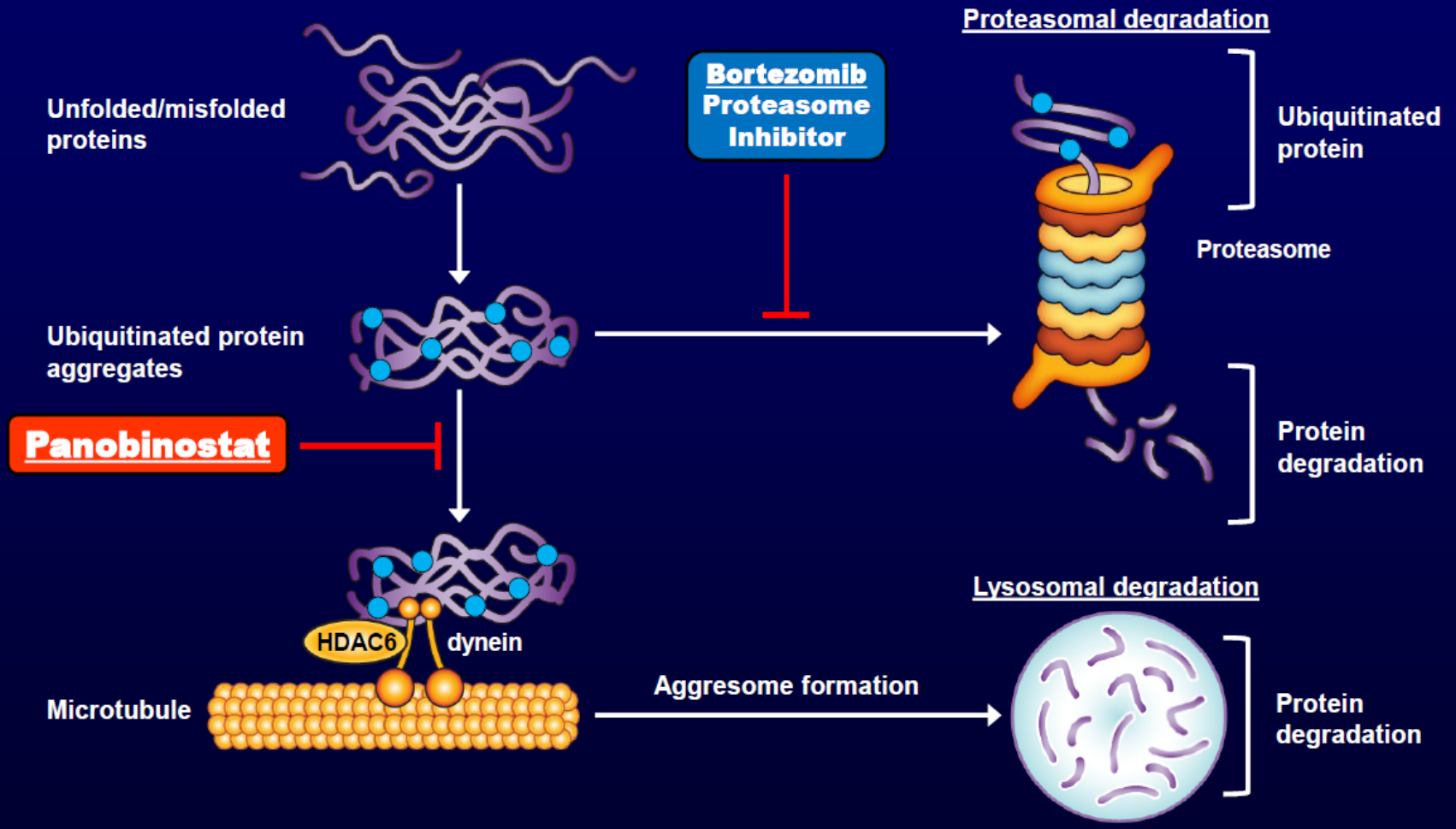


in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma who have received at least **two prior regimens including bortezomib and an immunomodulatory** agent

2015 Approval by EMA and FDA

Panobinostat + Bortezomib

Dual Inhibition of Protein Degradation Pathways



Hideshima T, et al. *Mol Cancer Ther*. 2011;10:2034-2042

Clinical trials

Panobinostat + BZT + dexamethasone (PANORAMA2)[1]

- Phase II (N = 55)
- ≥2 previous therapies, including an immunomodulatory drug, BTZ-refractory
- ORR: 34.5% (near complete response [nCR]: 1.8%)
- PFS: 5.4 months

Panobinostat + BZT + dex

Vs

Placebo+BZT+ dex (PANORAMA1)[2]

- Phase III (N = 768)
- 1-3 previous therapies (BORT refractory excluded)
- PFS: 12 vs 8.1 months (HR 0.63, *P* <.0001)
- ORR: 61% vs 55% (nCR/CR: 28% vs 16%)
- Duration of response: 13.1 vs 10.9 months

1. Richardson PG, et al. *Blood*. 2013;122:2331-2337
2. Richardson PG, et al. *J Clin Oncol*. 2014;32(5s):abstract 8510.

Summary of Other Notable HDAC Combinations

Regimen	Phase (N)	Outcomes	
		ORR	CBR
Ricolinostat ± bortezomib + dexamethasone[1]	1 (20)	25% (heavily pretreated)	60% (2 pts VGPR, 3 pts PR, 2 pts MR, 5 pts SD)
Ricolinostat + lenalidomide + dexamethasone[2]	1 (22)	64%	100% (1 pt CR, 5 pts VGPR, 8 pts PR, 3 pts MR, 5 pts SD)
Panobinostat + carfilzomib + dexamtheasone[3]	1 (36)	77%	88% (1 pt CR, 10 pts VGPR, 16 pts PR, 4 pts MR, 4 pts SD)

1. Raje N et al. *Blood*. 2013;122. Abstract 759.
2. Raje N et al. EHA 2014. Abstract P358.
3. Berdeja JG et al. *J Clin Oncol*. 2015;33. Abstract 8513.

Double Refractory

- Refractory to bortezomib
- Refractory to lenalidomide

Median EFS: 5 months

Median OS: 9 months

Kumar et al. Leukemia 2012

Carfilzomib Monotherapy in Heavily Pre-Treated MM, 003 Trial

	N	ORR %	Median DOR (month)	Median OS (month)	Median PFS (month)
Response-Evaluable Patients	257	23.7%	7.8*	15.6	3.7
Bz + len-refractory	169	15.4%	7.8	11.9	NR
Bz + len refractory/intolerant	214	20.1 %	7.4	13.2	NR

ORR ≥ partial response
* Calculated from 61 patients with partial response or better
Bz, bortezomib; len, lenalidomide; imid, lenalidomide or thalidomide; mo, month; NR, not reported.

Unfavorable cytogenetics did not significantly impact response rates or DOR

Siegel DS, et al. Blood. 2012 ;120(14):2817-25.

Pomalidomide in double refractory myeloma

Study	tretment	N° DR pz	ORR%	median PFS months	median OS months
Pomalide MTD Phase 1 (1)	MTD 4 mg/die	22	27%	-	-
IFM 2009-02 Phase 2 (2)	Pom 4mg/die+Dex 40 mg weakly 21/28 d vs 28/28	64	31%/31%	3.8	13.8
MM-02 Phase 1/2 (3)	POM 4 mg/ d1-21 with LoDEX or alone	136	31%/21%	3.8 /2.0	13.4/12.5
MM-03 Phase 3 (4)	POM 4 mg/d1-21 +Low dex vs HD DEX	238	29%/12%	3.7/2.0	-

(1) Richardson et al. Blood 2013
(2) Leleu et al. Blood 2015
(3) Richardson et al. Blood 2014
(4) San Miguel et al. Lancet Oncol 2013

Panobinostat + bortezomib (BTZ) + dexamethasone (PANORAMA2)	
• Phase II (N = 55) • ≥2 previous therapies, including an immunomodulatory drug, BTZ-refractory	
ORR	34.5% (near complete response [nCR]): 1.8%)
median PFS	5.4 months
median OS	17.5 months

Richardson PG, et al. *Blood*. 2013;122:2331-2337
Richardson PG et al. Blood 2013; 122:Abstract 1970

Daratumumab in Double Refractory MM: Sirius Trial

Refractory to, n (%)	n = 106
Last prior therapy	103 (97)
PI and IMiD	101 (95)
BORT	95 (90)
CARF	51 (48)
LEN	93 (88)
POM	67 (63)
Alkylating agent	82 (77)
BORT+LEN	87 (82)
BORT+LEN+CARF	42 (40)
BORT+LEN+POM	57 (54)
BORT+LEN+CARF+POM	33 (31)
BORT+LEN+CARF+POM+THAL	12 (11)

- Patients were heavily pretreated and most patients were refractory to multiple lines of PI and IMiD treatment
  - 97% refractory to their last line of therapy
  - 95% double refractory
  - 66% refractory to 3 of 4 therapies (bortezomib, lenalidomide, carfilzomib, and pomalidomide)
  - 63% refractory to pomalidomide
  - 48% refractory to carfilzomib

Lonial et al: ASCO 2015

87 pz double refractory ORR 26%

Carfilzomib Pomalidomide Low dose Dex in RRMM

Phase 1 dose-escalation study

- Median of 5 prior lines of therapy;
- 49% of pz had high/intermediate risk cytogenetics at baseline
- 100% lenalidomide refractory
- 91% bortezomib refractory

32 pz

ORR	50%
CBR	66%
≥ VGPR	16%
PFS (median)	7.2 months
OS (median)	20.6 months

Median follow-up 26.3 months

Well tolerated with no unexpected toxicities

Shah et al Blood 2015

Table 1 Selected phase 2 and 3 studies with reported activity of novel drugs/combinations in dual refractory myeloma

Study	Phase	Regimen	*N* (DR *N*)	ORR[a] (DR ORR)
Siegel et al. [7•]	2	Carfilzomib 20/27 mg/m^2 D1–2, 8–9, 15–16 (28-day cycle)[b]	257 (169)	24 % (15 %)
Leleu et al. [15]	2	Arm A: pomalidomide 4 mg D1–21, dexamethasone 40 mg/week Arm B: pomalidomide 4 mg D1–28, dexamethasone 40 mg/week (28-day cycle)	84 (64)	Arm A: 35 % Arm B: 34 % (31 % both arms)
Richardson et al. [16]	2	Pomalidomide 4 mg on D1–21, dexamethasone 40 mg/week (28-day cycle)	113 (69)	33 % (31 %)
Lacy et al. [18]	2	Cohort 1: pomalidomide 2 mg D1–28, dexamethasone 40 mg/week Cohort 2: pomalidomide 4 mg D1–28, dexamethasone 40 mg/week (28-day cycle)	70 (70)	Cohort 1: 26 % (26 %) Cohort 2: 28 % (28 %)
Sehgal et al. [19]	2	Cohort 1: pomalidomide 2 mg D1–28 Dexamethasone 40 mg/week[c] Cohort 2: pomalidomide 4 mg D1–21 Dexamethasone 40 mg/week[c] (28-day cycle)	39 (31)	Cohort 1: 21 % (N/A) Cohort 2: 45 % (N/A)
San Miguel et al. [17•]	3	Pomalidomide 4 mg D1–21 Dexamethasone 40 mg/week (28-day cycle)	302 (225)	31 % (28 %)
Larocca et al. [21]	2	Pomalidomide 2.5 mg D1–28, cyclophosphamide 50 mg QOD Prednisone 50 mg QOD (28-day cycle)	55 (16)	51 % (50 %)
Richardson et al. [30•]	2	Panobinostat 20 mg TIW, bortezomib 1.3 mg/m^2 D1, 4, 8, 11, dexamethasone 20 mg D1–2, 4–5, 8–9, 11–12 (21-day cycle)	55 (N/A)	31 % (N/A)
Lokhorst et al. [36•]	2	Daratumumab 16 mg/kg weekly ×8 weeks[d], then twice monthly	42 (27)	36 % (33 %)
Lonial et al. [38]	2	Daratumumab 16 mg/kg weekly ×8 weeks, then twice monthly	106 (87)	29 % (26 %)
Shah et al. [42]	2	ARRY-520 1.5 mg/m^2 D1-2, dexamethasone 40 mg/week, G-CSF D3-7 (14-day cycle)	18 (18)	22 % (22 %)

Abbreviations: *ORR* overall response rate, *DR* dual refractory, *D* day, *QOD* every other day, *TIW* three times weekly, *N/A*, not available

[a] ORR defined as ≥PR

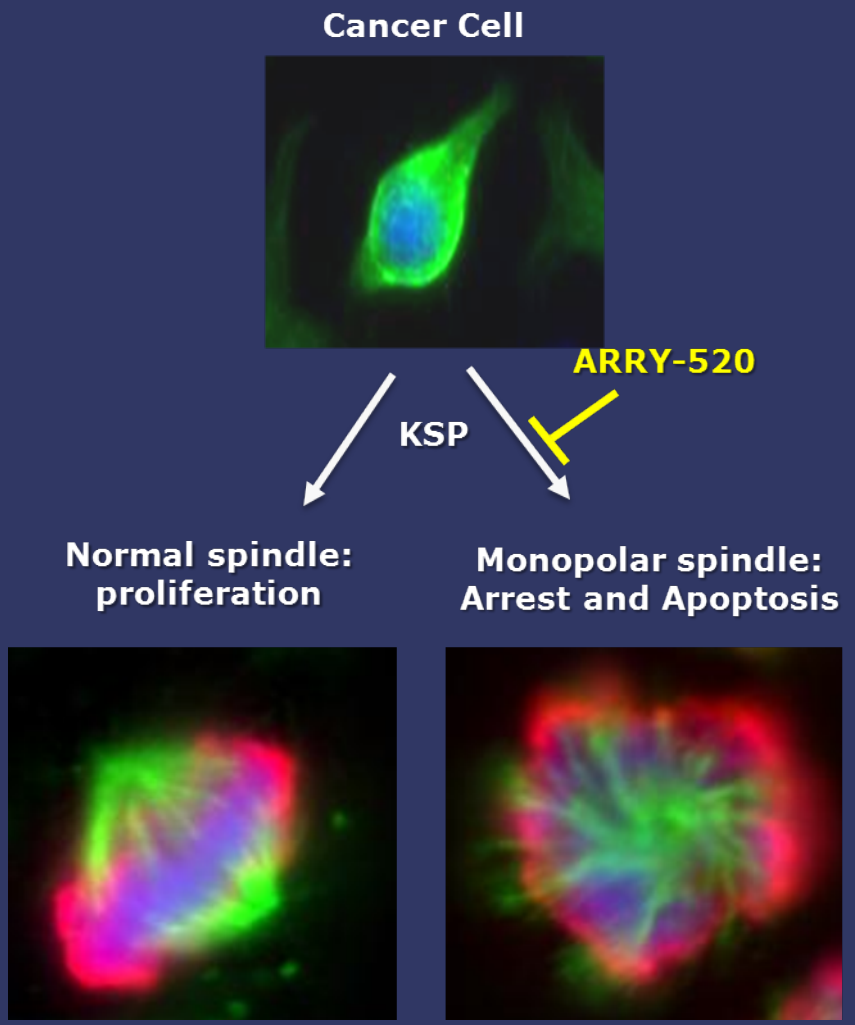
[b] Dose-escalated to 27 mg/m^2 with cycle 2, provided that 20 mg/m^2 dose with cycle 1 was well tolerated

[c] Weekly dexamethasone was added cycle 2

[d] First and second daratumumab doses were separated by 3 weeks for collection of pharmacokinetic data per protocol

Background: Targeting KSP with ARRY-520 (Filanesib)

- **Filanesib**is a targeted Kinesin Spindle Protein (KSP) inhibitor
  - KSP is a microtubule motor protein critical to the function of proliferating cells
- KSP inhibition induces aberrant mitotic arrest and rapid cell death
  - Novel mechanism of action for MM
  - Preferentially acts on MCL-1 dependent cells including MM
  - Not expected to be cross-resistant with other drugs



Lonial et al ASH 2013

High risk cytogenetic in RRMM

	High risk			
	Del(17p)		t(4;14)	
	Kd (n = 40)	Vd (n = 52)	Kd (n = 50)	Vd (n = 61)
PFS, median months (95% CI)	7.6 (5.6-11.2)	4.9 (3.9-7.5)	10.1 (6.9-NE)	6.8 (5.6-9.4)
Hazard Ratio (95% CI)	0.73 (0.42-1.27)		0.63 (0.38-1.02)	
ORR,[a] % (95%CI)	62.5 (45.8-77.3)	50.0 (35.8-64.2)	78.0 (64.0-88.5)	65.6 (52.3-77.3)
Odds ratio (95%CI)	1.67 (0.72-3.86)		1.86 (0.79-4.37)	

[a]Determined by Independent Review Committee according to International Myeloma Working Group Uniform Response Criteria. Patients evaluated for overall response rate had a best overall response of partial response or better
CI, confidence interval; Kd, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; Vd, bortezomib and dexamethasone

Chng W-W, et al. *Blood*. 2015;126: Abstract 30.

carfilzomib,pomalidomide, and dexamethasone (CPD) in an open-label, multicenter, phase 1

Table 5. Response rate in all intent-to-treat patients and by cytogenetic abnormalities

Response category, n (%)	All evaluable patients, N = 32	Hyperdiploid, n = 10	Del(13), n = 9	Del(17p), n = 5
ORR	16 (50)	5 (50)	1(11)	4 (80)
VGPR	5 (16)	1 (10)	1(11)	1 (20)
PR	11 (34)	4 (40)	0	3 (60)
MR	5 (16)	3 (30)	3 (33)	0
SD	8 (25)	2 (20)	5 (56)	1 (20)
PD	3 (9)	0	0	0

PD, progressive disease; SD, stable disease.

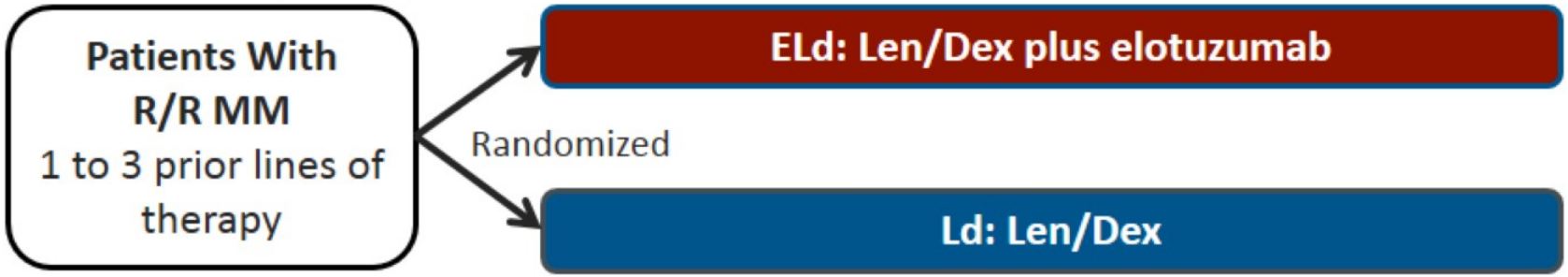
Shah et al. Blood 2015

	del(17p)		t(4;14)		Standard risk	
	POM + LoDEX (n = 44)	HiDEX (n = 23)	POM + LoDEX (n = 44)	HiDEX (n = 15)	POM + LoDEX (n = 148)	HiDEX (n = 72)
Median PFS, months	4.6	1.1	2.8	1.9	4.2	2.3
HR (*P*-value)	0.34 (<0.001)		0.49 (0.028)		0.54 (<0.001)	
Median OS, months	12.6	7.7	7.5	4.9	14.0	9.0
HR (*P*-value)	0.45 (0.008)		1.12 (0.761)		0.85 (0.380)	

Dimopoulos et al. Haematologica 2015

ELOQUENT-2: Subgroup Analyses
Elotuzumab Plus Len/Dex vs Len/Dex

ELOQUENT-2 Study Design



	Del(17p)+		t(4;14)+	
	ELd	**Ld**	**ELd**	**Ld**
n	206	431	61	575
Median PFS, mo	21.2	14.9	15.8	5.6*
Median OS, mo	NE	36.4	40.9	25.2

*Median PFS presented was 5.6 mo.

Lonial S, et al. *J Clin Oncol*. 2016;34(suppl). Abstract 8037.

Factors in Selecting Treatment in Relapsed/Refractory Myeloma

Disease-related factors

- High-risk cytogenetic (del (17p), t(4:14))

Regimen-related factors

- Prior drug exposures(relapsed vs refractory)
- Toxicity of regimen (combination vs single agent)
- Mode of administration (eg, oral or intravenous)

Patient-related factors

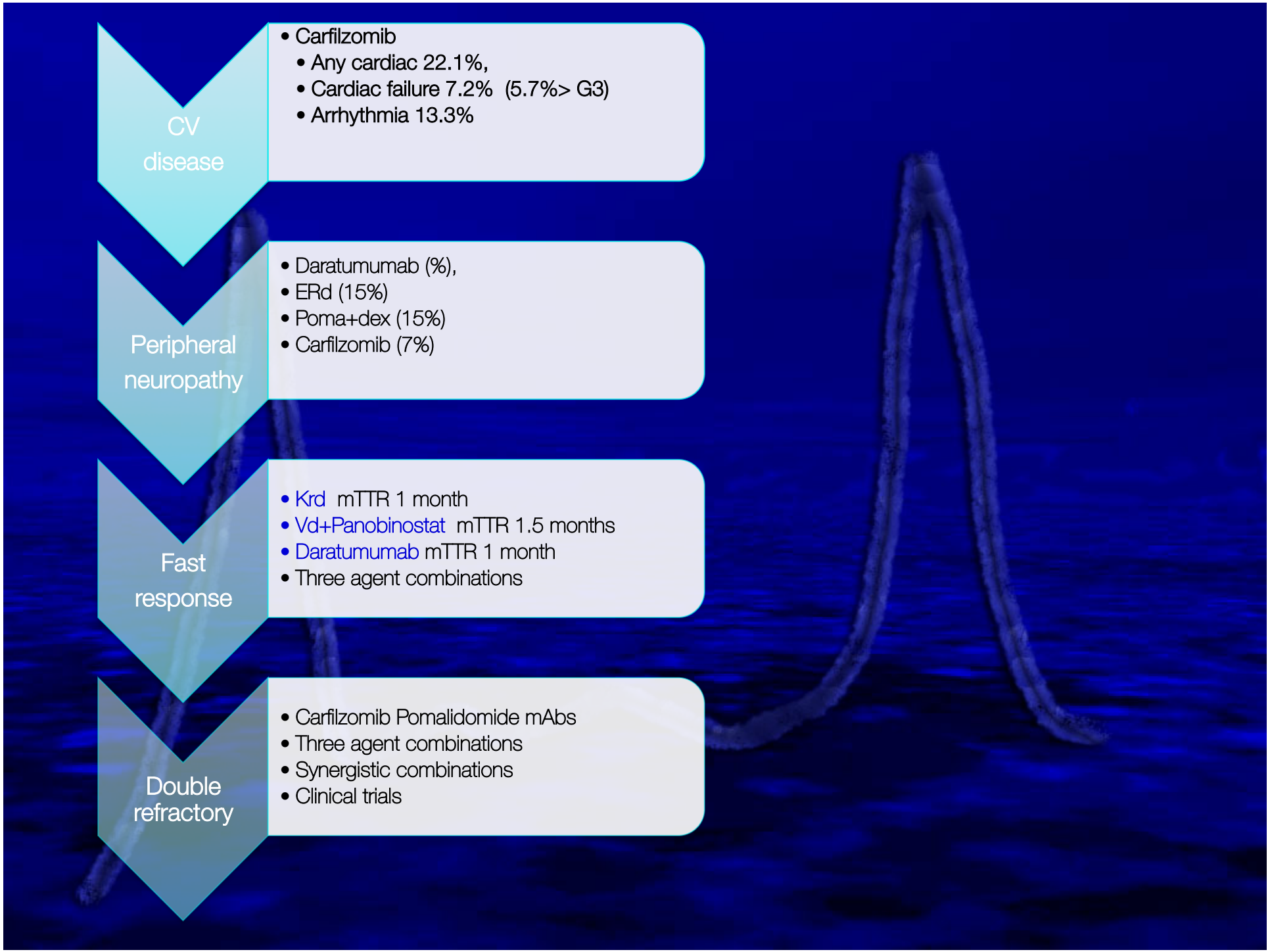
- Pre-existing toxicity from therapy (peripheral neuropathy, myelosuppression)
- Renal function, Age, PS, comorbidities

Balance efficacy, tolerability and quality of life

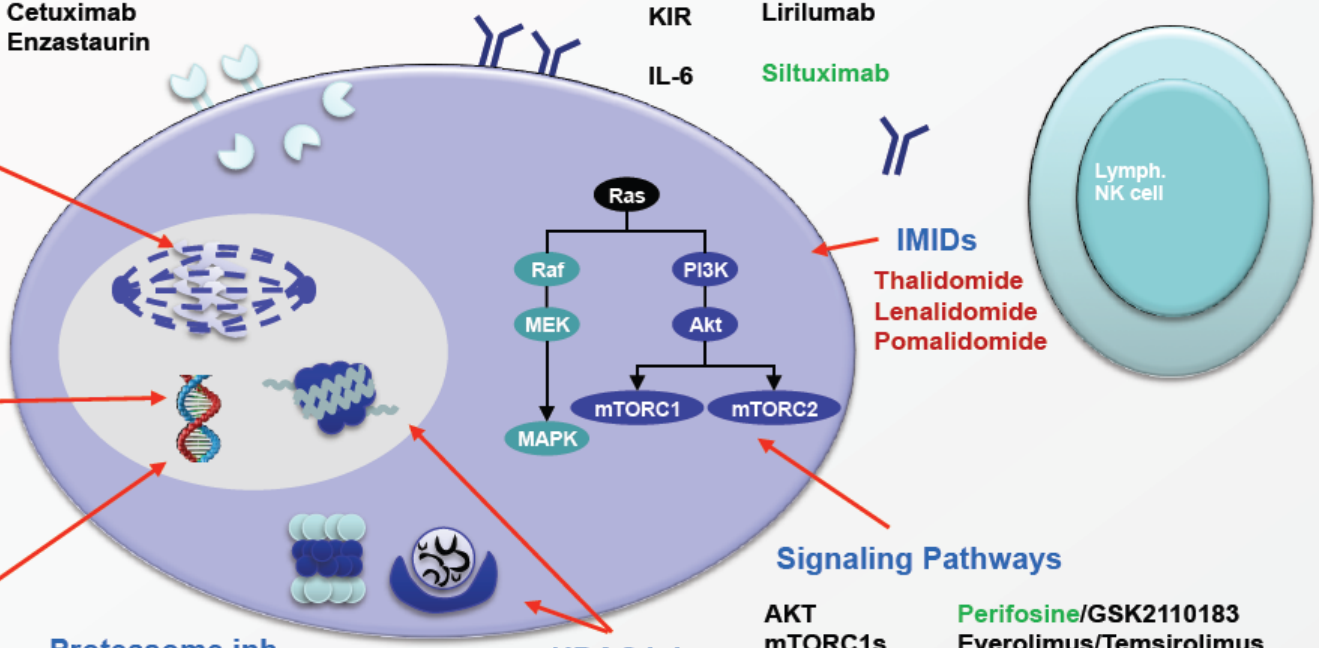
AEs

	CFZ+LEN+DEX[4] [4]	DARA[4] [9]	ELO+LEN+DEX[4] [5]	IX+LEN+DEX [46,67]	PAN+BOR+DEX [47]	POM+LoDEX[4] [8]
Discontinuation due to AEs	15%	5%	13%	13%	36%	9%
All serious AEs	60%	30%$^{\alpha}$	65%	40%$^{\beta}$	60%	61%
Treatment-related Death	2%	0	2%‡	NR	3%	4%
Grade ≥3 AEs						
Fatigue	8%	3%	8%	NR	24%	5%
Diarrhea	4%	1%*	5%	6%	25%	1%
Peripheral neuropathy	3%	NR	4%	2%	18%	1%
Anemia	18%	24%	19%	9%	18%	33%
Thrombocytopenia	17%	19%	19%	13%	67%	22%
Neutropenia	30%	12%	34%	19%	34%	48%
Leukopenia	25%	40%*	32%	NR	23%	9%

*Data were pooled from 3 trials reported in FDA Prescribing Information; α treatment-emergent serious AE; β 68% experienced AE ≥ Grade 3; ǂ Death from an adverse event; AE=adverse event; NR=not reported


CV disease
• Carfilzomib
• Any cardiac 22.1%,
• Cardiac failure 7.2% (5.7%> G3)
• Arrhythmia 13.3%
Peripheral neuropathy
• Daratumumab (%),
• ERd (15%)
• Poma+dex (15%)
• Carfilzomib (7%)
Fast response
• Krd mTTR 1 month
• Vd+Panobinostat mTTR 1.5 months
• Daratumumab mTTR 1 month
• Three agent combinations
Double refractory
• Carfilzomib Pomalidomide mAbs
• Three agent combinations
• Synergistic combinations
• Clinical trials

Main Targets in MM Plasma Cells and Drugs Tested Against Them



Kinase inh

CDK 1, 2, 5, 9	Dinaciclib
FGFR3	Dovitinib/AB1010/MFGR 1877S
cKit/PDGFR	Imatinib/Dasatinib
VEGF-R	Bevacizumab
IGF-1R	AVE1642 / CP-751, 851
EGF-R	Cetuximab
PKC	Enzastaurin

Monoclonal antibodies

SLAMF7	Elotuzumab
CD38	Daratumumab/SAR650984
CD138	nBT062-DM4
CD56	Lorvotuzumab
CD40	Dacetuzumab/Lucatumumab
KIR	Lirilumab
IL-6	Siltuximab

Cell cycle inh

KSP inh	Arry-520
Aurora K	Inh MLN8237
CDK 4/6 inh	Seliciclib

IMIDs

Thalidomide
Lenalidomide
Pomalidomide

Alkylators

Melphalan
Cyclophosphamide
Bendamustine
Melflufen

Other DNA damaging

DNA damaging	Zalypsis
PARP inhibitor	Veliparib
Hypoxia act alkylator	TH-302

Proteasome inh

Bortezomib
Carfilzomib
Ixazomib
Oprozomib
Marizomib

Hsp-90 inh

Tanespimycin
AUY922

HDAC inh

Panobinostat
Vorinostat
Romidepsin
Givinostat
Rocilinostat

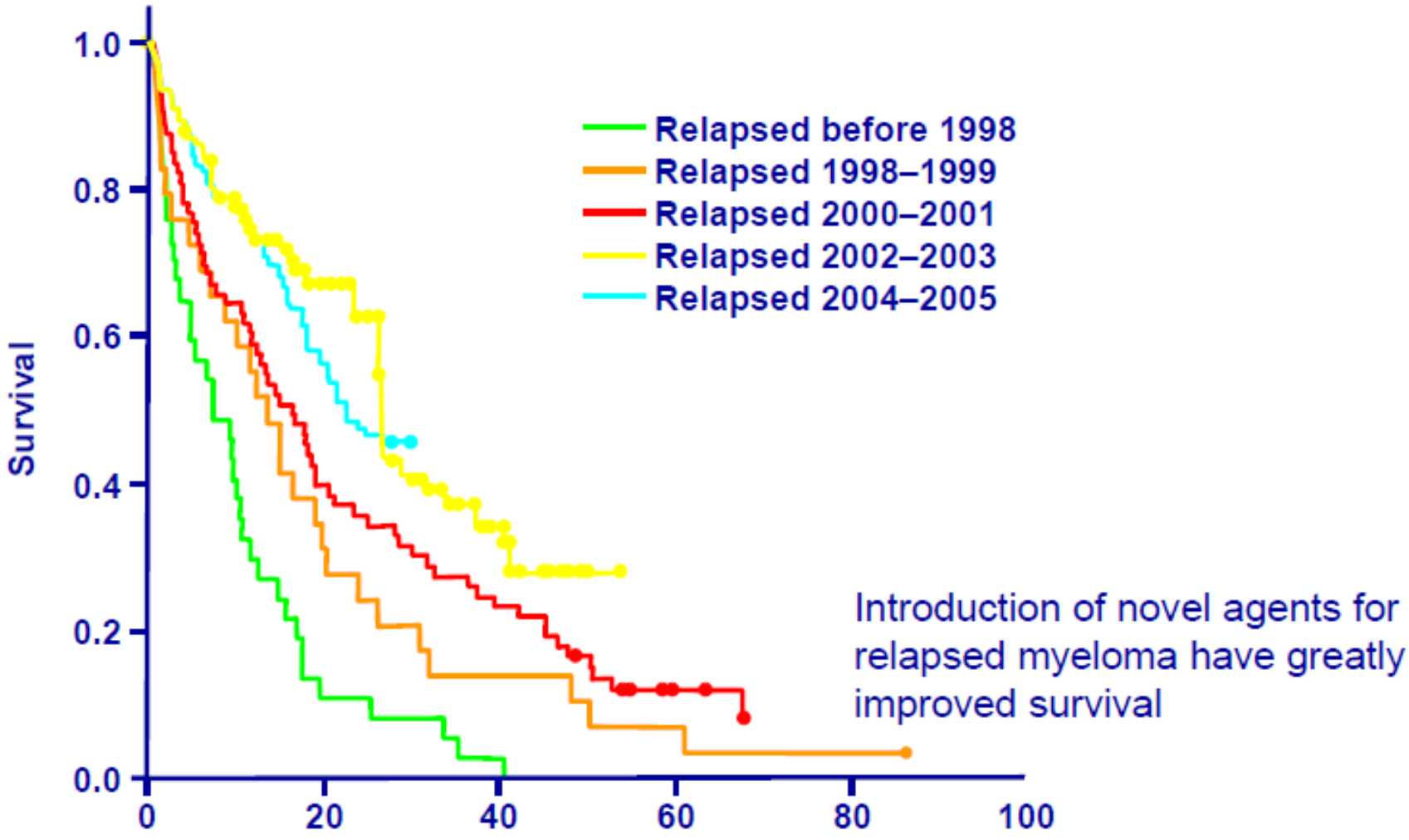
Signaling Pathways

AKT	Perifosine/GSK2110183
mTORC1s	Everolimus/Temsirolimus
mTOR C1/C2	MLN0128/INK128
Farn transf	Tipifarnib
p38/MAPK inh	Aplidin
p38/JNK act	SCIO-469
MEK	Selumetinib

Red: approved; Green: in phase III

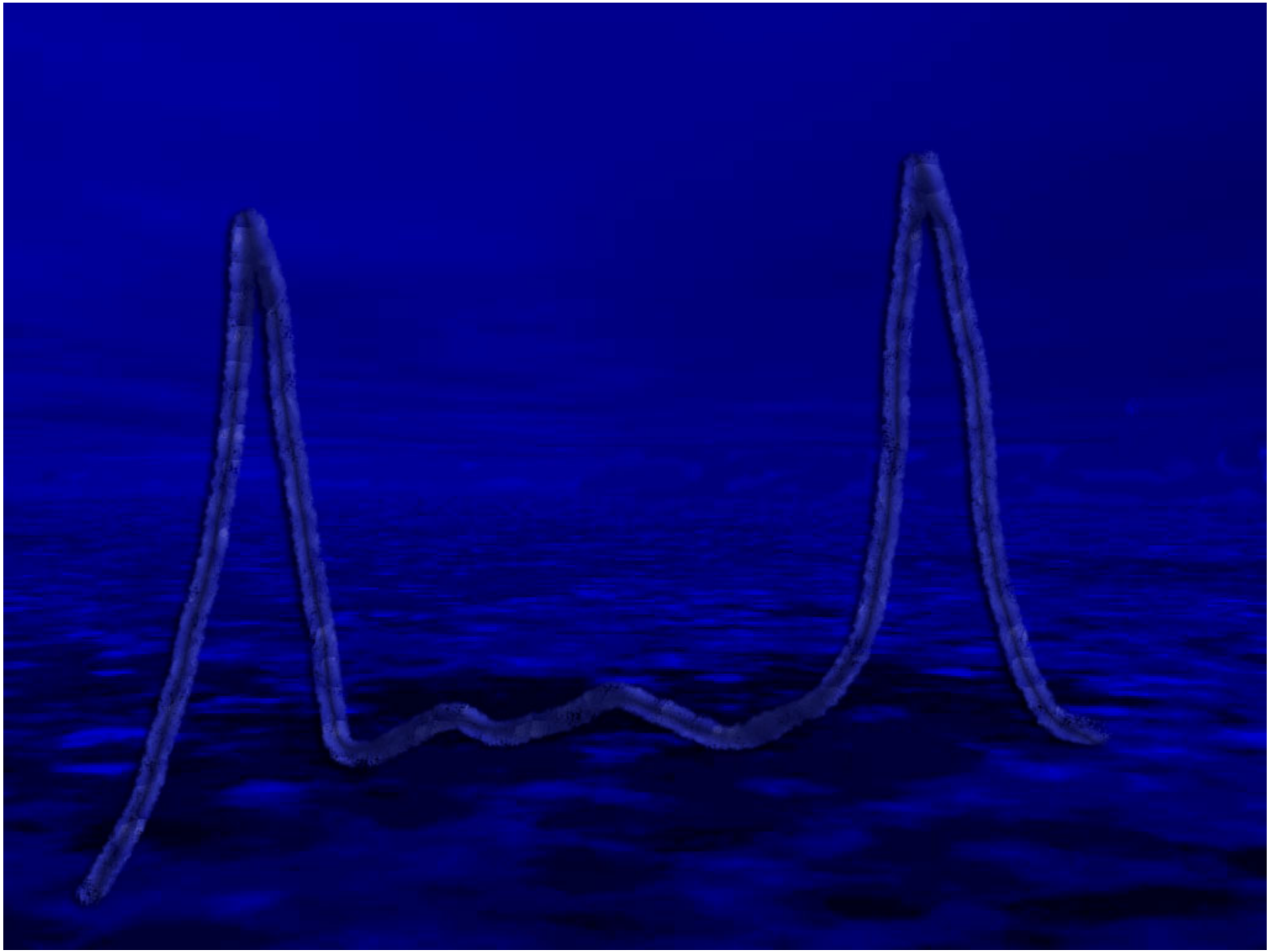
Adapted from Ocio EM et al. *Leukemia*. 2014;28:525 -542.

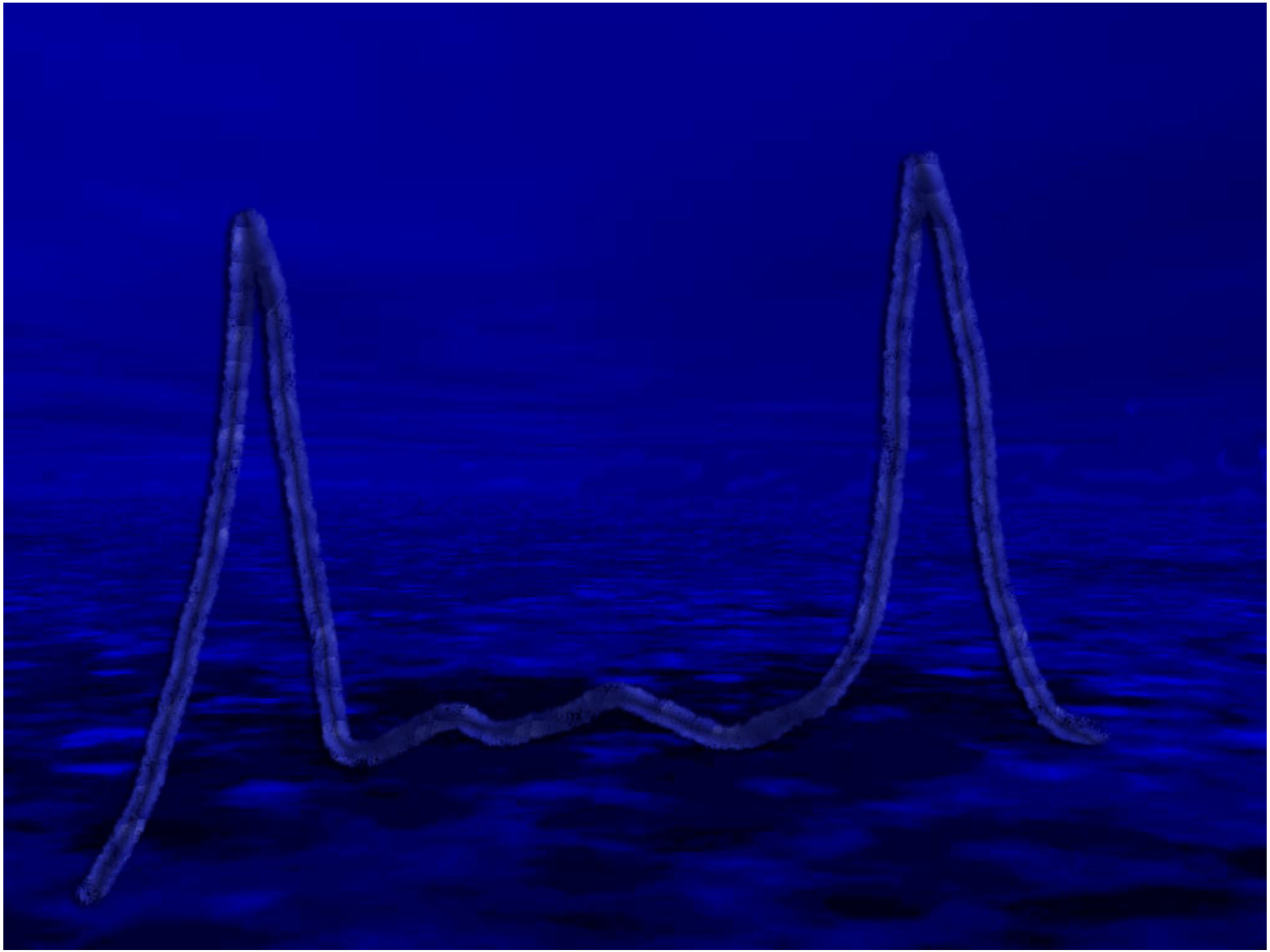
Impact of Novel Agents on the Outcome in Relapsed/Refractory Disease (n=387)



Introduction of novel agents for relapsed myeloma have greatly improved survival

Kumar et al, Blood, 2008, 111, 2516-2520

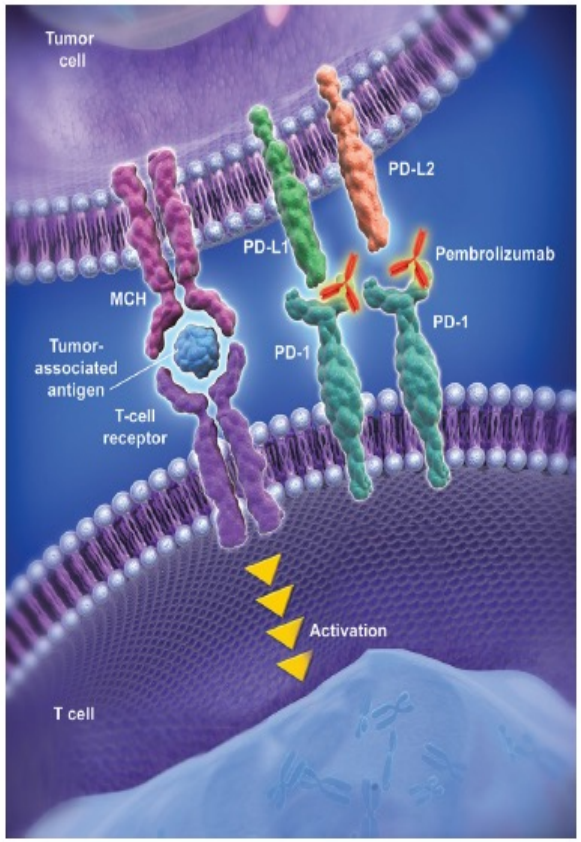




Pembrolizumab: Targeting PD-1
"Releasing The Brakes"

- **Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype against PD-1**
  - **Directly blocks interaction between PD-1 and PD-L1/PD-L2**

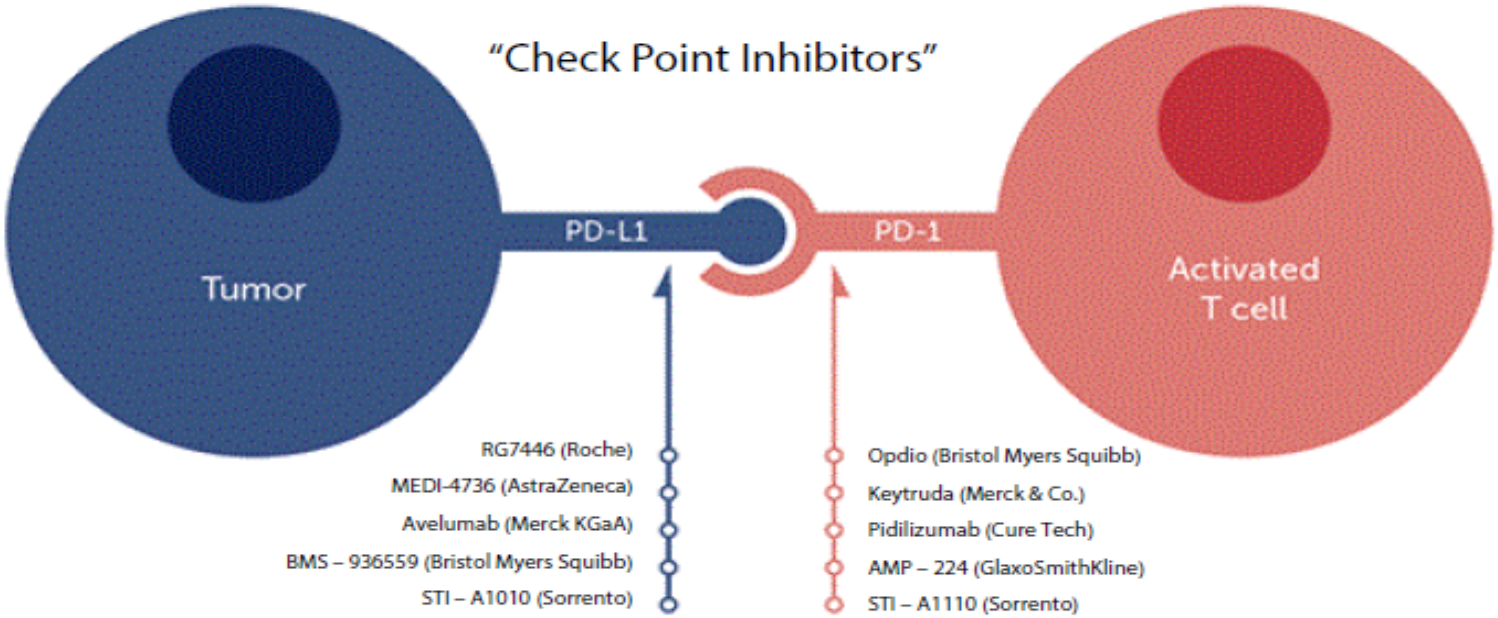
- **Approved for advanced melanoma and NSCLC**
  - **Demonstrated robust antitumor activity and manageable safety in multiple cancers[1-3]**



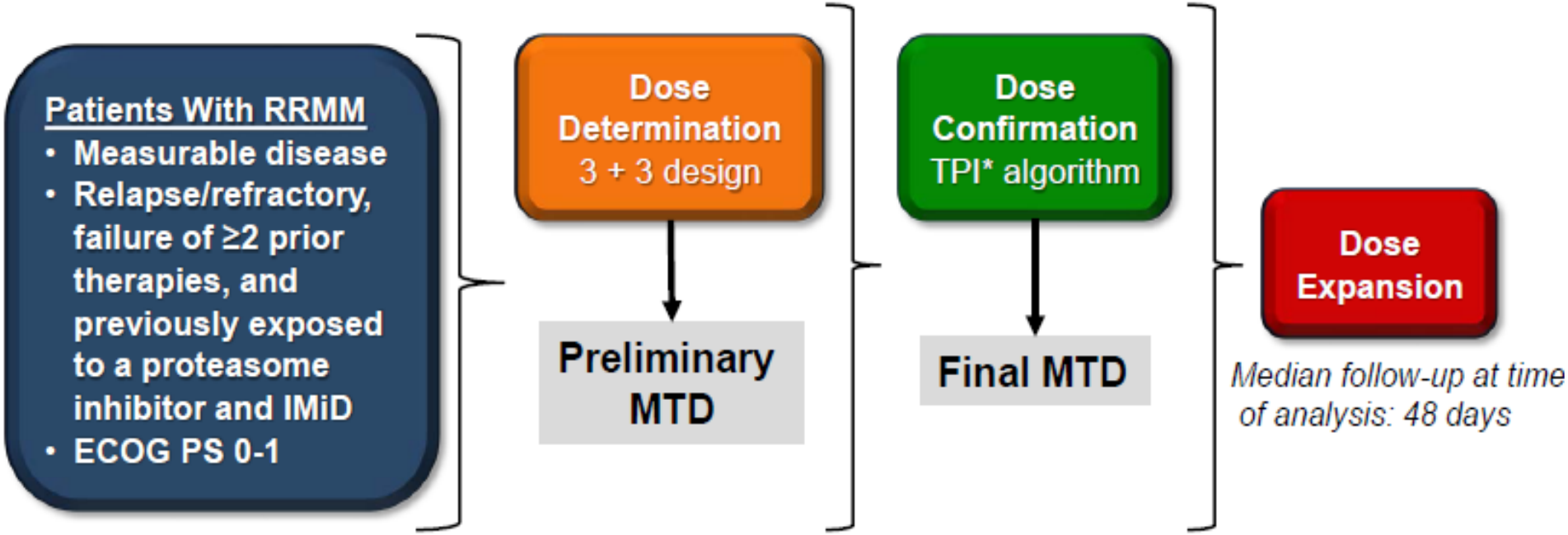
1. Keir ME ,et al. *Annu Rev Immunol.* 2008;26:677-704. 2. Hallett WH, et al. *Biol Blood Marrow Transplant.* 2011;17:1133-1145. 3. Homet Moreno B, et al. *Br J Cancer.* 2015;112:1421-1427.

San Miguel J, et al. *Blood.* 2015;126: Abstract 505.

PD-1 and PD-L1 Inhibitors



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



Median Follow-Up: 296 days

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

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

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

San Miguel J, et al. *Blood*. 2015;126: Abstract 505.

KEYNOTE-023: Antitumor Activity

Dose Determination and Dose Confirmation

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

San Miguel J, et al. *Blood*. 2015;126: Abstract 505.