Proteasome Inhibitors (PIs) in MM: New agents

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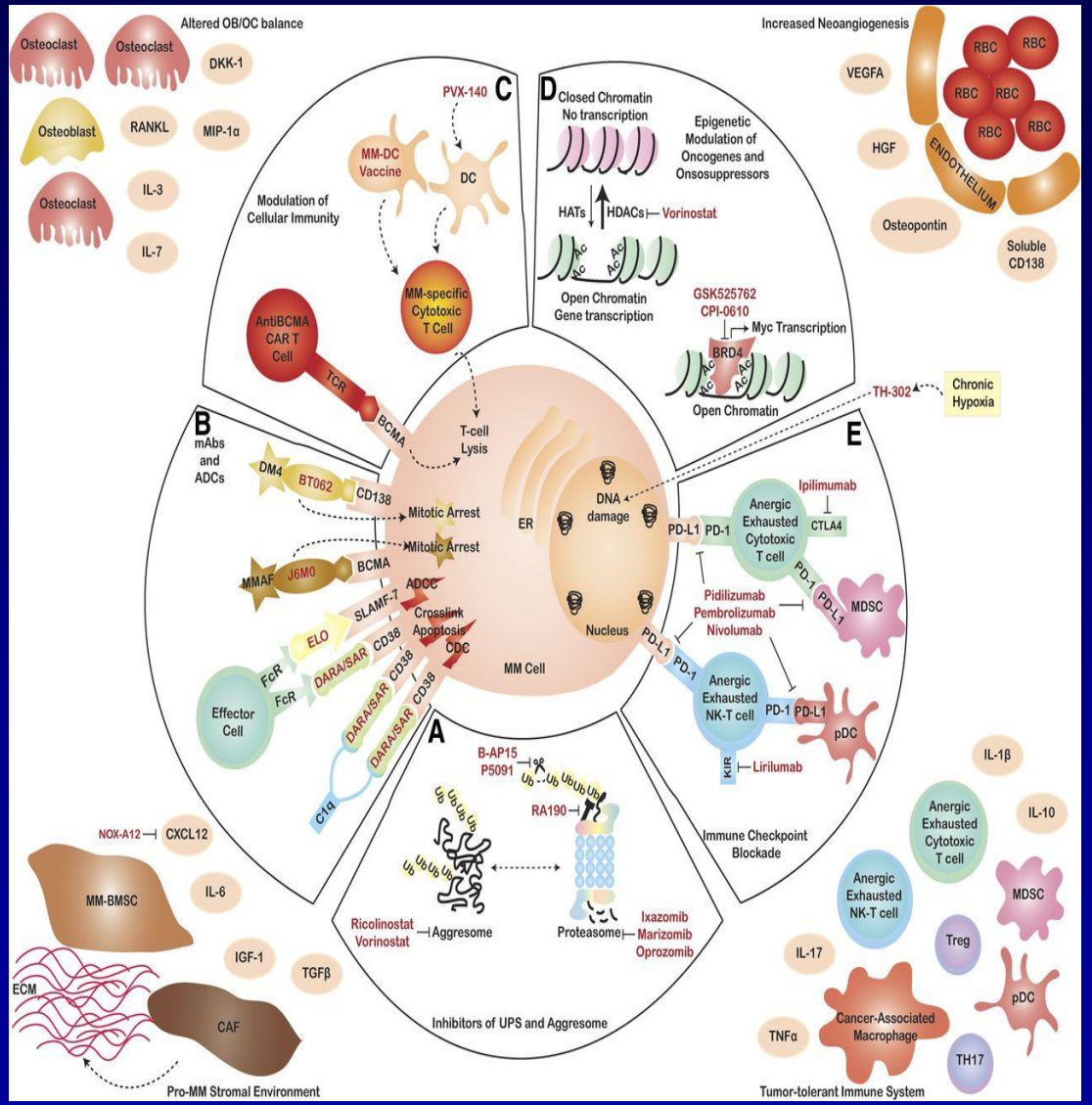
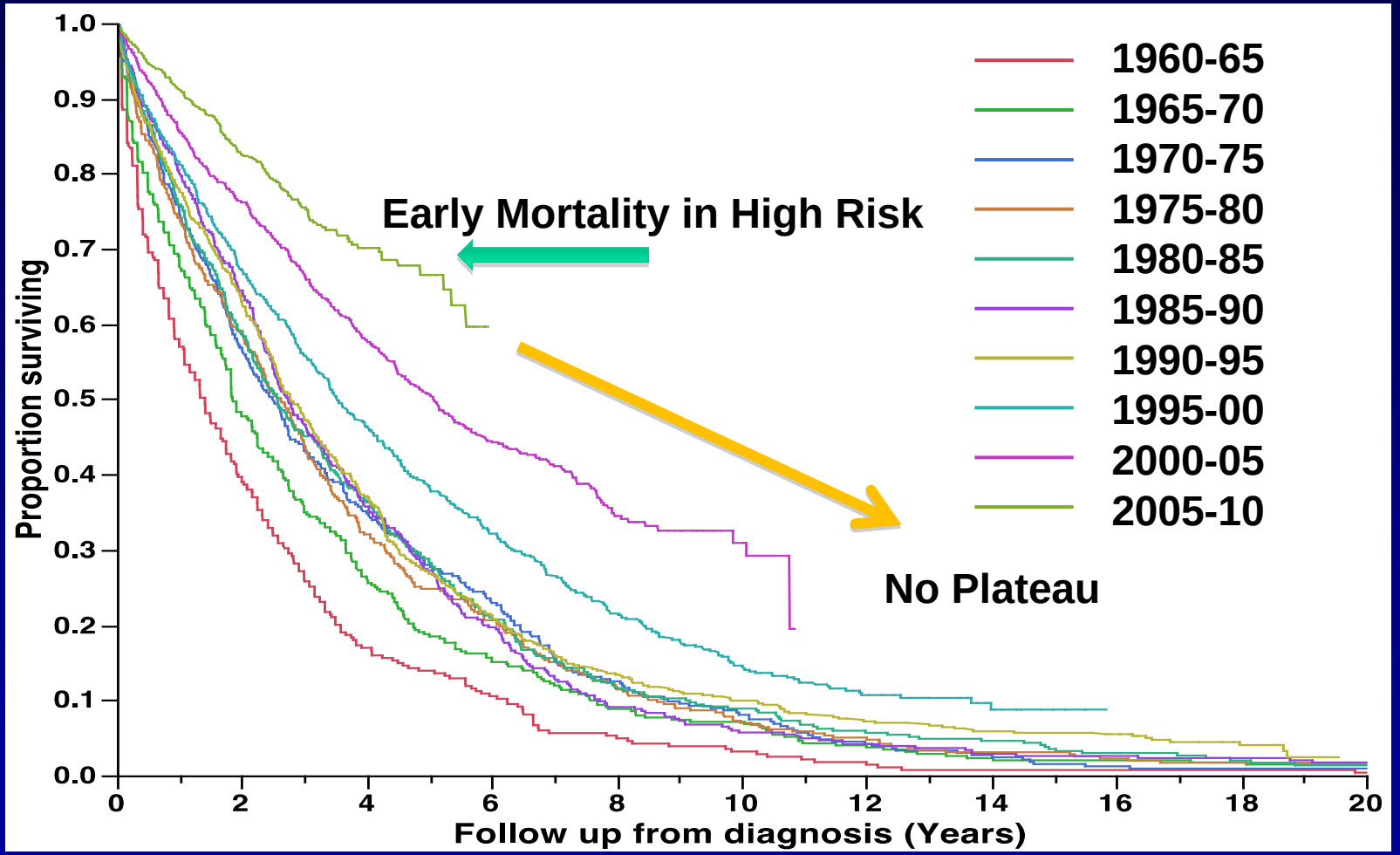
Multimodality targeting of MM in the context of the BM microenvironment



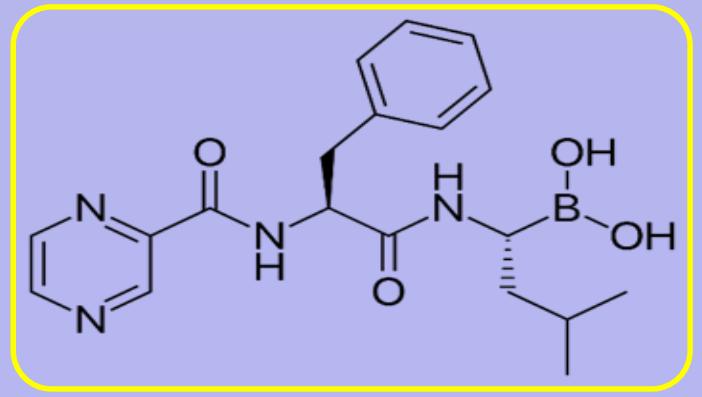
G. Bianchi, PG. Richardson and KC. Anderson, *Blood* 2015; 126:300-310.

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



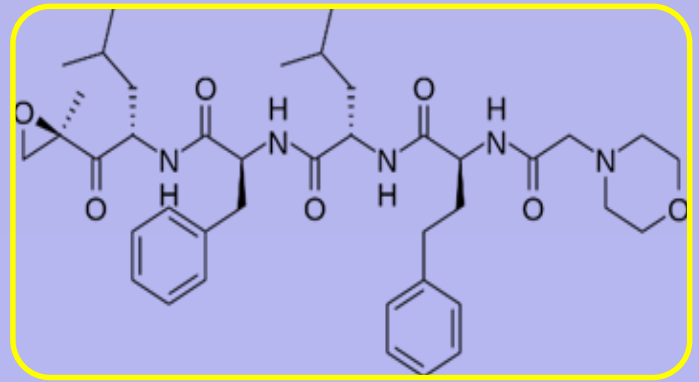
Adapted from Kumar et al *Leukemia* 2014

Three FDA/EMA-approved PIs



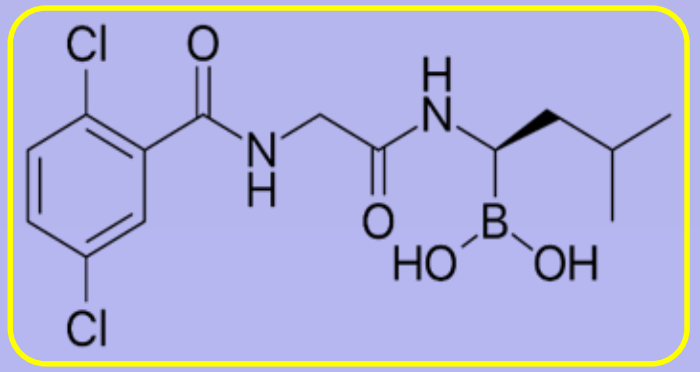
Bortezomib

- Boronate peptide
- Reversible binding
- IV or SC
- Approved for treatment of MM



Carfilzomib

- Epoxyketone
- Irreversible binding
- IV
- Approved with Rd or Dex for treatment of MM after 1–3 prior lines

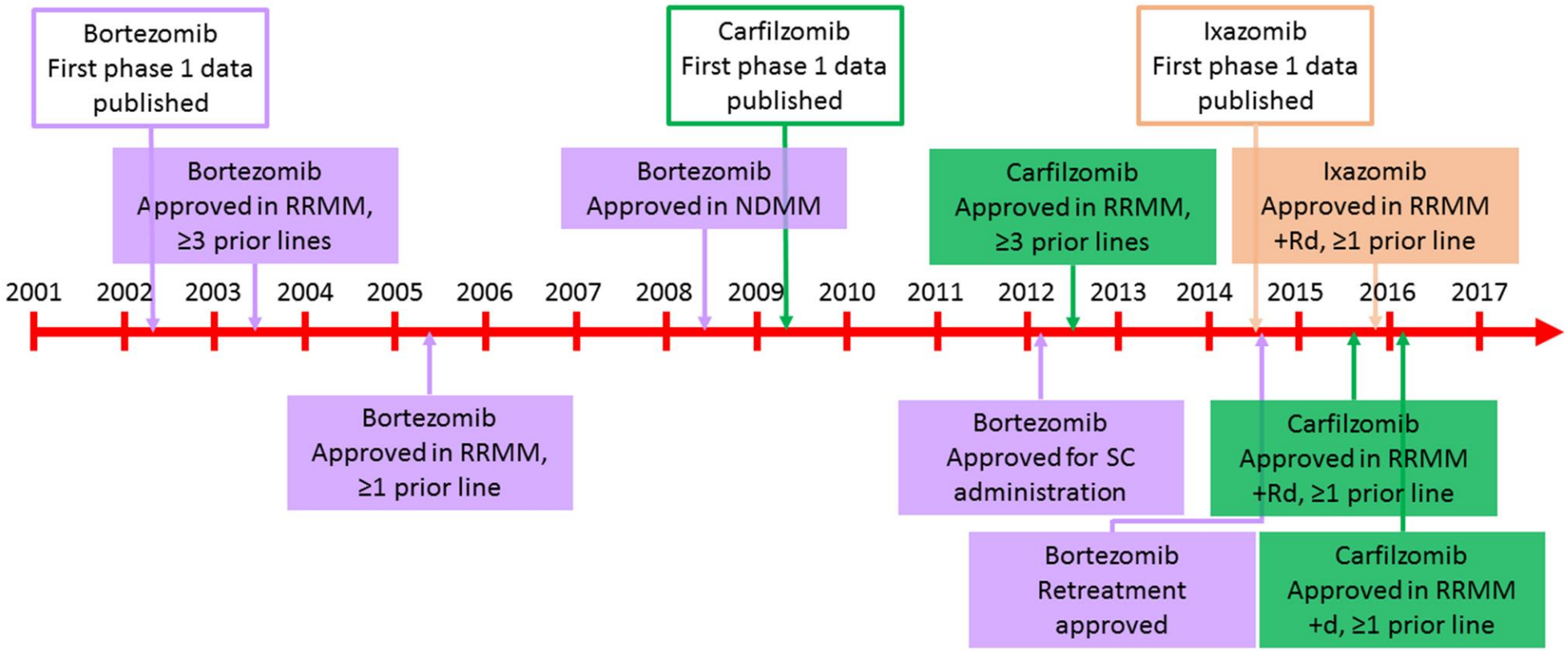


Ixazomib

- Boronate peptide
- Rapidly reversible binding
- Oral
- Approved with Rd for treatment of MM after ≥1 prior line

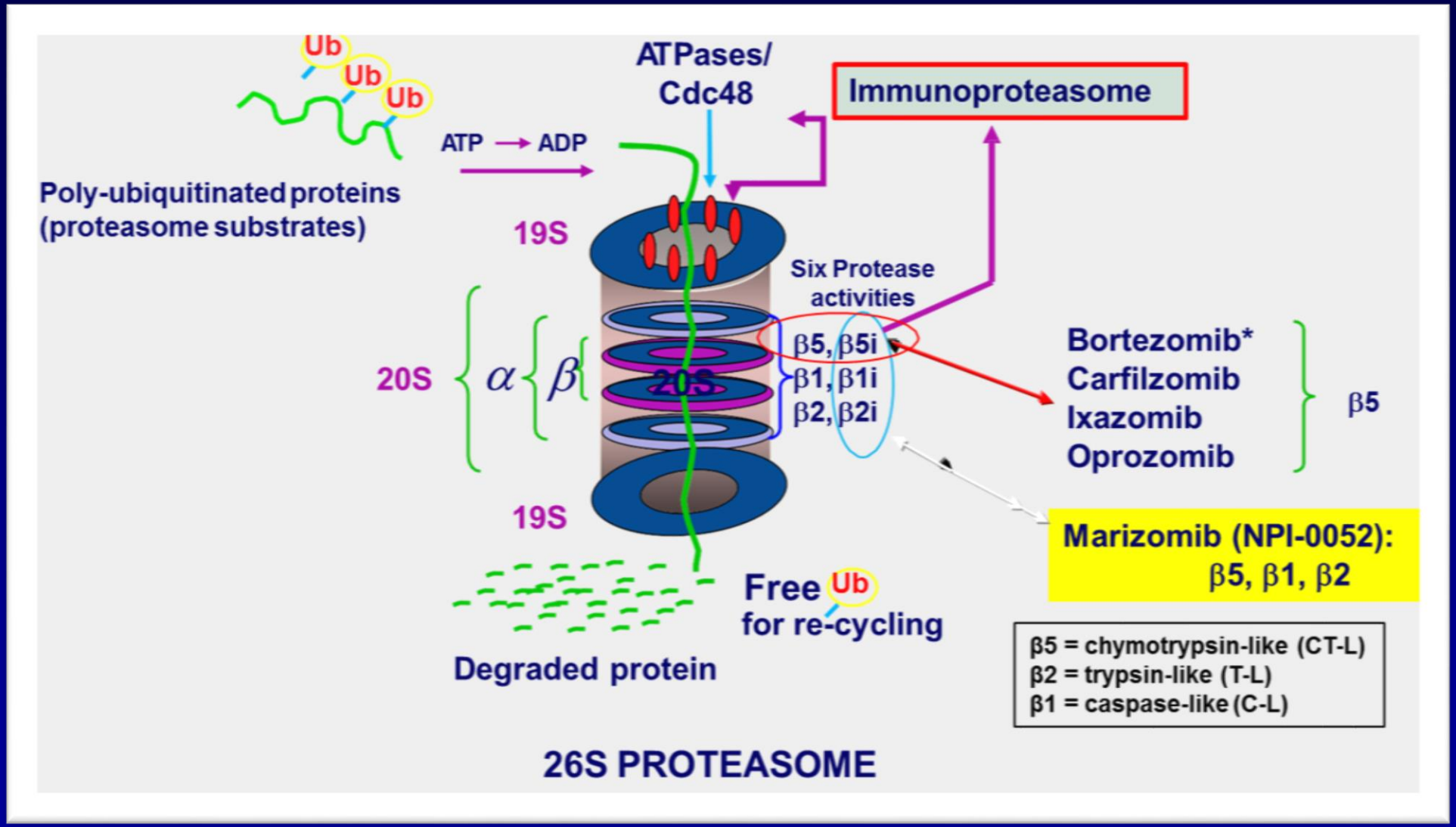
1. www.velcade.com; 2. www.kyprolis.com; 3. www.ninlaro.com
4. Gandolfi S, et al. Cancer Metastasis Rev 2017;36(4):561–84.

Timeline of PI approvals in MM



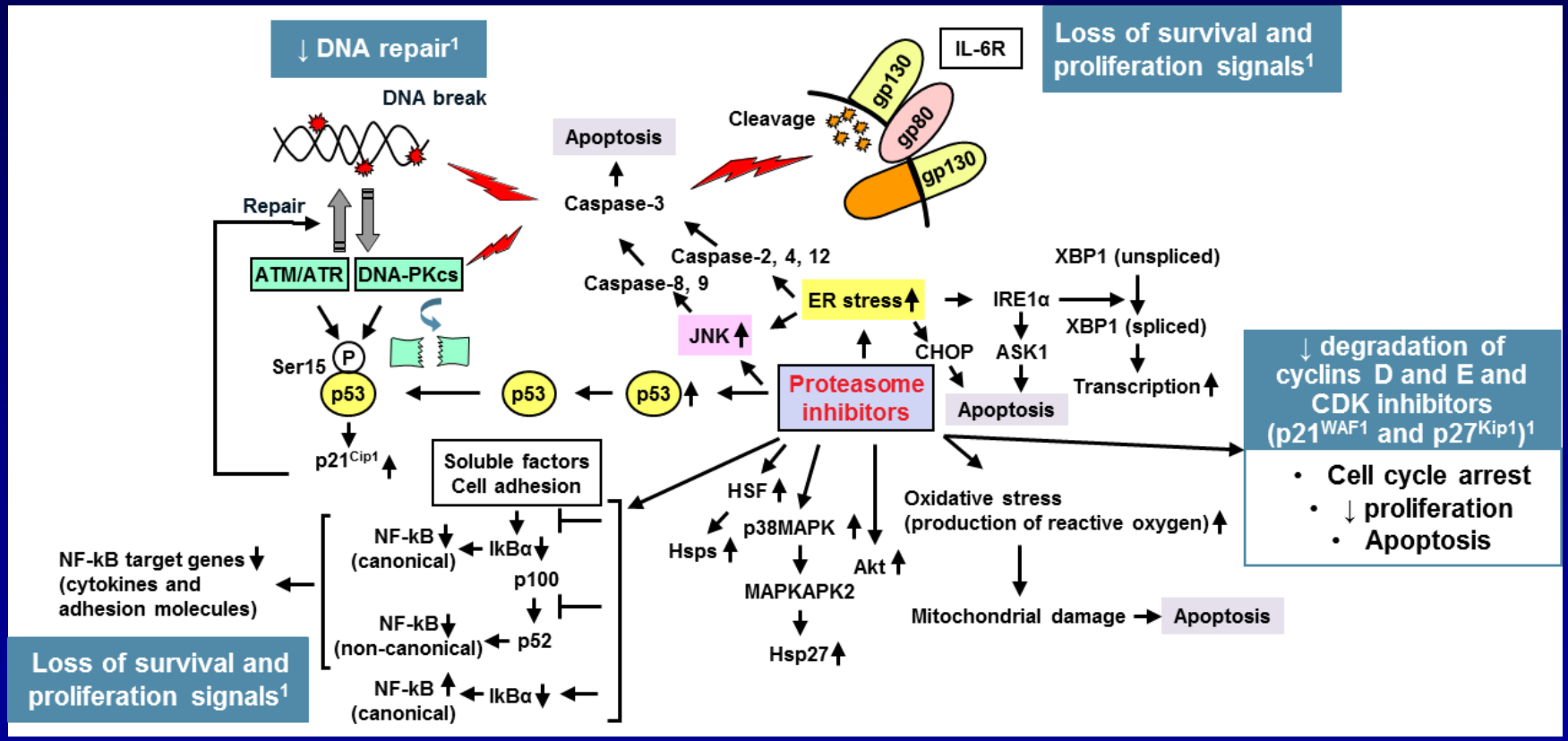
1. Gandolfi S, et al. Cancer Metastasis Rev 2017;36(4):561–84.

The MOA of Proteasome Inhibition



1. Lawasut P, et al. Curr Hematol Malig Rep 2012;7(4):258–66.

Biologic consequences of proteasome inhibition; downstream effects similar across all PIs



MM plasma cell

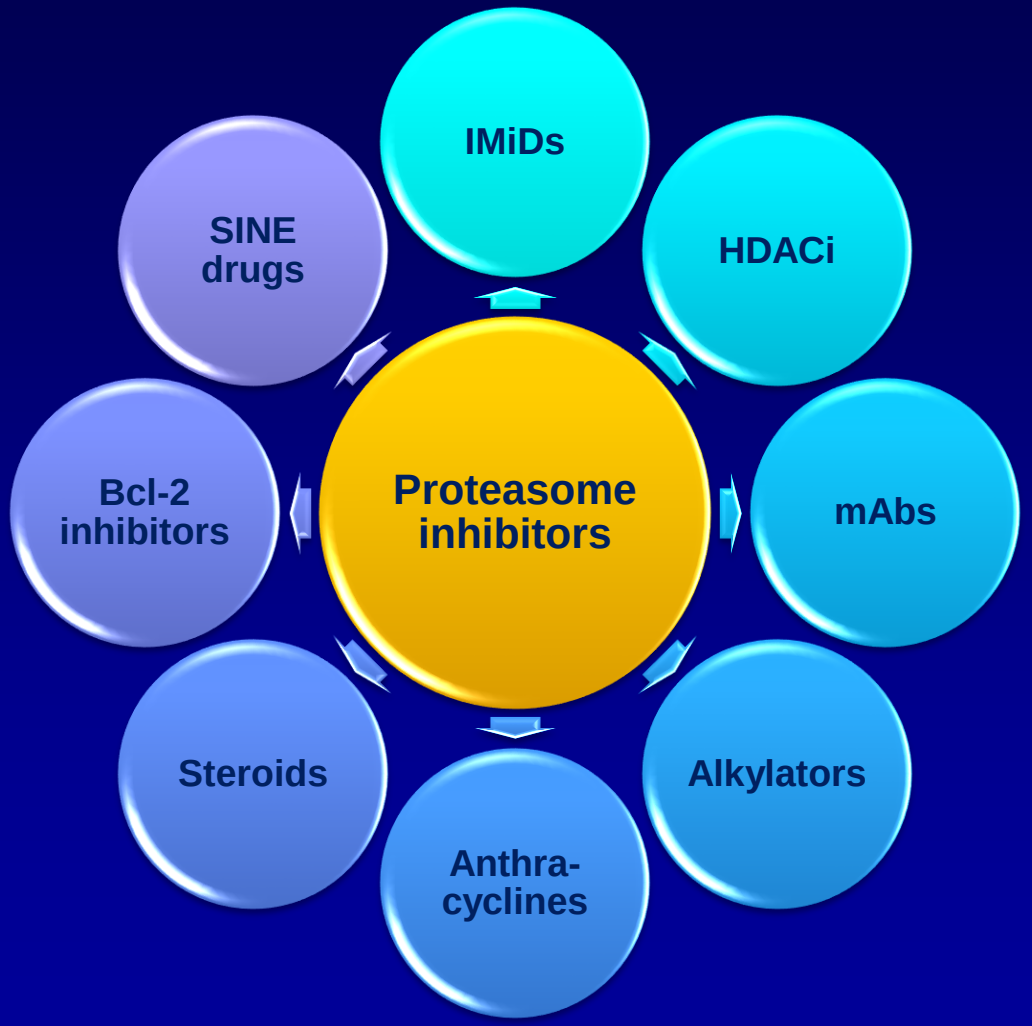
- Decreased growth and survival
- Apoptosis
- Cell cycle arrest
- ER stress induction
- Autophagy
- Decreased DNA repair
- Decreased cell adhesion

Microenvironment

- Decreased cytokine secretion
- Anti-osteoclastic activity
- Anti-angiogenic activity

1. Hideshima T & Anderson KC. Semin Hematol 2012;49(3):223–27.
2. Gandolfi S, et al. Cancer Metastasis Rev 2017;36:561–84.
3. Hideshima T, et al. Nat Rev Cancer 2007;7:585–98.

PIs: a therapeutic backbone



- Multiple biologic consequences of proteasome inhibition
- Synergistic/additive activity with other chemotherapeutic and targeted agents
- PIs are key combination partners across the treatment algorithm

1. Gandolfi S, et al. Cancer Metastasis Rev 2017;36:561–84.

Established PI-based treatment options: US NCCN recommended regimens

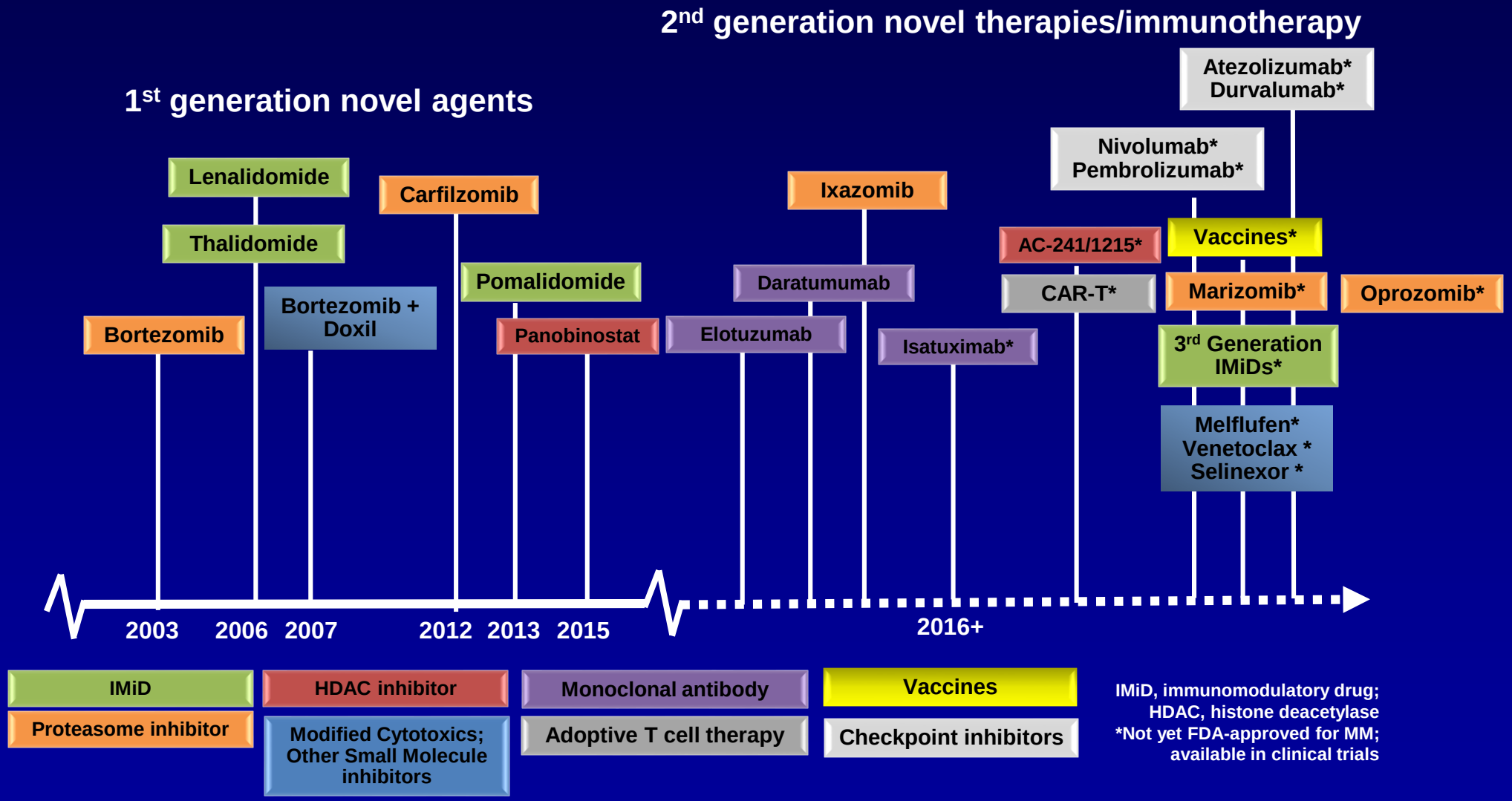
Primary therapy for transplant candidates	Primary therapy for non-transplant candidates	Therapy for previously treated MM: preferred	Therapy for previously treated MM: other

• Preferred
  • VRd
  • VCd
• Other recommended
  • PAD
  • KRd
  • IRd
• Useful in certain circumstances
  • Vd
  • VTd
	• Preferred
	  • VRd
	  • VCd
	  • Dara-VMP
	• Other recommended
	  • KRd
	  • KCd
	  • IRd
	• Useful in certain circumstances
	  • Vd
		• VRd
		• Kd
		• KRd
		• Dara-Vd
		• IRd
			• Benda-Vd
			• VDd
			• VCd
			• KCd
			• Vd
			• Elo-Vd
			• Id
			• Pano-Vd
			• Pano-K
			• Pom-Vd
			• Pom-Kd
			• Pom-Id

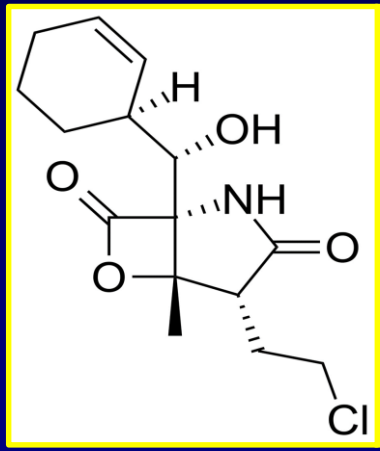
A, doxorubicin; Benda, bendamustine; C, cyclophosphamide; d/D, dexamethasone (except VDd – bortezomib, Doxil, dex); Elo, elotuzumab; Dara, daratumumab; I, ixazomib; K, carfilzomib; M, melphalan; P, prednisone; Pano, panobinostat; Pom, pomalidomide; R, lenalidomide; T, thalidomide; V, bortezomib

1. US NCCN Guidelines. Multiple Myeloma, Version 1.2019.

Continuing evolution of MM treatment: selected new classes and targets 2016-2018



Two novel investigational PIs

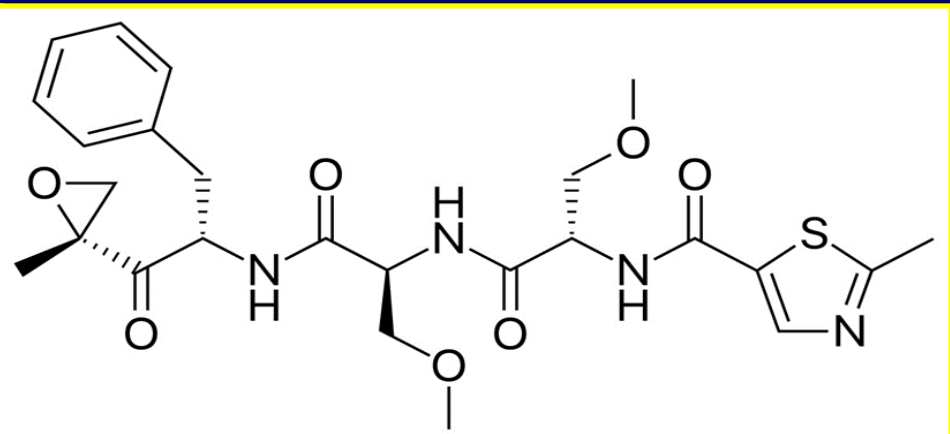


Marizomib[1-3]

- Marine-derived β-lactone compound (non-peptide bicyclic γ-lactam–β-lactone)
- Irreversible binding; differing proteasome inhibition profile from bortezomib
- IV, Oral
- Under investigation as treatment for RR MM, CNS-MM

Oprozomib[2-4]

- Peptide epoxyketone
- Irreversible binding
- Oral
- Under investigation as treatment for RR MM



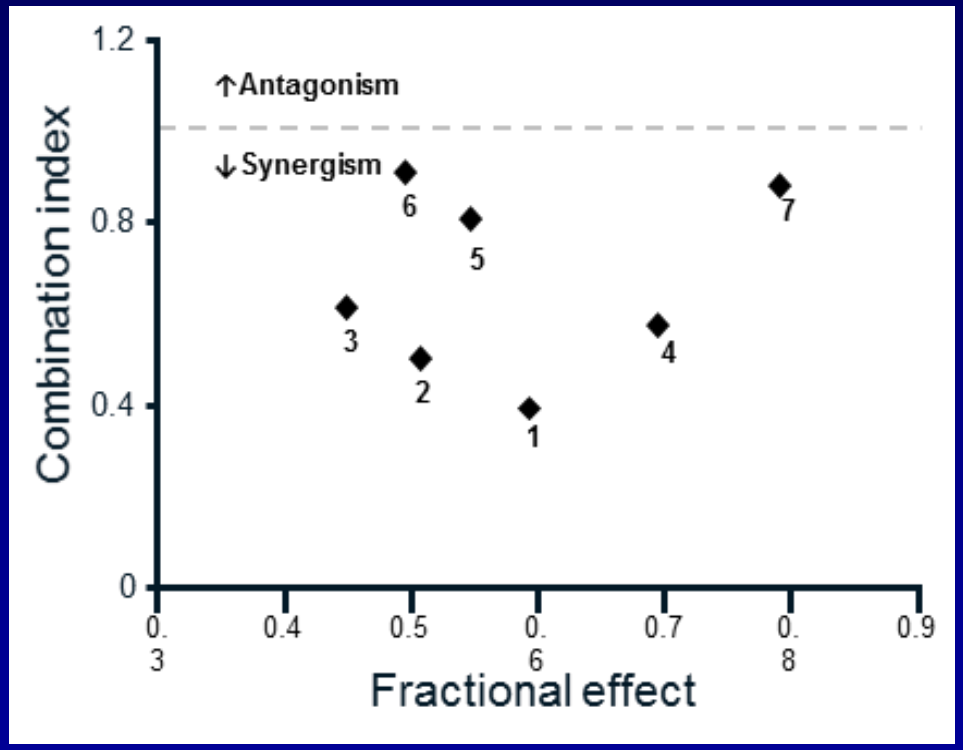
1. Chauhan D, et al. Cancer Cell 2005;8(5):407–19. 2. Dick L, Fleming P. Drug Discov Today 2010;15(5-6):243–9.
3. Gandolfi S, et al. Cancer Metastasis Rev 2017;36(4):561–84. 4. Chauhan D, et al. Blood 2010;116(23):4906–15.

Proteasome Inhibitors (PIs) in MM: New agents

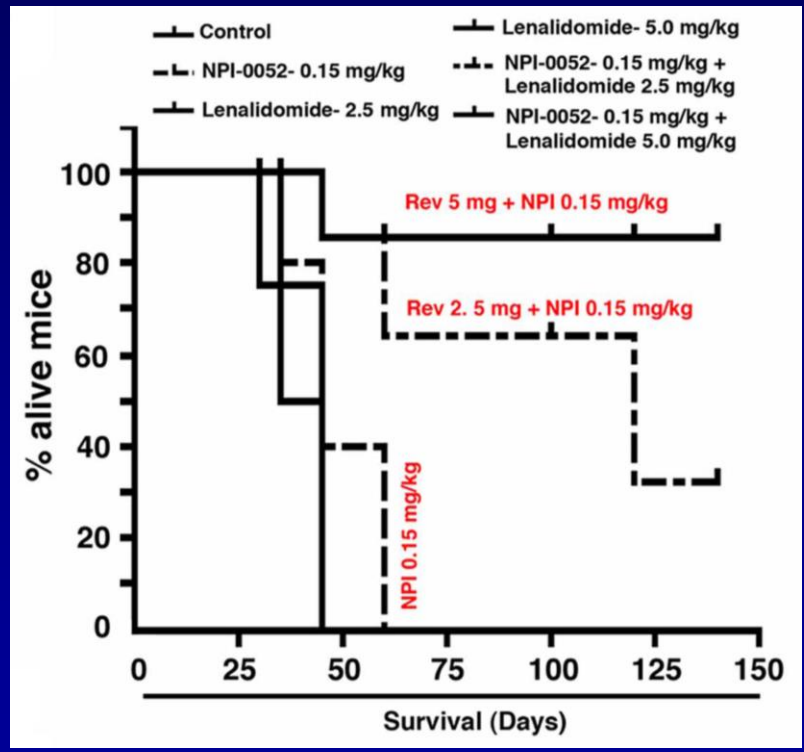
Marizomib

Marizomib: preclinical synergy with immunomodulators

Marizomib + pomalidomide: synergistic anti-MM activity in MM1S cells[1]



Marizomib + lenalidomide: significantly increased survival in mouse xenograft model[2]



1. Das DS, et al. Br J Haematol 2015;171:798–812.
2. Chauhan D, et al. Blood 2010;115(4):834–45.

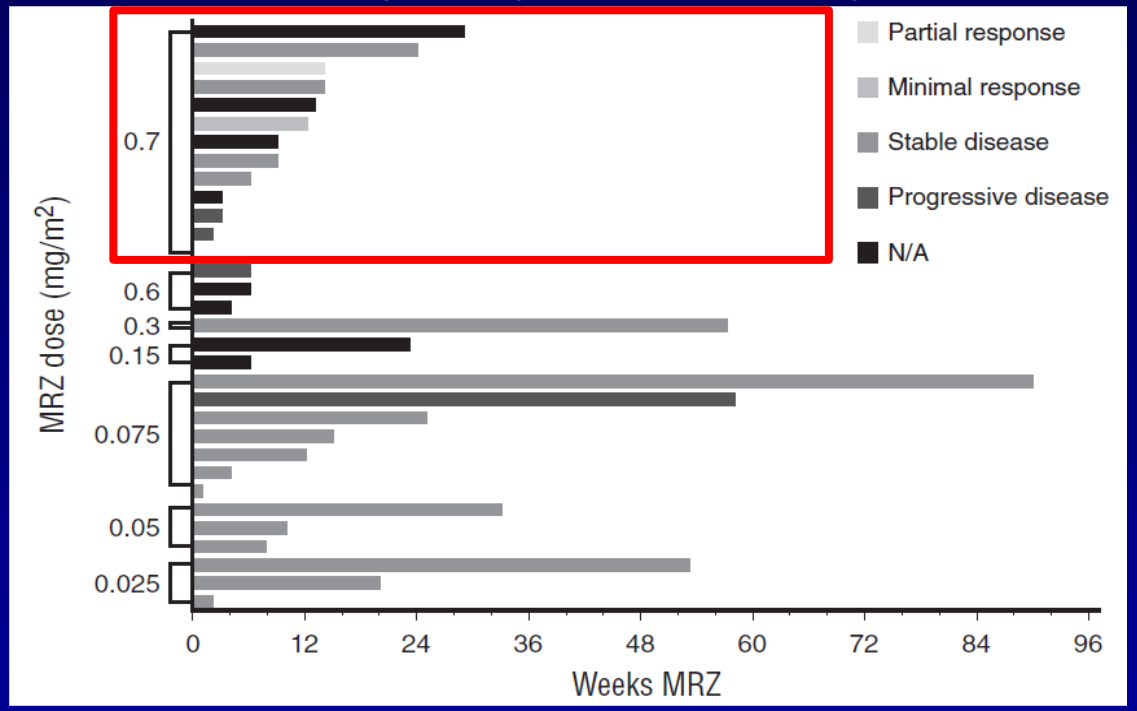
Marizomib in MM: Clinical trial data

Study	Regimen	Setting	Response rates	Outcomes
NPI-0052-101[1] Phase 1	Single-agent marizomib / marizomib-dex	RRMM (median 4–6 prior regimens; N=68)	CBR: 9% ORR: 7%	NR
NPI-0052-102[2] Phase 1	Single-agent marizomib	Advanced malignancies including RRMM (median 7 prior regimens; N=35) 19% btz-refractory	CBR: 30% ORR: 15% VGPR: 4%	NR
NPI-0052-107[3] Phase 1	Marizomib-pomalidomide-dexamethasone	RRMM (median 4 prior regimens; N=38) 61% btz-refractory; 29% cfz-refractory 84% len-refractory; 53% btz/len-refractory; 21% triple refractory	CBR: 64% ORR: 53% VGPR: 6%	PFS: 4.0 mos OS: 13.6 mos

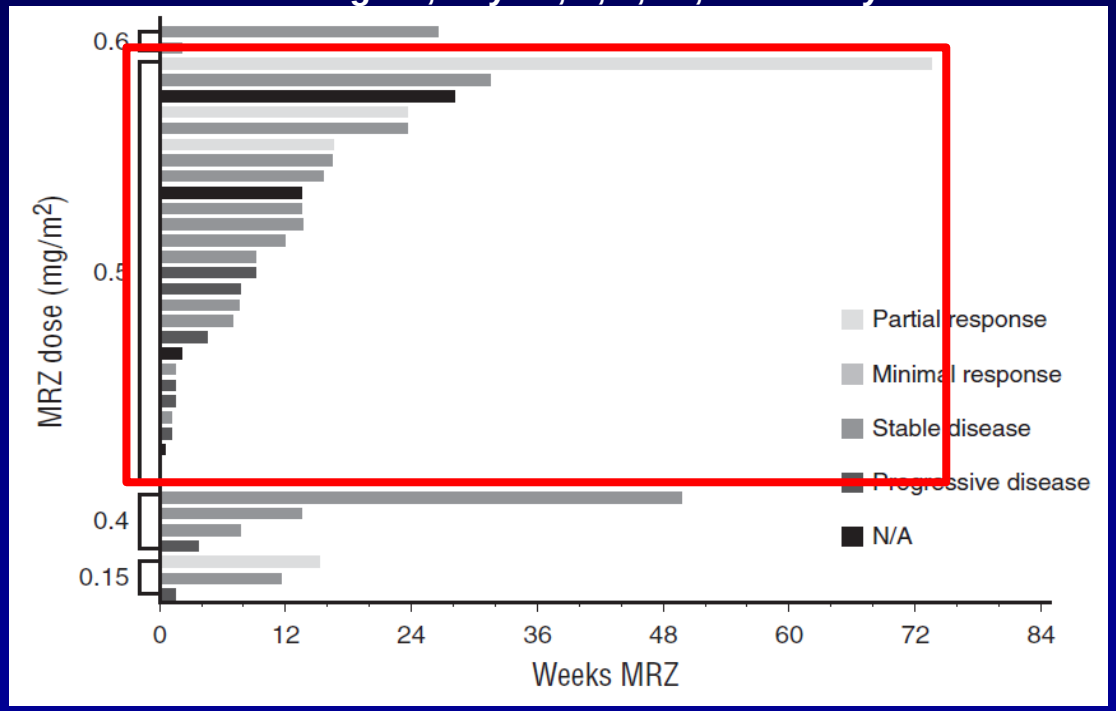
1. Richardson PG, et al. Blood 2016;127(22):2693–700.
2. Harrison SJ, et al. Clin Cancer Res 2016;22(18):4559–66.
3. Spencer A, et al. Br J Haematol 2018;180(1):41–51.

Phase I NPI-0052-101 study[1]
Single-agent marizomib: Clinical responses

Weekly marizomib in RRMM:
MTD 0.7 mg/m², days 1, 8, 15, 4-week cycles



Twice-weekly marizomib in RRMM:
MTD 0.5 mg/m², days 1, 4, 8, 11, 3-week cycles

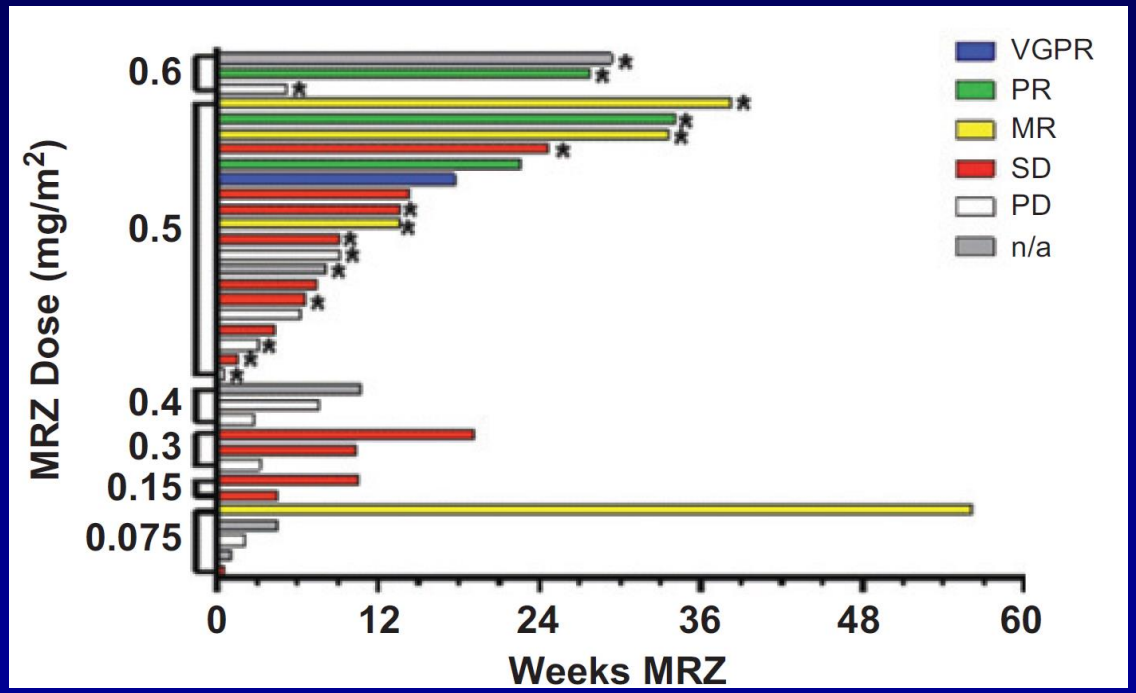


- 1 PR at weekly MTD, 1 PR with twice-weekly 0.15 mg/m², 3 PRs at twice-weekly MTD
- These responses were in patients who had received prior bortezomib, lenalidomide, and/or thalidomide
- Twice-weekly MTD of 0.5 mg/m² determined as regimen of choice for further development

1. Richardson PG, et al. Blood 2016;127(22):2693–700.

Phase I NPI-0052-102 study[1]
Single-agent marizomib: Clinical responses in MM

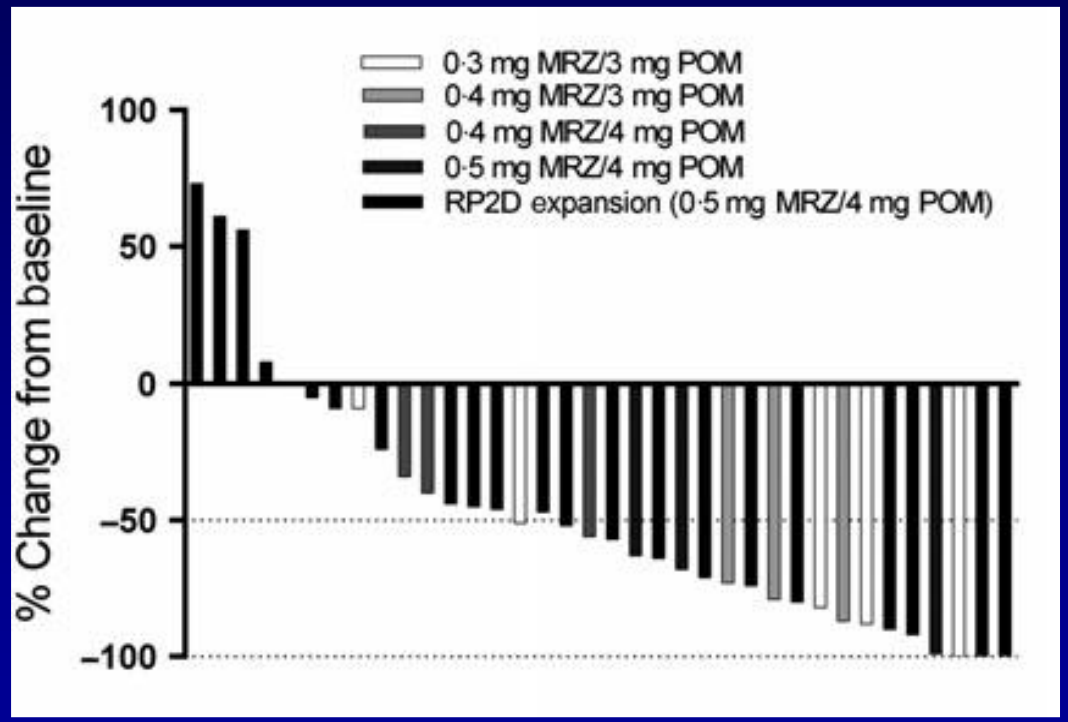
- Twice-weekly schedule
  - 44 patients treated in 6 dose cohorts
  - 10 patients treated at RP2D – 0.5 mg/m^2 administered over 2 hours
  - 35 RRMM patients treated on twice-weekly schedule
- 27 evaluable RRMM patients
  - 4 objective responses
  - 1 VGPR at 0.5 mg/m^2 (10-min infusion)
  - 3 PRs at 0.5 (mg/m^2) (10-min infusion), 0.6 mg/m^2 (2-hr infusion), and 0.5 mg/m^2 (2-hr infusion)
  - Median DOR: 27 weeks
  - Median PFS (RP2D cohort, n=10): 20.4 weeks



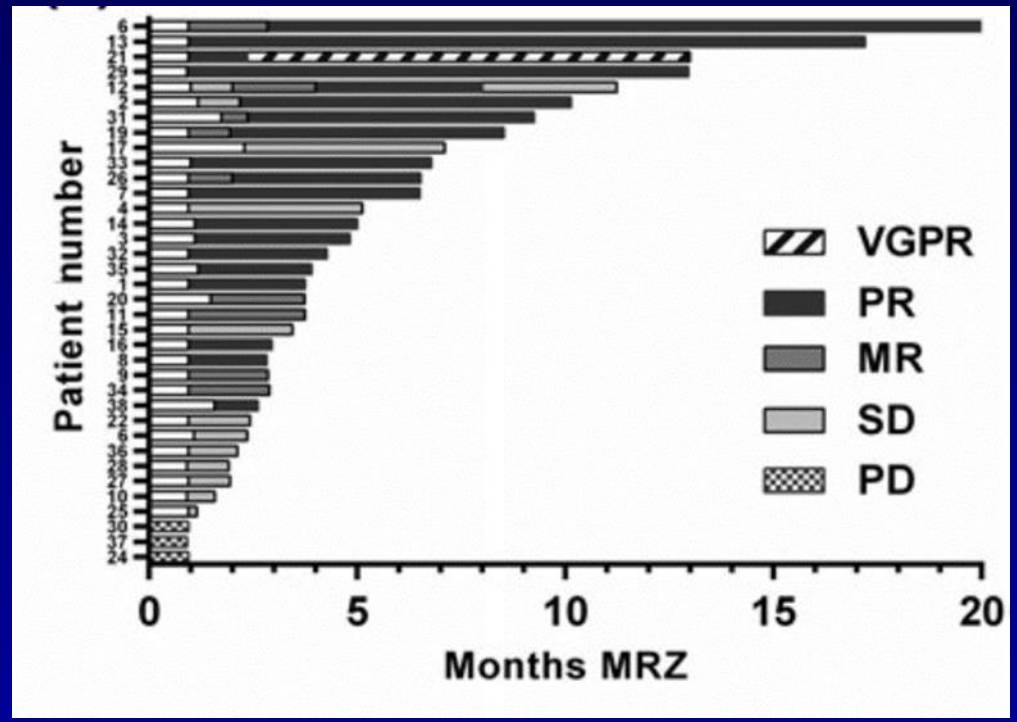
1. Harrison SJ, et al. Clin Cancer Res 2016;22(18):4559–66.

Phase Ib NPI-0052-107 study[1] Marizomib+pomalidomide+dex: Clinical responses

Waterfall plot: Best percentage change in paraprotein from baseline



Swimmer plot showing responses with time on marizomib



- MTD: twice-weekly marizomib 0.5 mg/m^2, pomalidomide 4 mg
- 2 VGPRs, 17 PRs (including 5 maintained for ≥10 months); 31/36 patients had M-protein reductions
- Median DOR: 7.5 months

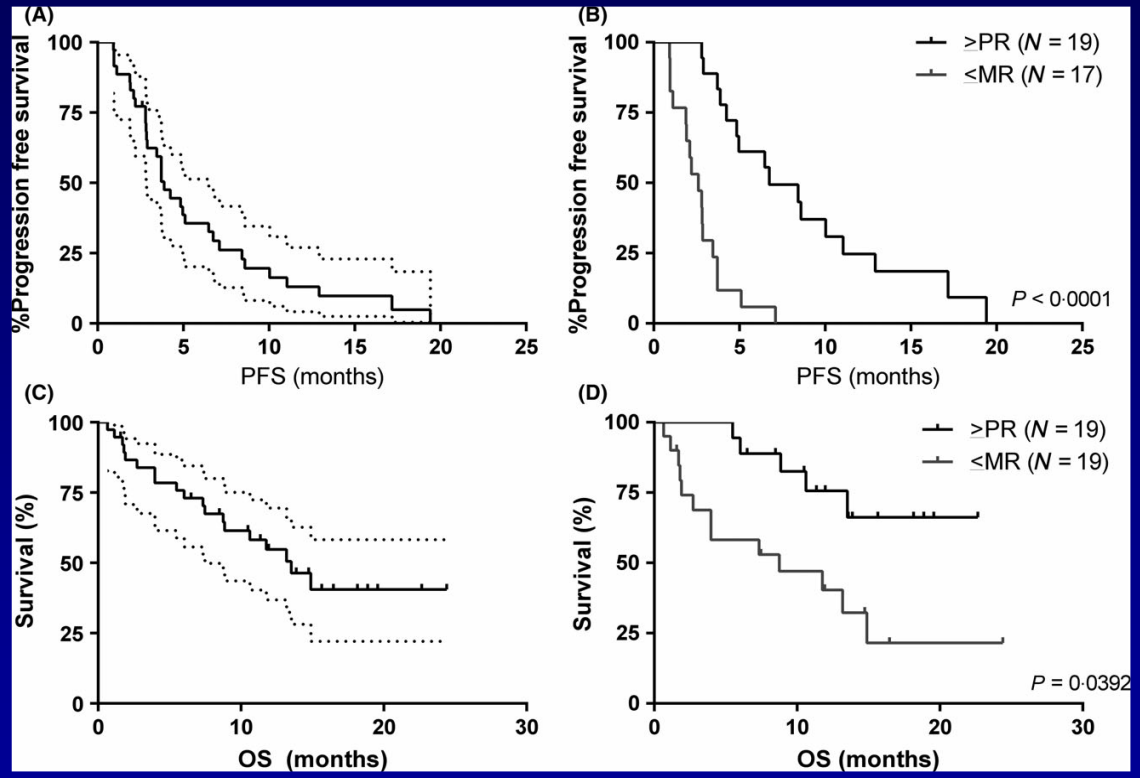
1. Spencer A, et al. Br J Haematol 2018;180(1):41–51.

Phase Ib NPI-0052-107 study[1] Marizomib+pomalidomide+dex: Clinical responses

Subgroup	N	ORR	CBR
All	36	53%	64%
High-risk cytogenetics	10	50%	70%
Standard-risk cytogenetics	18	56%	61%
Prior lenalidomide/bortezomib	36	53%	64%
Prior carfilzomib	11	82%	91%
Refractory to lenalidomide	30	50%	63%
Refractory to bortezomib	21	57%	62%
Refractory to carfilzomib	10	80%	90%
Refractory to lenalidomide/bortezomib	18	56%	67%
Refractory to lenalidomide/bortezomib/carfilzomib	7	71%	87%
Refractory to lenalidomide in last regimen	15	47%	67%
Refractory to bortezomib in last regimen	7	43%	57%
Refractory to carfilzomib in last regimen	7	86%	86%

1. Spencer A, et al. Br J Haematol 2018;180(1):41–51.

Phase Ib NPI-0052-107 study[1] Marizomib+pomalidomide+dex: outcomes



PFS (top) and OS (bottom) in all patients (left) and by response to marizomib+pomalidomide+dex (right)

- Median PFS: 4.0 months
  - 6.7 vs 2.6 months in patients achieving ≥PR vs ≤MR
  - 3.8 months in double-refractory (lenalidomide/bortezomib) patients
- Median OS: 13.6 months
  - Significantly prolonged in patients achieving ≥PR vs ≤MR
  - 13.6 months in double-refractory patients
- Median PFS/OS similar to overall population in triple-refractory (lenalidomide/bortezomib/carfilzomib) patients

1. Spencer A, et al. Br J Haematol 2018;180(1):41–51.

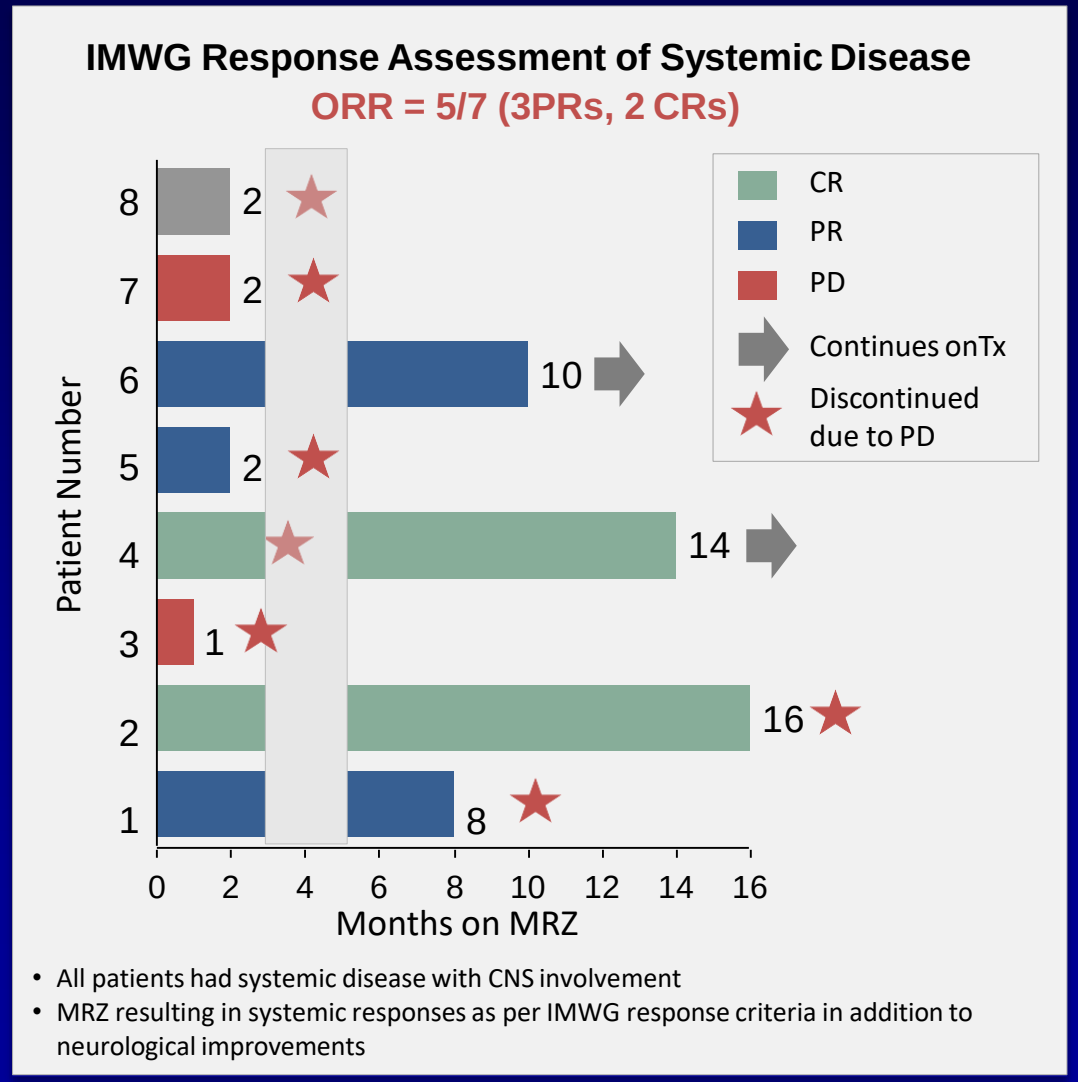
Marizomib: ongoing studies

Study	NCT	Regimens	Patients	Primary endpoint	Date of primary data availability
EORTC-BTG-1709 Phase 3	NCT03345095	Marizomib + temozolomide + RT	Newly diagnosed glioblastoma	OS	July 2022
MRZ-108 Phase 1	NCT02330562	Marizomib + bevacizumab	Malignant glioma / GBM	MTD / activity	February 2019
MRZ-112 Phase 1	NCT02903069	Marizomib + temozolomide + RT	Newly diagnosed brain cancer	MTD / AEs	June 2019

- Currently studies in RR MM/CNS MM are in development (ClinicalTrials.gov, Sept 2018)
- Clinical experience in glioblastoma and CNS-MM suggests marizomib has positive impact on these CNS malignancies – hence the focus of ongoing studies

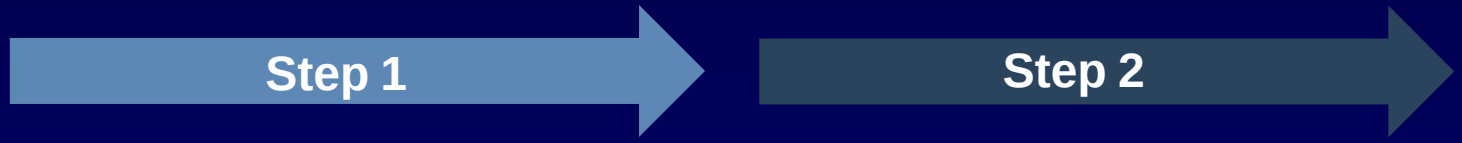
Marizomib: Current Results in CNS-MM

- Initial experience in 2 patients with safety shown, and responses reported [1]
- 8 patients treated under single patient compassionate use protocol with for CNS-MM
- Marizomib well tolerated
  - No CNS adverse events reported despite 10 min infusion and dose similar to GBM
- Marizomib is showing promising activity
  - 5-6 of 8 patients ≥PR
  - 4 of 8 patients: survival > 4 months which exceeds the median survival for this disease
  - 2 of 8 patients on study over 1 year with another one patient still on treatment at 10 months (10/17)
- Treatment:
  - 3 started with marizomib + dex; 1 pomalidomide, 1 daratumumab added
  - 5 started with marizomib+pomalidomide (lenalidomide)+dex



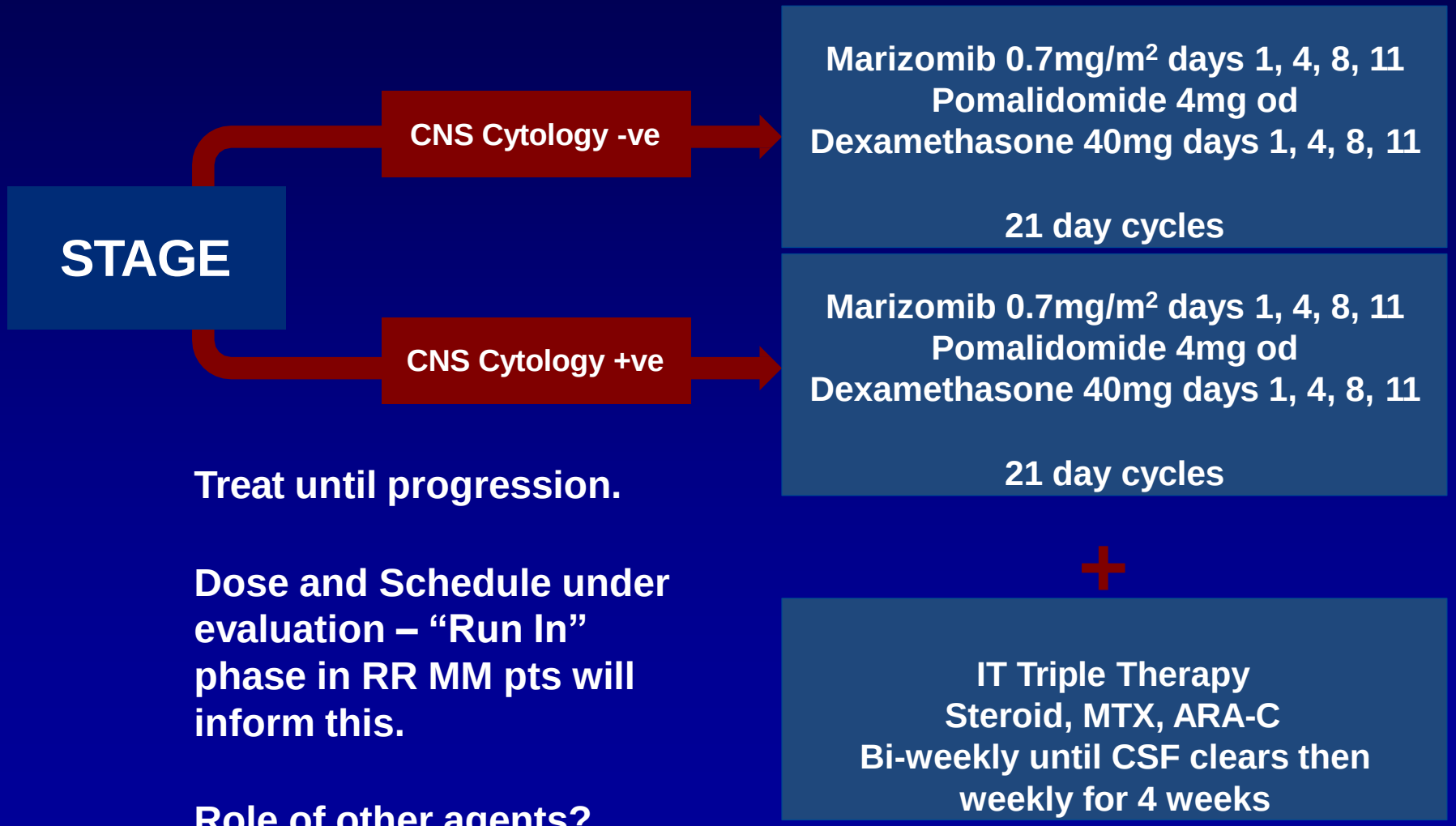
1. Badros A, et al. Br J Haematol 2017;177(2):221–5.

Evaluating Marizomib in CNS-MM in a 2-step approach



- Formal single-arm phase 2 study, after “run in” for RR MM
  - Based on initial findings of exploratory trials
  - Clear eligibility criteria
  - Single agent, combination, IT administration, XRT ?
  - Consistent disease evaluation criteria
  - Include relevant Patient Outcome evaluation
  - Aim to start Q3-4 2019

Evaluating marizomib in CNS-MM: study design (in development)



Treat until progression.

Dose and Schedule under evaluation – “Run In” phase in RR MM pts will inform this.

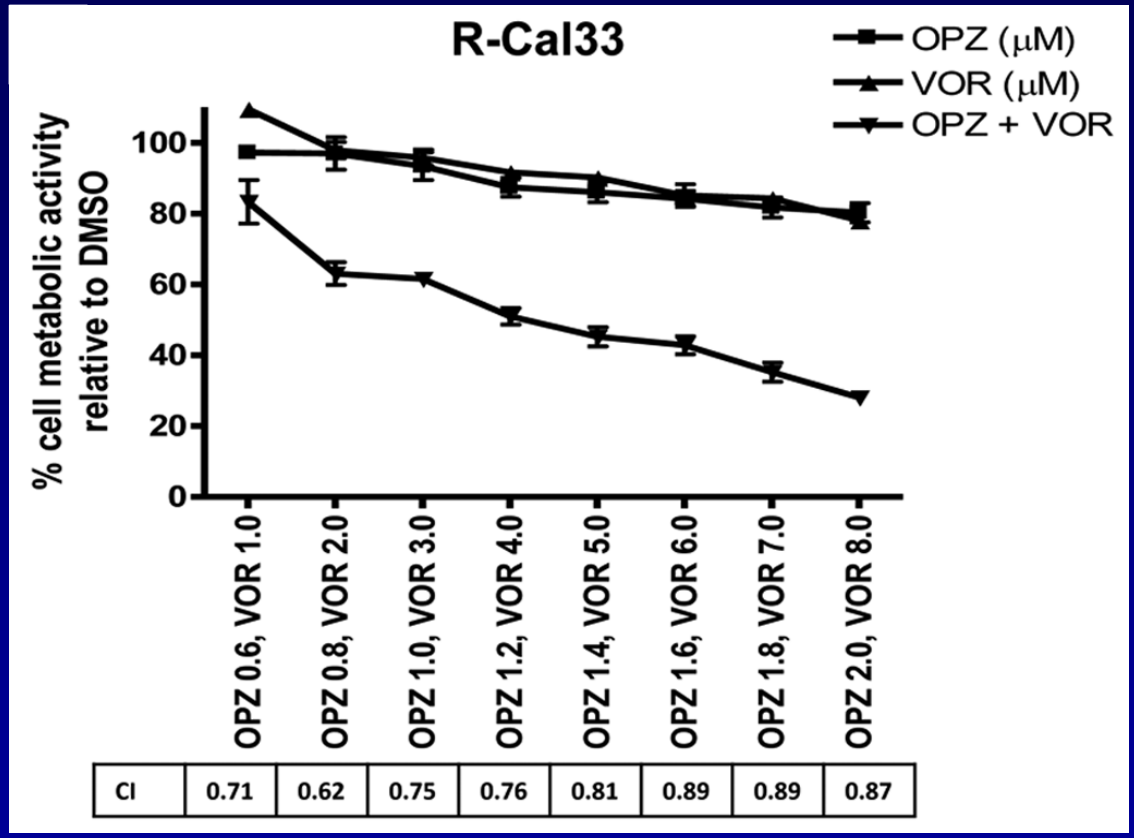
Role of other agents?

Proteasome Inhibitors (PIs) in MM: New agents

Oprozomib

Oprozomib: preclinical synergies

- Enhanced anti-MM activity of:[1]
  - Bortezomib
  - Lenalidomide
  - Dexamethasone
  - Pan-HDACi
- Anti-MM synergy with pomalidomide + dexamethasone[2]
- Synergy with vorinostat (HDACi) in carfilzomib-resistant HNSCC cells (right)[3]



1. Chauhan D, et al. Blood 2010;116(23):4906–15.
2. Sanchez E, et al. Leuk Res 2017;57(June):45–54.
3. Zang Y, et al. Cancer Biol Ther 2014;15(9):1142–52.

Oprozomib in MM: Clinical trial data

Study	Regimen	Setting	Response rates	Outcomes
Ghobrial et al[1] Phase 1b/2	Single-agent oprozomib + dex	RRMM (median 3–5 prior regimens; phase 2, N=102) 62-71% btz-refractory; 33% cfz-refractory; 74-78% len-refractory; 44-46% pom-refractory	Phase 2: CBR: 31–51% ORR: 25–41% ≥VGPR: 9–13%	PFS: 3.7–6.1 mos
Shah et al[2] Phase 1b	Oprozomib-pomalidomide-dex	RRMM (median 8 prior regimens; N=21) 71% btz-refractory; 38% cfz-refractory 86% IMiD-refractory	CBR: 57% ORR: 57% ≥VGPR: 24%	NR

1. Ghobrial IM, et al. manuscript submitted.
2. Shah J, et al. Blood 2015;126(23):378.

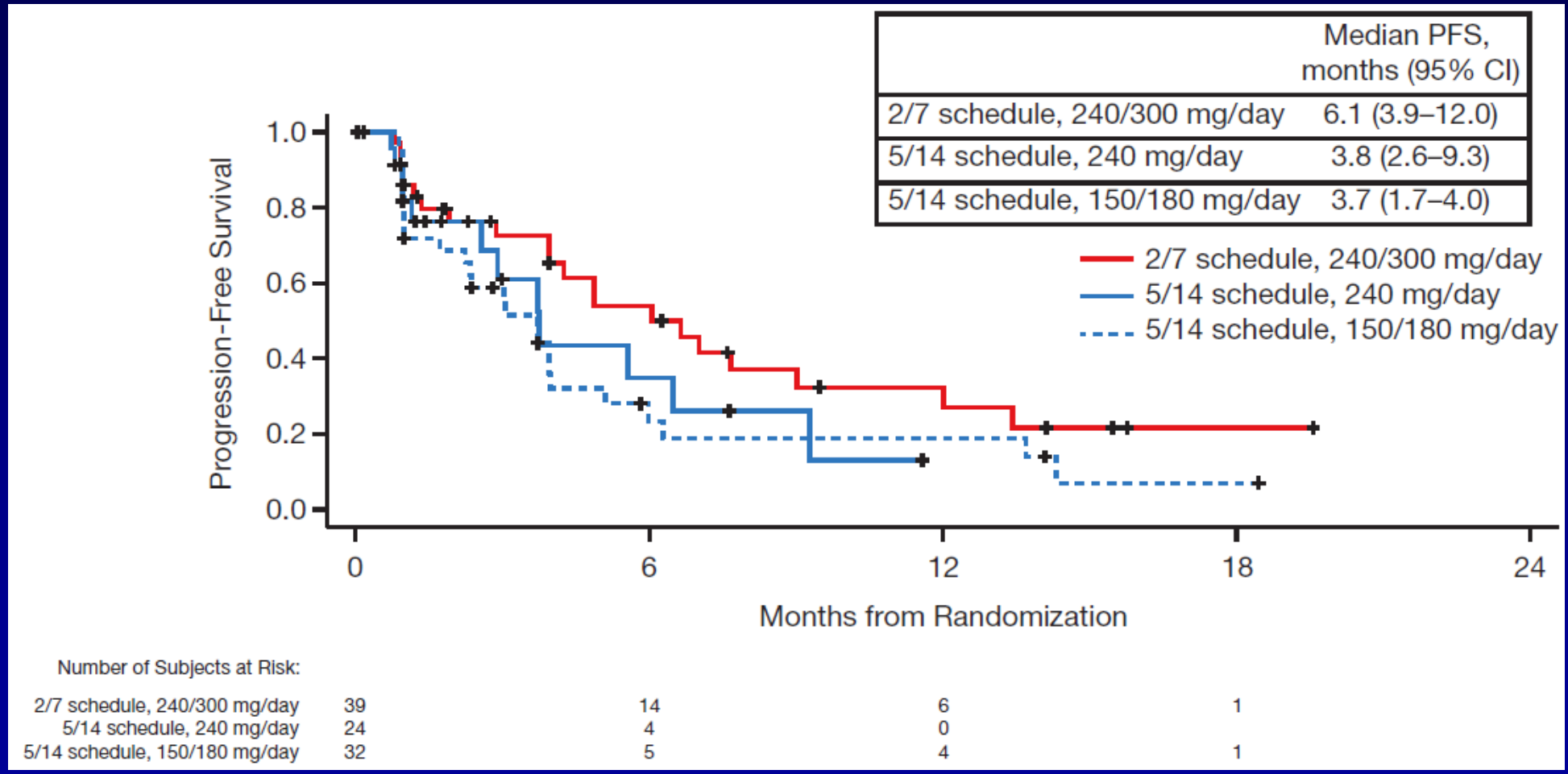
Phase I/II 2011-001 study[1]
Single-agent oprozomib: responses

Outcome	2/7 schedule, 240/300 mg/day (n = 39)	5/14 schedule, 150/180 mg/day (n = 32)	5/14 schedule, 240 mg/day (n = 24)
ORR, n (%)	16 (41)	9 (28)	6 (25)
VGPR, n (%)	5 (13)	3 (9)	3 (13)
PR, n (%)	11 (28)	6 (19)	3 (13)
CBR, n (%)	20 (51)	10 (31)	8 (33)
Median DOR, months	10.2	12.5	5.6
Patients refractory to bortezomib, N	29	39	
ORR, n (%)	9 (31)	7 (18)	
CBR, n (%)	11 (38)	10 (26)	
Patients refractory to carfilzomib, N	14	21	
ORR, n (%)	2 (14)	2 (10)	
CBR, n (%)	3 (21)	2 (10)	

- 2/7 schedule: days 1, 2, 8, 9, 14-day cycles
- 5/14 schedule: days 1–5, 14-day cycles

1. Ghobrial IM, et al. manuscript submitted.

Phase I/II 2011-001 study[1] Single-agent oprozomib: PFS



1. Ghobrial IM, et al. manuscript submitted.

Oprozomib in MM: ongoing studies

Study	NCT	Regimens	Patients	Primary endpoint	Date of primary data availability
OPZ003 Phase 1/2	NCT01881789	Oprozomib-cyclo/len-dex	NDMM	MTD, AEs, ORR	February 2019
2012-001 Phase 1b/2	NCT01832727	Oprozomib-dex	RRMM, 1–5 prior therapies	MTD, safety, ORR	February 2019
OPZ007 Phase 1b	NCT01999335	Oprozomib-pom-dex	RRMM, ≥2 prior therapies	MTD, AEs, PFS	February 2019
INTREPID-1 Phase 1b	NCT02939183	Oprozomib-(pom)-dex	RRMM, ≥2 prior therapies	MTD of different OPZ formulations	April 2020

- INTREPID-1 is studying two new formulations of oprozomib designed to improve GI tolerability: immediate-release formulation and gastro-retentive formulation
- Prior studies utilized modified-release tablet that is not being continued

Which PI?
Two investigational PIs: different safety considerations

PI	Key toxicities
Marizomib[1]	Drug-related AEs: Fatigue 47%, headache 43%, nausea 38%, diarrhea 28%, dizziness 27%, vomiting 25% (all grades) CNS toxicities ~ manageable Limited PN, minimal cardiac AEs, Limited heme toxicity
Oprozomib[2]	Common grade ≥3 AEs: Diarrhea 12–33%, anemia 9–30%, fatigue 9–20%, thrombocytopenia 3–33%, Nausea/vomiting (40%) Discontinuations due to AEs in 12–44% Dose-limiting GI hemorrhage

- Some of the potential class effects of PIs seen with investigational agents
  - Hematologic toxicity, especially thrombocytopenia (oprozomib)
  - GI toxicities (both agents, especially oprozomib)
  - Limited CV toxicities
- Minimal PN and heme tox seen with marizomib
- GI toxicity dose-limiting with oprozomib
  - Development ongoing with novel formulations to overcome GI issues

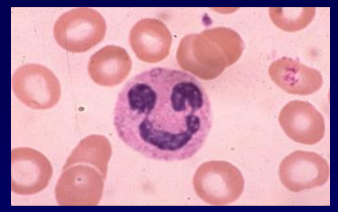
1. Richardson PG, et al. Blood 2016;127(22):2693–700.
2. Ghobrial IM, et al. manuscript submitted.

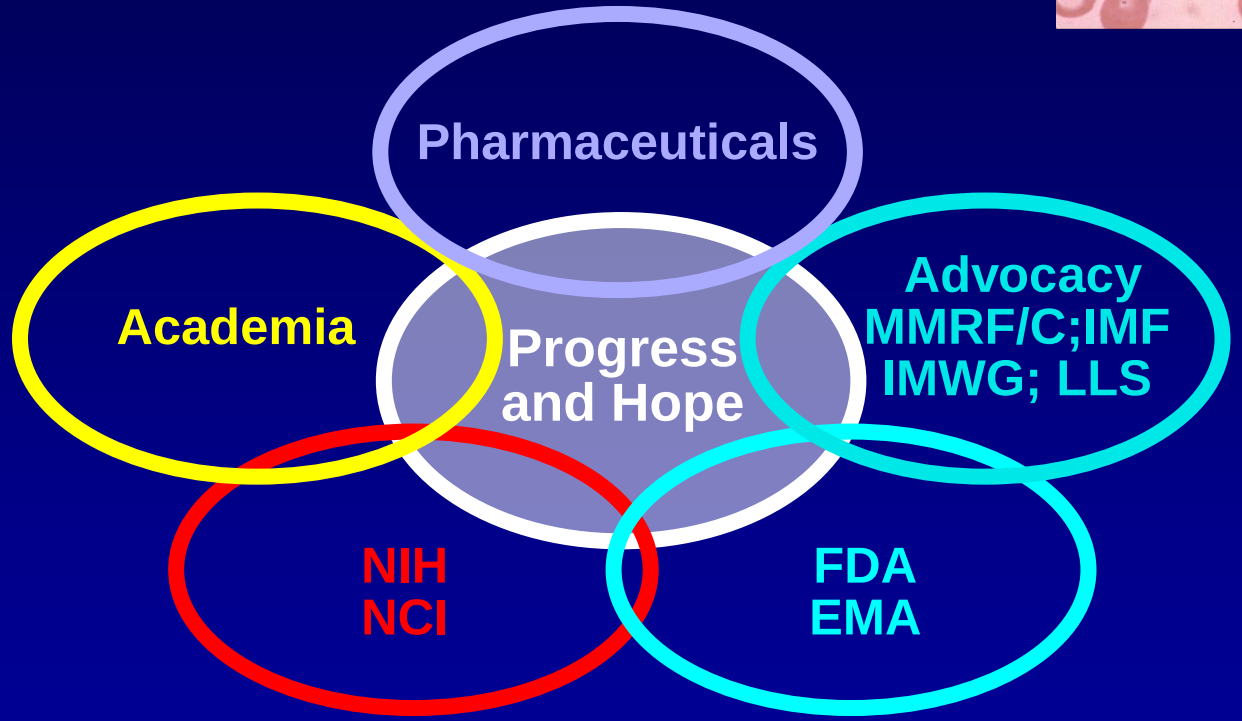
Conclusions and Future Directions

- Three approved PIs form the backbone of the NDMM and RRMM treatment algorithm (Bz, CFLz, IXA)
  - Currently utilized in multiple combinations and settings
  - Ongoing phase 3 studies potentially expanding roles of carfilzomib and ixazomib in the future
- Ongoing phase 3 studies evaluating novel PI-based combinations
  - Further broadening range of PI-based options for MM over the next 5 years
    - Particularly with monoclonal antibodies (e.g. Dara, Isatuximab, Elo, MOR 202, GSK916)
    - Other novel investigational agents (e.g. venetoclax, selinexor)
- Next-generation PIs in development
  - Marizomib – unique MoA, highly active in combination, potential utility in CNS-MM
  - Oprozomib – activity noted, ongoing development in RR MM with novel formulations to improve tolerability

Ongoing MM collaborative model for rapid translation from bench to bedside

Grazie Mille!





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

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