2000-2016: Dal bortezomib ai nuovi inibitori del proteasoma

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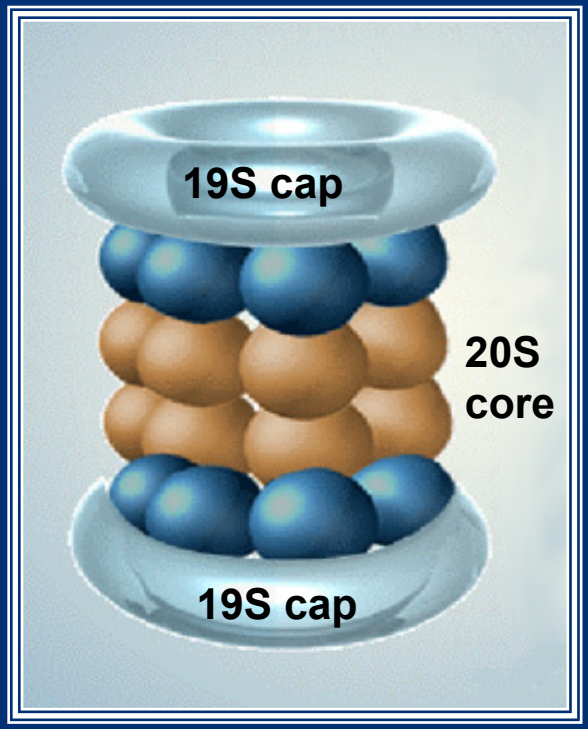
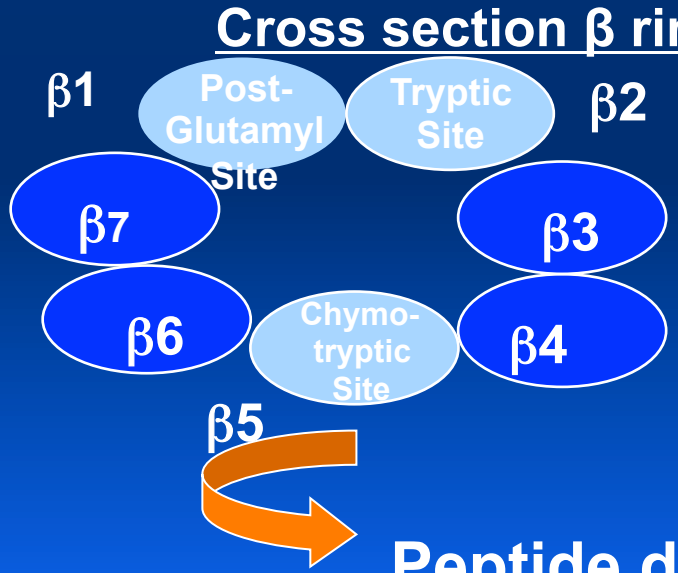
PROTEASOMA

- Complesso enzimatico proteolitico per la degradazione delle proteine ubiquitinate
- Presente nel citoplasma e nel nucleo di tutte le cellule eucariote
- Core 20S con attività catalitica

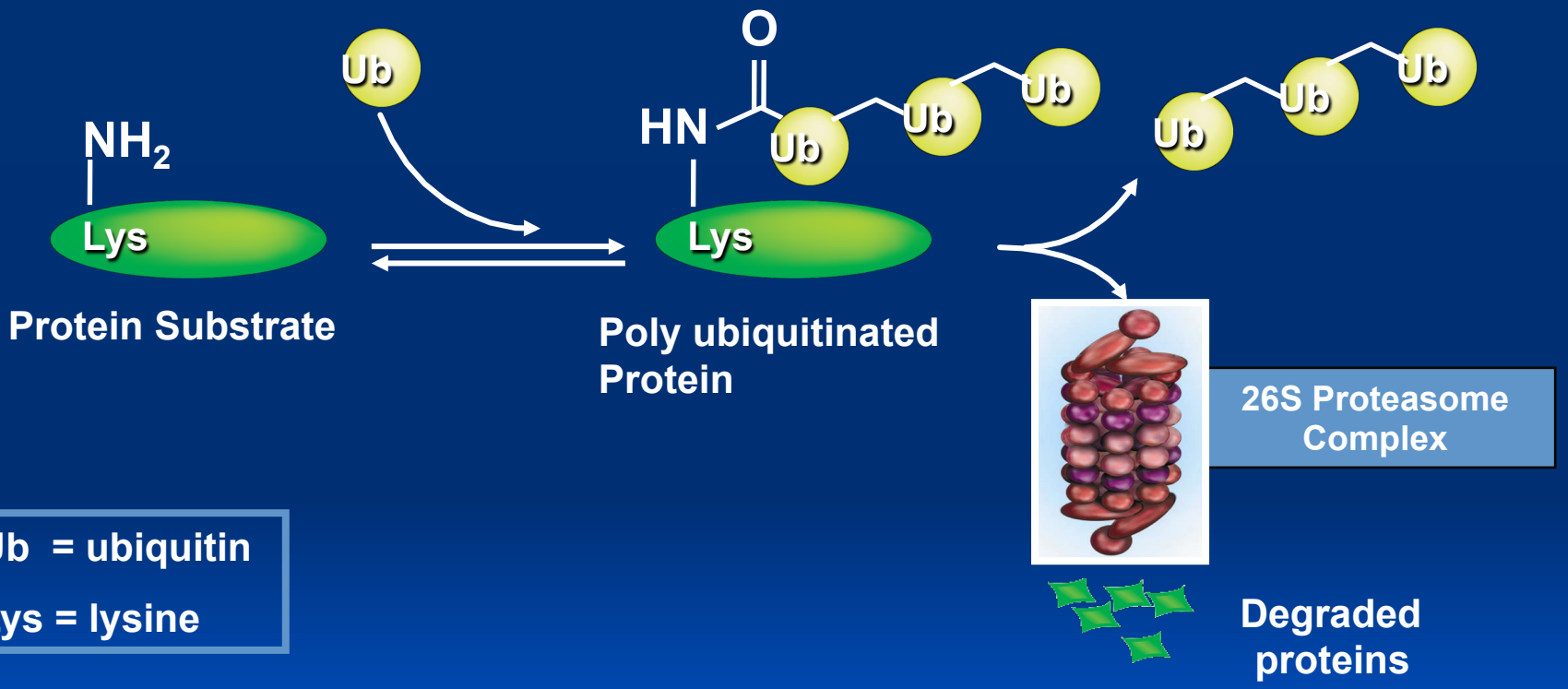




Ciechanover A, EMBO J. 1998
Konstantinova IM, Int. Rev Cell Mol Biol. 2008

Peptide degradation 3 – 25 AA

Ubiquitin-Proteasome Pathway



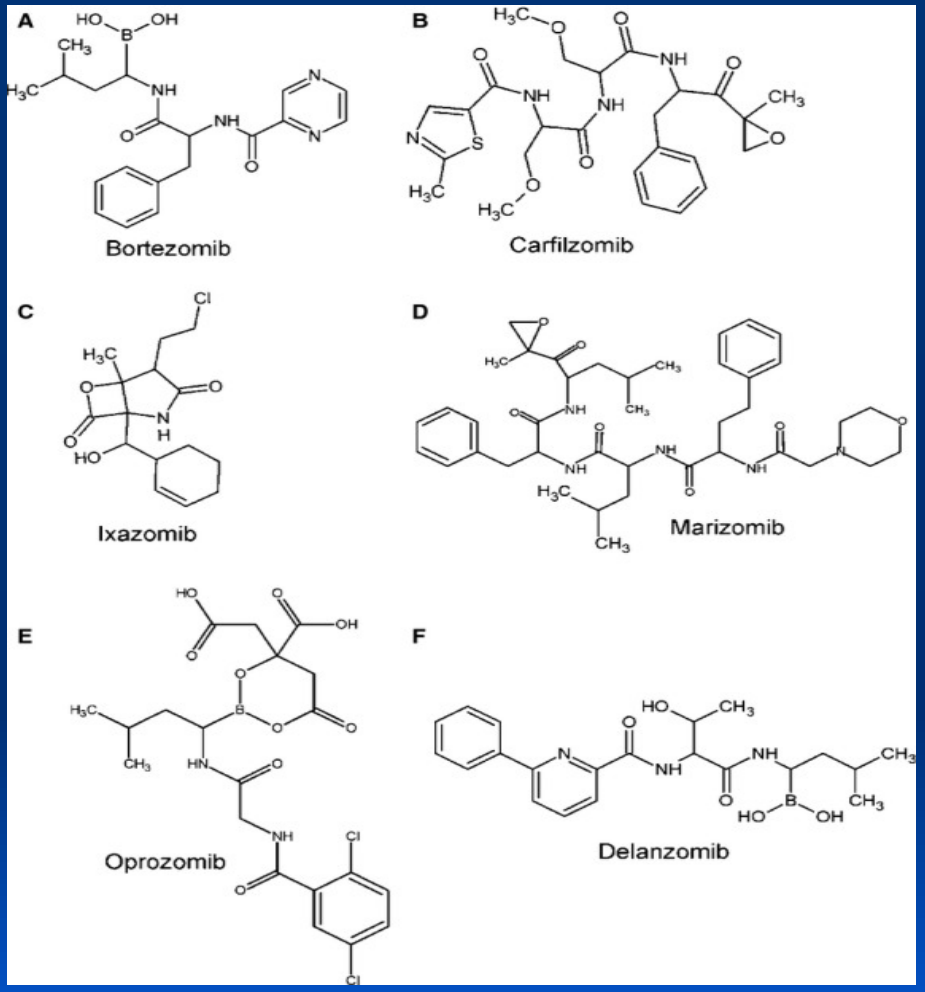
Ub = ubiquitin

Lys = lysine

Myung J. Med Res Rev. 2001
De Martino GN. J Biol Chem. 1999

INIBITORI DEL PROTEASOMA

- piccoli peptidi contenenti gruppi atomici in grado di legarsi al sito catalitico del proteasoma (20S) impedendone l'attività



Harousseau JL, JCO 2010
Cavo M, Lancet 2010
Sonneveld P, JCO 2012
Rosinol L, Blood 2012

Table 1 Overview of some of the molecular effects of proteasome inhibitors that contribute to their antimyeloma activity

Target	*Mechanism*	*Consequence*	*References*
α4-Integrin	Downregulate expression of VLA-4	Overcome adhesion-mediated drug resistance	180
BH3 proteins	Stabilize BIK, NOXA and BIM	Contribute to activation of Bax and Bak	181–183
Calcium	Disrupt mitochondrial calcium uniporter	Dysregulate intracellular calcium storage; induce caspase activation	184
Caveolin 1	Inhibit VEGF-triggered caveolin phosphorylation; decrease caveolin expression	Reduce myeloma cell migration and survival	185
Cdkis	Stabilize Cdkis such as p21 and p27	Arrest the cell cycle	15
HIF-1α	Stimulate FIH	Inhibit tumor angiogenesis and tumor adaptation to hypoxia	186
HLA	Downregulate surface expression of class I molecules	Enhance natural killer cell-mediated lysis of myeloma cells	187
HSP-90	Induce HSP-90 expression and cell-surface exposure	Enhance dendritic cell-mediated induction of immunity	188
IL-6	Reduce stromal cell production of IL-6 through NF-κB; also down-regulate gp130 through a caspase-mediated process	Suppress IL-6-mediated growth and survival signals	189,190
IGF-1	Downregulate IGF-1 and IGF-1R expression	Suppress IGF-1-mediated growth and survival signals	82
JNK	Activate JNK	Upregulate Fas and activate caspase-8 and caspase-3	82
Mcl-1	Induce Mcl-1 cleavage	Reduce antiapoptotic Mcl-1; produce proapoptotic Mcl-1 fragments	183,191
MKP-1	Induce MKP-1 expression	Inhibit p44/42 MAPK-mediated growth and survival signals	74,76
NF-κB	Stabilize IκB	Multiple mechanisms (please see text for more details)	70,192
p53	Cause accumulation and phosphorylation of p53	Induce downstream targets such as p21, NOXA and Bax	193
ROS	Induce reactive oxygen species production	Promote mitochondrial injury with release of pro-apoptotic factors	157
UPR	Induce proapoptotic UPR genes; suppress antiapoptotic UPR responses	Activate caspase-mediated apoptosis	86,194,195
VEGF	Suppress stromal cell production of VEGF	Reduce myeloma cell migration and marrow angiogenesis	196

BORTEZOMIB IN RRMM

BORTEZOMIB(PSI-341): first-in-class proteasome inhibitor, reversible, targets the chymotrypsin site of the proteasome (20S)

2003-2004: approved by FDA and EMA for the treatment of refractory MM;

2005: approved by FDA and EMA for the treatment of patients with MM who had received **at least 1 prior therapy**

Dipeptidyl boronic acid ; bortezomib ; PS341

BORTEZOMIB ± DEX IN RRMM

Study	Regimen*	N	ORR,† %	CR/nCR, %	Outcomes	Common grade ≥ 3 AEs, %
Phase 2 SUMMIT[27,98]	Btz ± dex	202	≥ MR: 35	10	DOR: 12.7 mo	Thrombocytopenia 31; neutropenia 14; PN 12; fatigue 12; diarrhea 8; vomiting 8; anemia 8
			≥ PR: 27		TTP: 7 mo	
					OS: 17 mo	
Phase 2 CREST[28,29]	Btz 1.0 (± dex)	28	≥ MR: 33 (44)	11 (19)	DOR: 9.5 mo	Thrombocytopenia 29; neutropenia 11; lymphopenia 11; hyponatremia 11; limb pain 11; PN 8
			≥ PR: 30 (37)		TTP: 7.0 mo	
					OS: 26.8 mo	
	Btz 1.3 ± dex	26	≥ MR: 50 (62)	4 (4)	DOR: 13.7 mo	Thrombocytopenia 23; neutropenia 23; pneumonia 15; PN 15; lymphopenia 12; weakness 12; limb pain 8; hyponatremia 8
			≥ PR: 38 (50)		TTP: 11.0 mo	
					OS: 60 mo	
Phase 3 APEX[30,31]	Btz	333	43	15	DOR: 7.8 mo	Thrombocytopenia 30; neutropenia 14; anemia 10; PN 8; diarrhea 7
					TTP: 6.2 mo	
					OS: 29.8 mo	
	Dex	336	18	2	DOR: 5.6 mo	Anemia 11; thrombocytopenia 6; diarrhea 2; PN 1; neutropenia 1
					TTP: 3.5 mo	
					OS: 23.7 mo	
Phase 3 MMY-3021[42]	SC Btz	148	52	20	DOR: 9.7 mo	Neutropenia 18; thrombocytopenia 13; anemia 12; leucopenia 6; sensory PN 5; pneumonia 5; neuralgia 3
					TTP: 10.4 mo	
					PFS: 10.2 mo	
					1-y OS: 73	
	IV Btz	74	52	22	DOR: 8.7 mo	Thrombocytopenia 19; neutropenia 18; sensory PN 15; neuralgia 9; anemia 8; pneumonia 8; leucopenia 7
					TTP: 9.4 mo	
					PFS: 8.0 mo	
					1-y OS: 77	

The combination of Bort and Dex led to improved response in 18% (SUMMIT) and 33% (CREST) of patients

Moreau P et al, Blood 2012

BORTEZOMIB IN RRMM

Phase III APEX trial: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma

	Bortezomib	Dex	p
ORR, %	38	18	< 0,001
TTP, median, months	6,2	3,5	< 0,001
1-year OS, %	80	66	0,003

Updated analysis with a median follow-up of 22 months

Superior TTP: 6.2 mos vs 3.5 mos
Superior survival despite cross-over (> 62%)
Median OS: 29.8 mos vs 23.7 mos (*p* = 0.0272)

Richardson P et al, NEJM 2005; Richardson P et al, Blood 2007

RETREATMENT WITH BORTEZOMIB

META-ANALYSIS of the efficacy and safety of Bortezomib retreatment in patients with multiple myeloma

	ORR, %	TTP, months	OS, months	PN G 3-4, %
All patients (n = 1051)	39	7,5	16,6	3
Prior therapies: ≤ 4 > 4	 43 29	 8,2 7,1	 13,3 20,0	
Therapy: - Bortezomib ± Dex (5 studies) - Combination (18 studies)	 51 36	 7,9 7,1	 19,2 16,1	
Only relapsed not refractory to Bortezomib	57	8,5	19,7	

Knopf K et al, ASH 2012

BORTEZOMIB in NEWLY DIAGNOSED MULTIPLE MYELOMA

Meta-analysis: Bortezomib-based versus non-bortezomib-based induction prior to ASCT

- Integrated analysis (n=1572) of 3 randomized trials: Bortezomib-based versus non-bortezomib-based induction regimens

Response rate	Bortezomib-based induction (n=775)	Non-bortezomib-based induction (n=772)	OR	95% CI	P
Post-transplant (%)					
CR+nCR	38	24	2.05	1.64–2.56	< 0.001

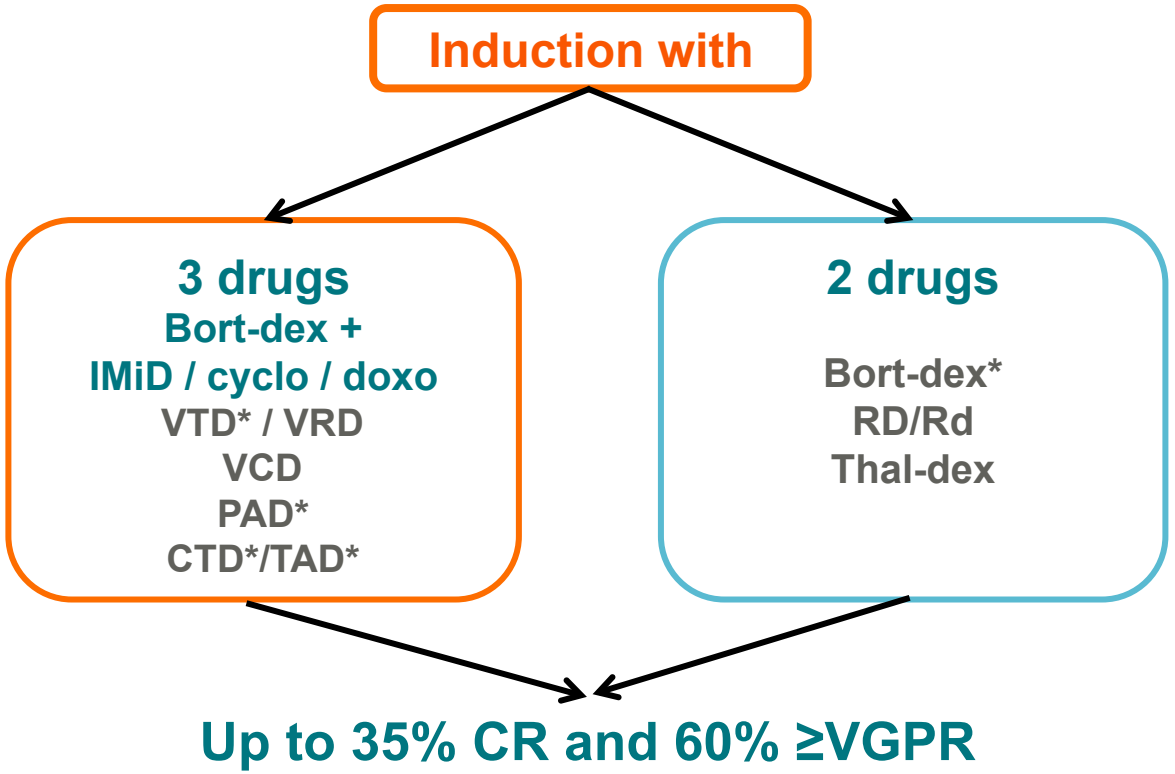
- Median follow-up ~37 months

	Bortezomib-based induction	Non-bortezomib-based induction	HR	95% CI	P
Median PFS, mos	35.9	28.6	0.75	0.65–0.85	< 0.001
3-yr PFS, %	50.0	41.1			

Primary end point: Post transplant CR+nCR and PFS

Sonneveld et al. J Clin Oncol 2013;31(26):3279-87

New treatment paradigm for ASCT eligible patients
Novel agent-based induction regimens



Strong preference for 3-drug bortezomib-based regimens

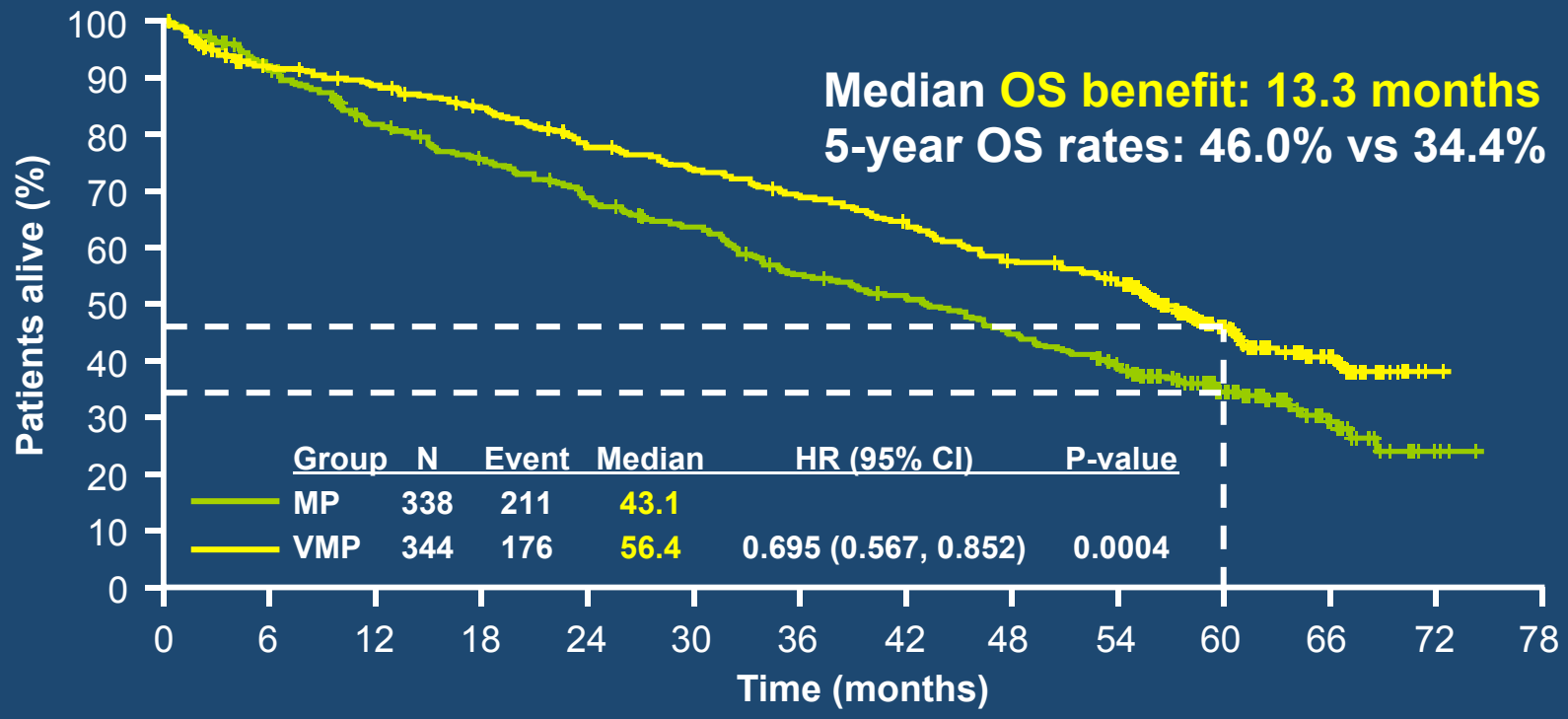
- **VTD and VD have been approved by the EMA (2011)** for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for transplant

Cavo M et al. Blood 2011;117(23):6063-73

VISTA: Final updated OS analysis

VMP approved by FDA and EMA 2008

Median follow-up 60.1 months



- Meta-analysis of six phase 3 trials of thalidomide–MP (MPT) vs MP:[1]
  - Median OS: 39.3 vs 32.7 months (6.6-month benefit), HR 0.83, 17% reduced risk of death

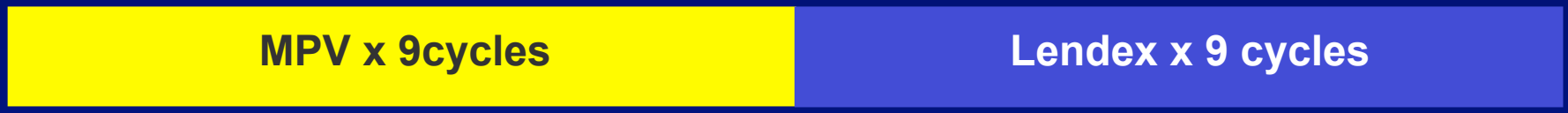
San Miguel J et al. NEJM 2008

San Miguel J et al. JCO 2013

Total Therapy approach for elderly MM : GEM2010: VMP/Rd

Symptomatic newly diagnosed MM pts > 65 y

Sequential scheme



Alternating scheme*

Hypothesis:
- Higher efficacy for the alternating scheme
- Less probability of cell tumor scape
- Lower cumulative toxicity

Median PFS sequential vs alternating: 32 vs 34 months

OS at 3 years sequential vs alternating: 72% vs 74%

N: 240 pts

Mateos MV et al. Blood 2015

BORTEZOMIB as BACKBONE FOR COMBINATIONS THERAPIES IN R/R AND NEWLY DIAGNOSED MM

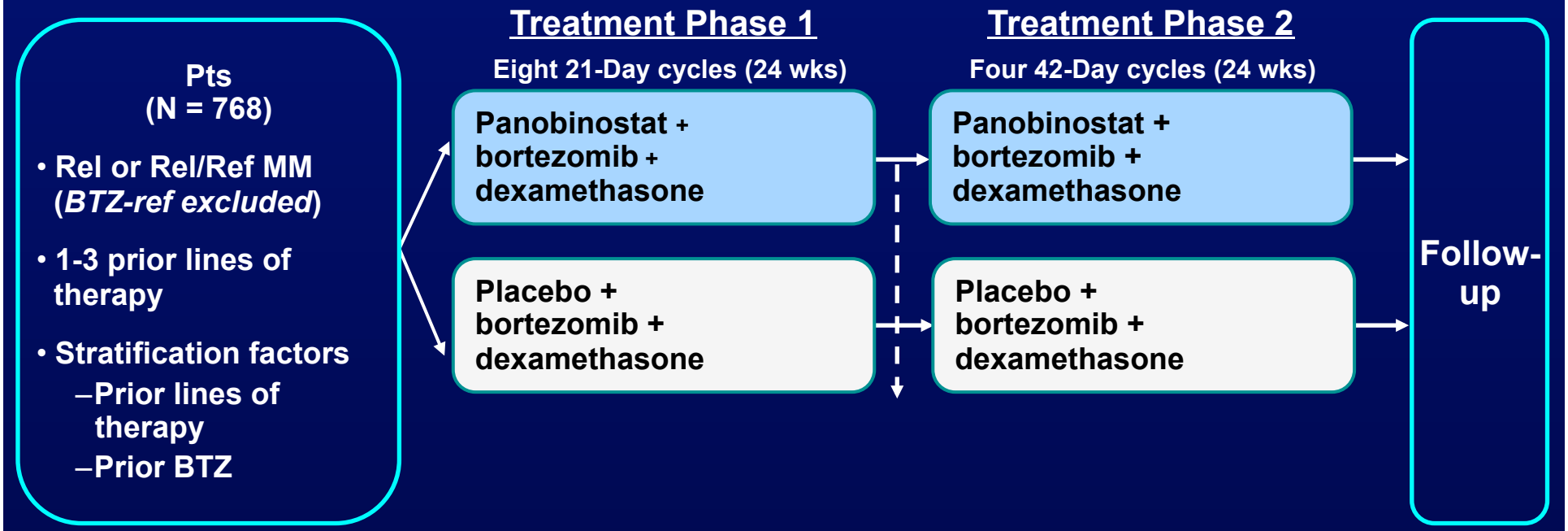
BENDAMUSTINE + BORTEZOMIB + DEX (BVD)

Study	N°	Treatment	Population	Prior tx median	ORR	Survival/ Outcomes
Ludwig[4] **BVD** prospective	79	**Benda 70 mg/mq D1,4/28** Bort 1.3 mg/mq D1,4,8,11/28 Dex 20 mg D1,4,8,11/28 Up to 8 cycles	R/R ≥ 1 prior tx prior bort 63%, prior lena 53%, prior B+L 37%	2 (1-6)	**≥PR 61%** prior B: 56% prior B+L 47% (p = ns)	**PFS 9.7** OS 25.6 longer PFS/OS: <3 lines, no prior L, no prior L+B
Offidani[5] **BVD** prospective	75	**Benda 70 mg/mq D1,8/28** Bort 1.3 mg/mq D1,4,8,11/28 Dex 20 mg D1,2,4,5,8,9,11,12/28 **4 cycles** for pts ≥PR → 2 more cycles + consolidation (6 cycles, every 2 mos)	≤ 4 prior tx, no bort refractory prior bort 47% prior B+L 20% IMiDs refr. 32%	1 (1-4)	After 4 BVD: **≥PR 72%** CR16% Best ORR: 77%, prior bort: 55%	**PFS 15.5** (prior bort: 11) OS 78% @ 1-y longer PFS: <3 lines, no prior B, no prior L+B
Rodon[6] **BVD** prospective	73	**Benda 70 mg/mq D1,8/28** Bort 1.3 mg/mq D1,8,15,22/28 Dex 20 mg D1,8,15,22/28 **4 cycles**; for pts ≥PR → 2 more cycles + maintenance (6 cycles, every 2 mos)	Elderly pts at first relapse, bort-naive	1	After 4 BVD: **≥PR 58%** CR11% Best ORR: 70%	**PFS 10.8** OS 23

[4]Ludwig H et al, Blood 2014
[5]Offidani M et al, Blood Cancer Journal 2013
[6]Rodon et al, Haematologica 2015

2014: BVD approved for R/R MM

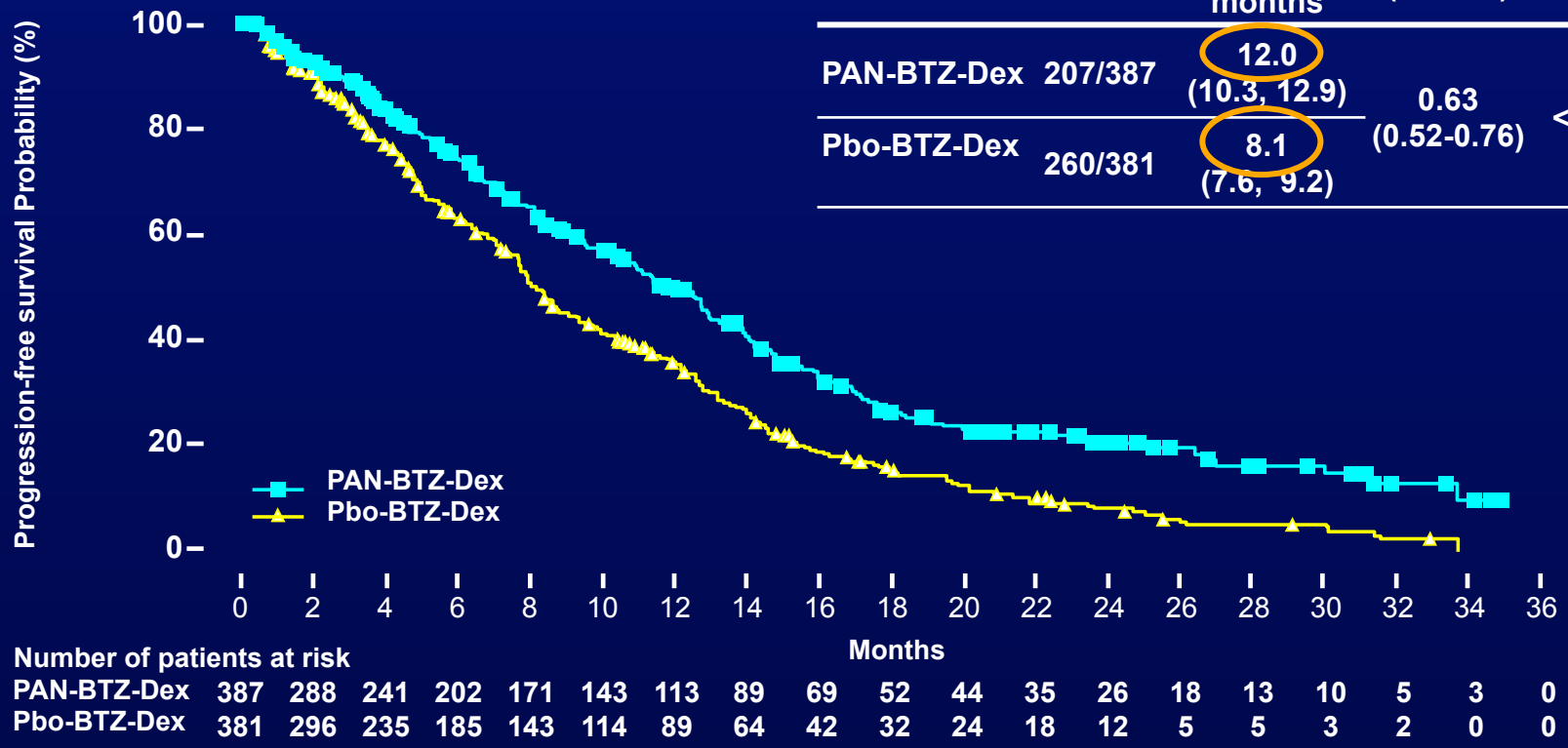
PANORAMA 1- Phase 3 Study in Relapsed or Relapsed and Refractory MM



- Primary endpoint: PFS
- Key secondary endpoint: OS

San Miguel et al. Lancet Oncology 2014 Online September 19, 2014

Primary Endpoint (PFS)



	Events	Median PFS (95% CI) months	HR (95% CI)	*P* value
PAN-BTZ-Dex	207/387	12.0 (10.3, 12.9)	0.63 (0.52-0.76)	< .0001
Pbo-BTZ-Dex	260/381	8.1 (7.6, 9.2)		

- **Primary endpoint met (*P* < .0001), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm**

2015: Panobinostat approved by FDA and EMA for R/R MM treated with at least 2 lines, including bortezomib and IMiDs. Warning on GI toxicity

CASTOR: Study Design

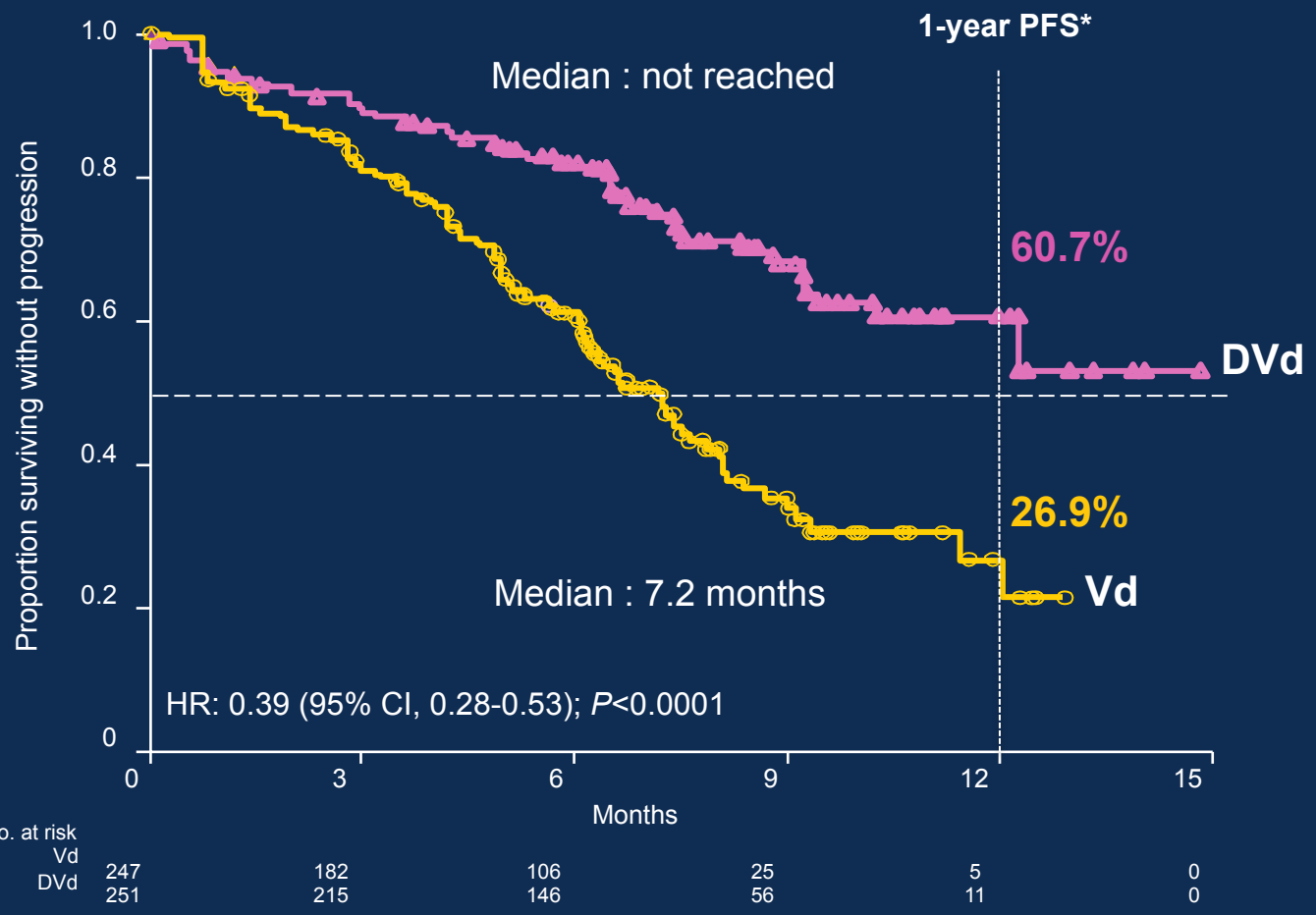
Multicenter, randomized, open-label, active-controlled phase 3 study

- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

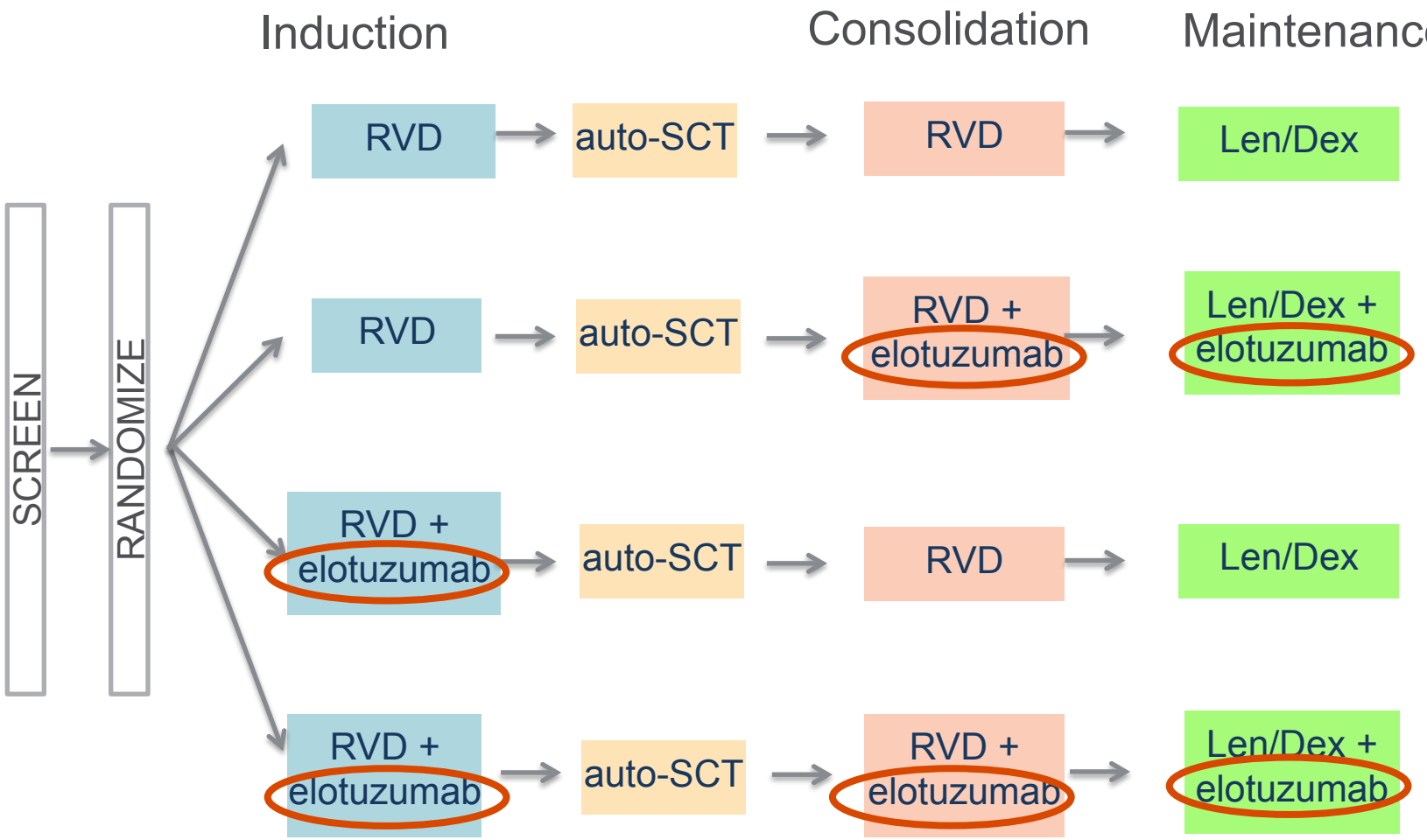
Progression-free Survival



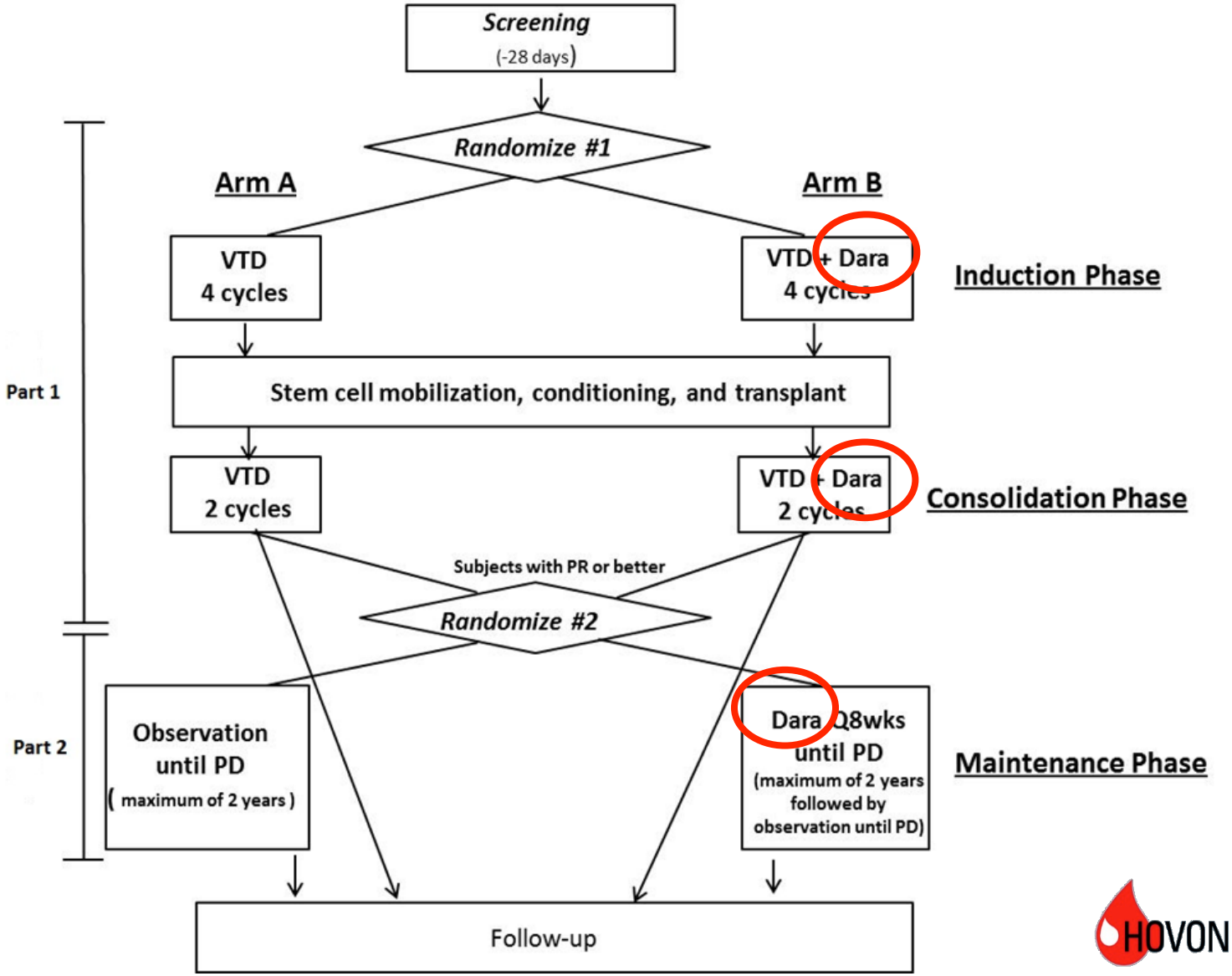
61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.

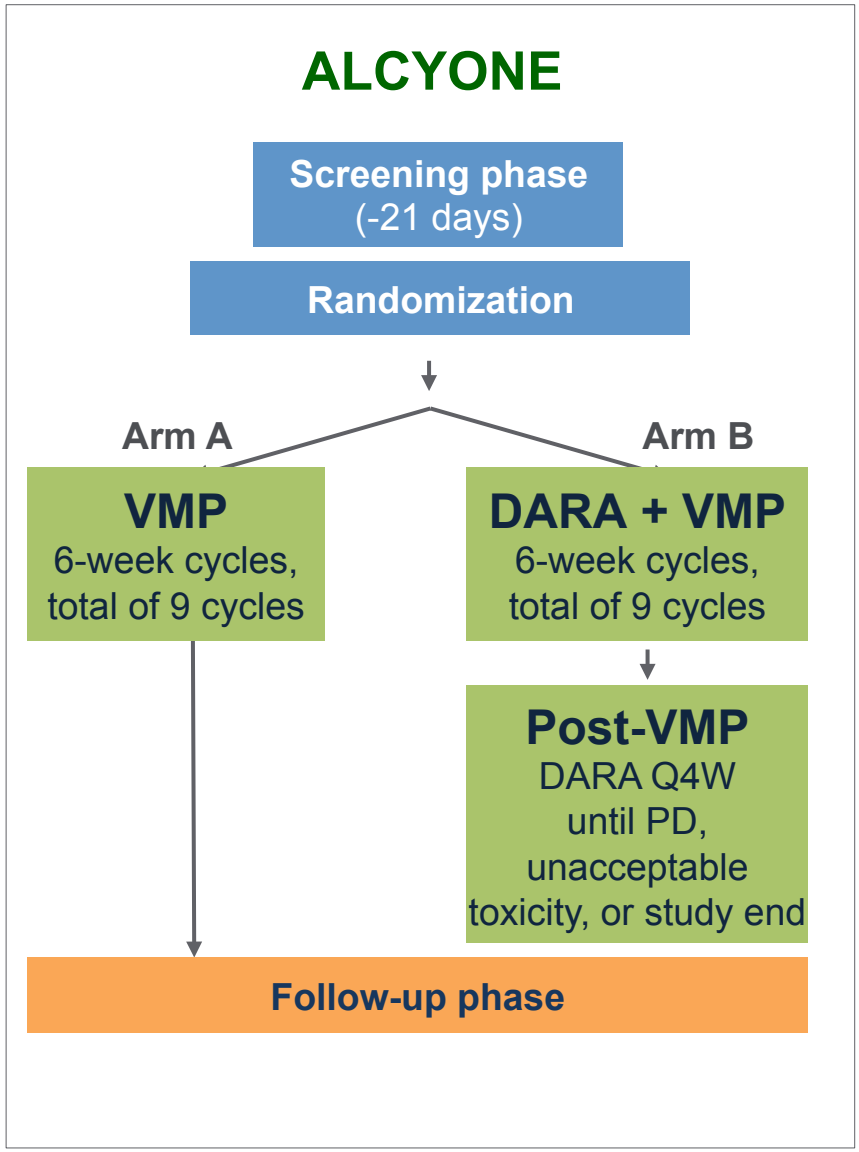
Phase 3: Elotuzumab + VRD induction/consolidation + maintenance in newly diagnosed MM (GMMG-HD6)



Phase 3: Daratumumab + VTD induction/consolidation + maintenance in newly diagnosed MM (CASSIOPEA)



Ongoing daratumumab studies in the non-transplant setting



THE ISSUE OF TOLERABILITY

A Phase 3 Prospective, Randomized, International Study (MMY-3021) Comparing SC vs IV Bortezomib in Patients with R/R MM

Peripheral Neuropathy (PN)

	Bortezomib IV (N=74)	Bortezomib SC (N=148)	P-value
Any PN			**.04**
Grade			**.01**
Grade			**.03**
Risk fac			
Grade 1 PN at baseline	28	23	
Diabetes at baseline	11	13	
Exposure to prior neurotoxic agents	85	86	
ORR (CR + PR)	**42**	**42**	**0.99 (0.71, 1.37)**

Bort sc available since 2012

Moreau P et al. Lancet Oncol 2011

VMP BW a OW
beneficio clinico e dose cumulativa

Dopo 9 cicli	VMP VISTA	VMP OW
5-year OS (%)	**46**	**51**
mOS (m)	56,4	60,6
Total planned dose, mg/m^2	67.6	46.8
Median cumulative dose, mg/ m^2	**38.5**	**40.3**
% of planned dose	57	86.1

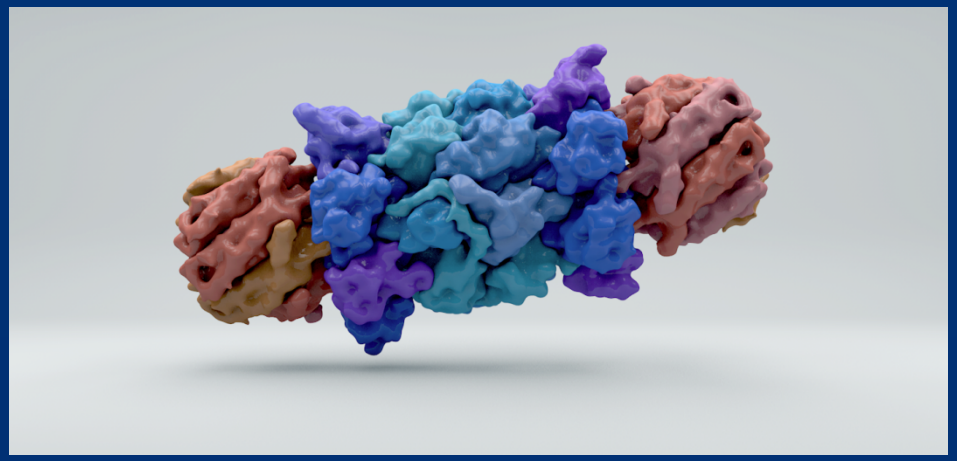
L' outcome è dato dalla **dose cumulativa** somministrata e dal **completamento** della **terapia (9 cicli)**

San Miguel *et al*. J Clin Oncol 30 2012 ;41:61-80; Palumbo A, et al. ASH 2012. Abstract 200

CARFILZOMIB

- Epoxyketone

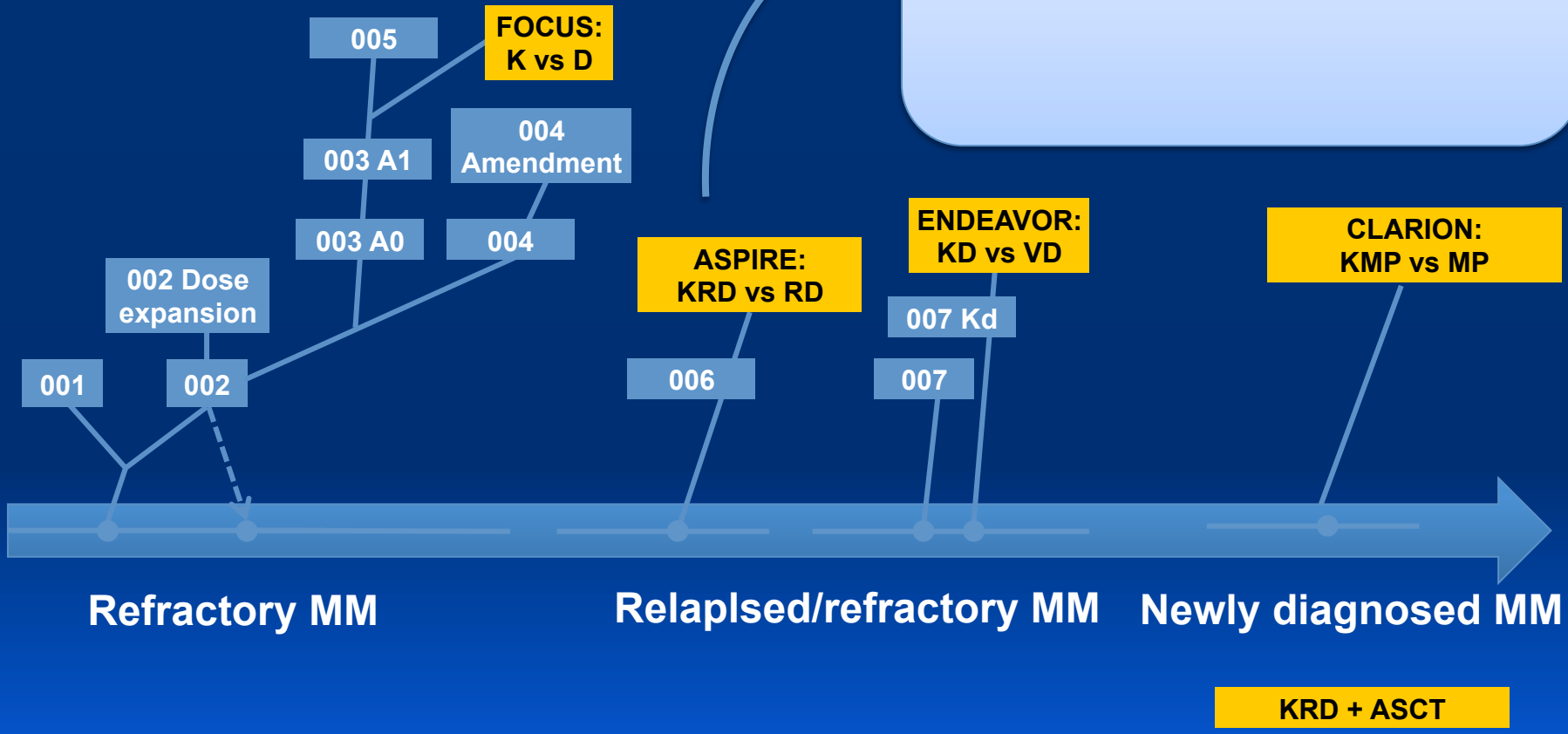
- **Inibitore irreversibile**
  - Lega subunità β5 (chymotrypsin-like) del core 20S [1,2]
  - Rispetto a bortezomib[1]
    - > selettività per β5
    - < attività off target
  - Estensiva penetrazione nei tessuti tranne SNC
  - ↑ apoptosi (caspasi 3,7,8,9), NOXA, ER, JNK
  - ↑ attività osteoblastica
- Somministrazione ENDOVENOSA



1. Kortuem KM, Stewart AK. Blood 2013;121:893–7;
2. Moreau P. Blood 2014;124:986–7.

Carfilzomib clinical: development in multiple myeloma

2015: KRD FDA and EMA approved for the treatment of MM who have received **at least one prior therapy**



Amgen Europe. Kyprolis summary of product characteristics, 2015.

ASPIRE Study Design

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

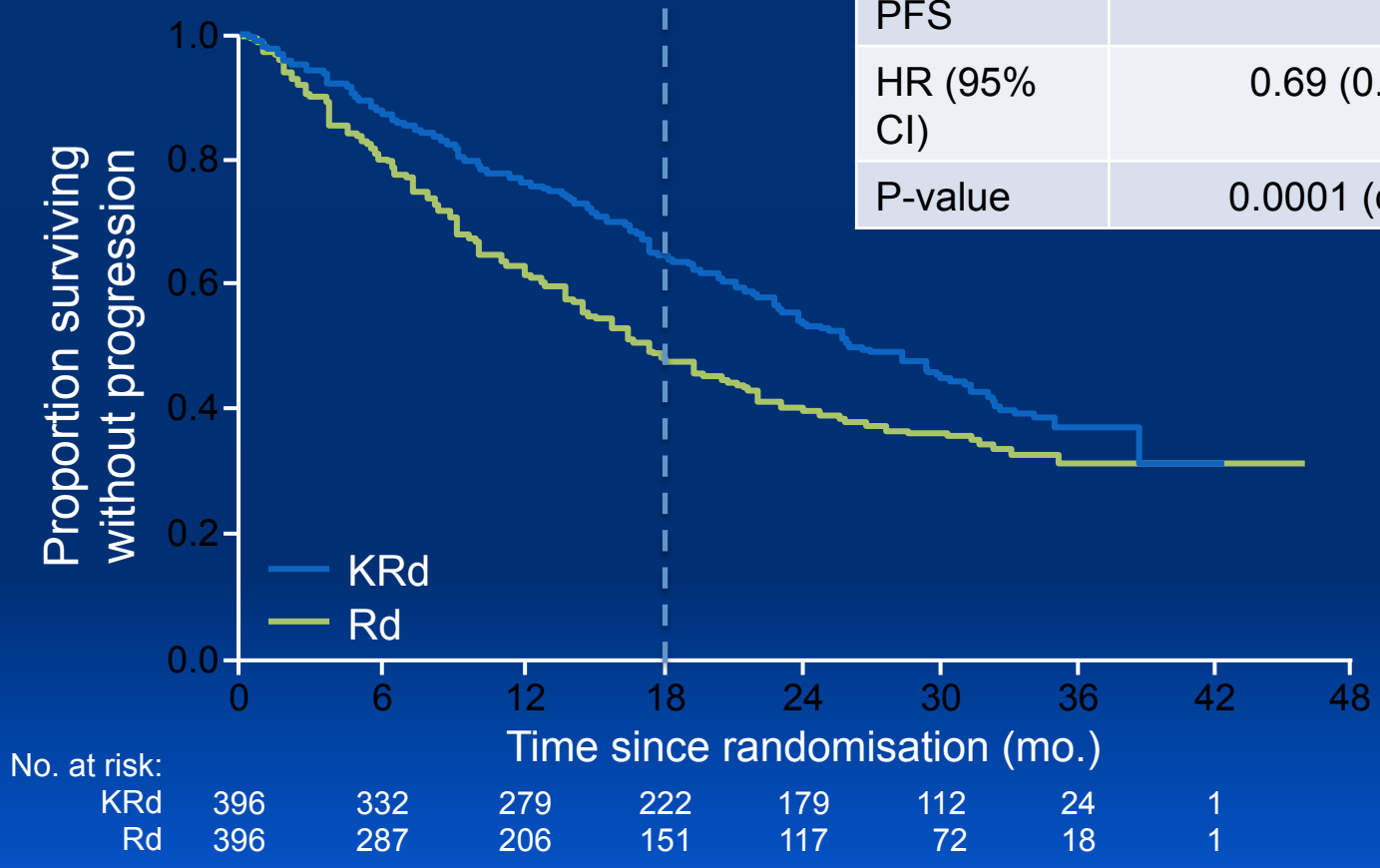
Lenalidomide 25 mg *Days 1–21*

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

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

ASPIRE: significantly longer PFS with KRd vs Rd (primary endpoint)

	KRd (N = 396)	Rd (N = 396)
Median PFS	**26.3 mo.**	**17.6 mo.**
HR (95% CI)	0.69 (0.57–0.83)	
P-value	0.0001 (one-sided)	



No. at risk:

KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

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

ENDEAVOR Study Design

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

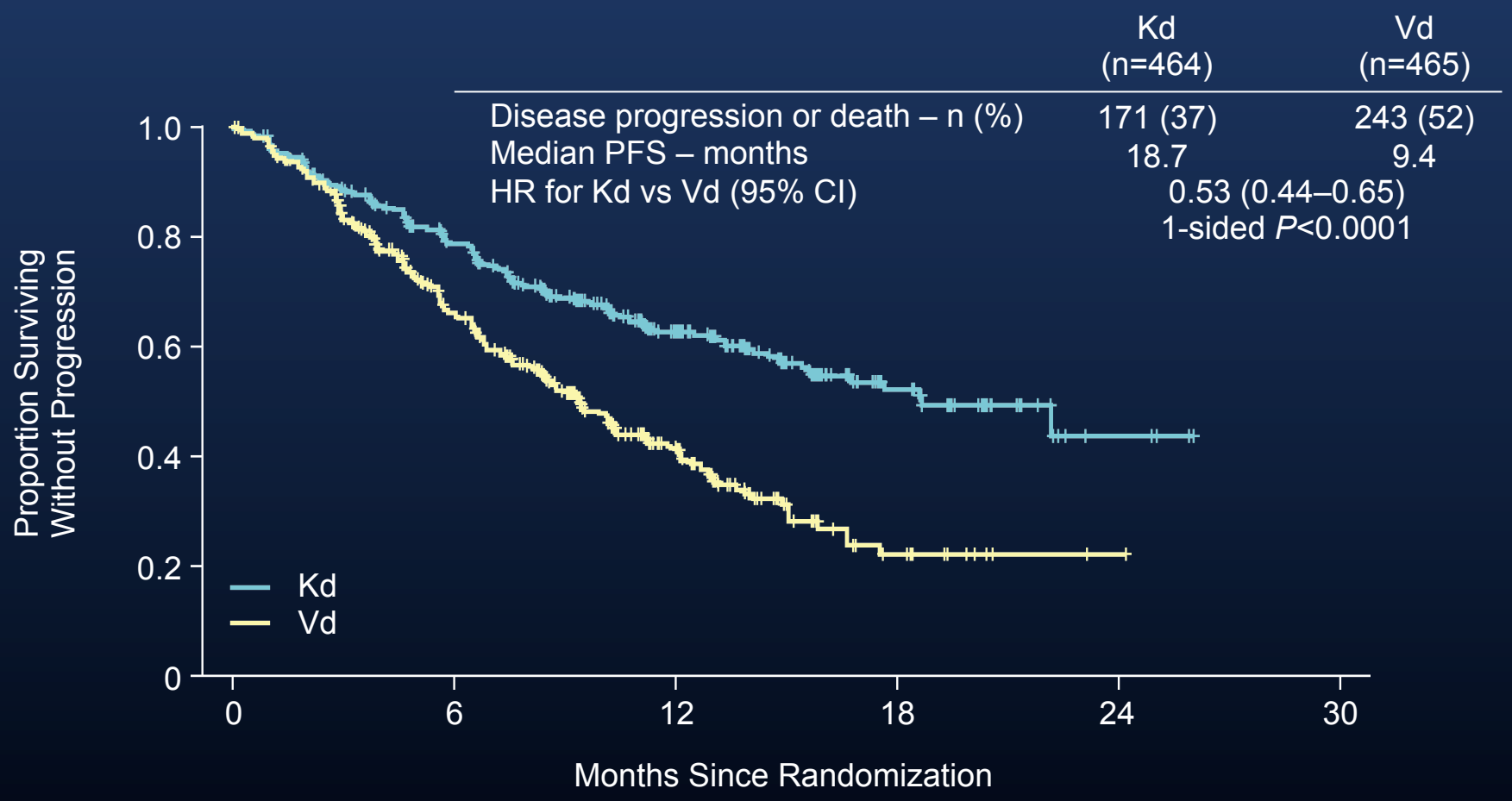
Dexamethasone 20 mg

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

21-day cycles until PD or unacceptable toxicity

Dimopoulos MA, et al. Lancet Oncology 2015

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



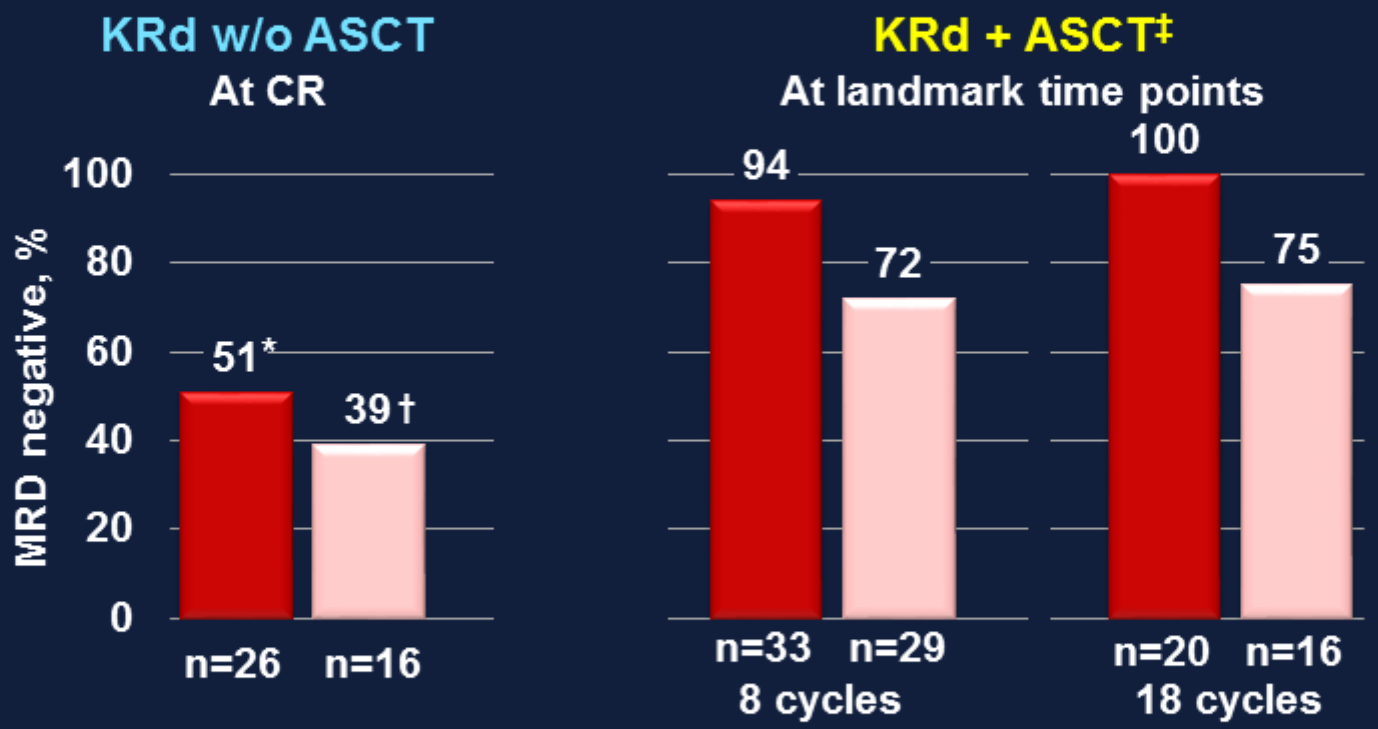
- **Median follow-up: 11.2 months**

Dimopoulos MA, et al. Lancet Oncology 2015

MRD Evaluation

Multiparameter Flow Cytometry (MFC)
10 color
Sensitivity: 10^{-4} – 10^{-5}

Next generation sequencing (NGS)
Adaptive Biotechnologies
Sensitivity: 10^{-6}



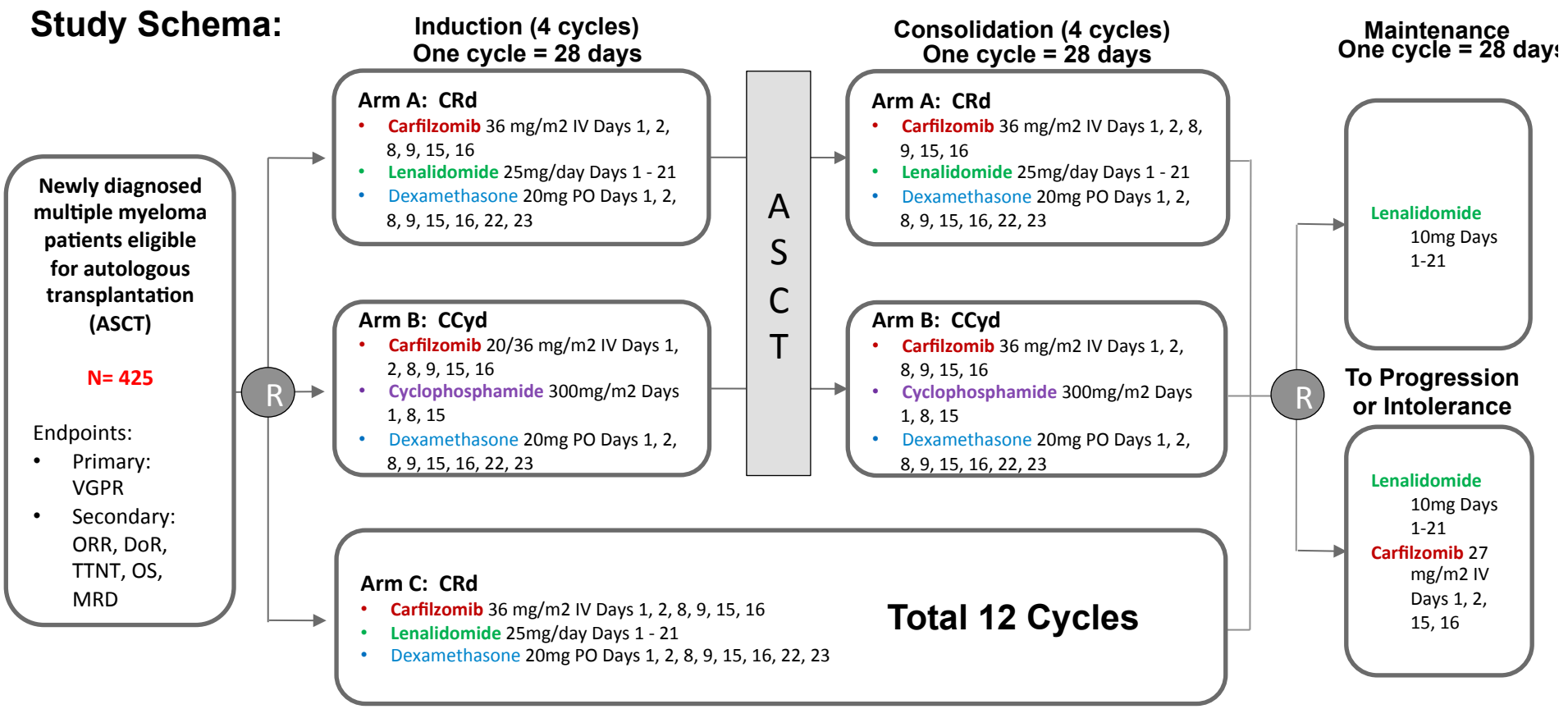
*Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR

†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS

‡Actual rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles regardless of level of response with all pts achieving sCR as their best response

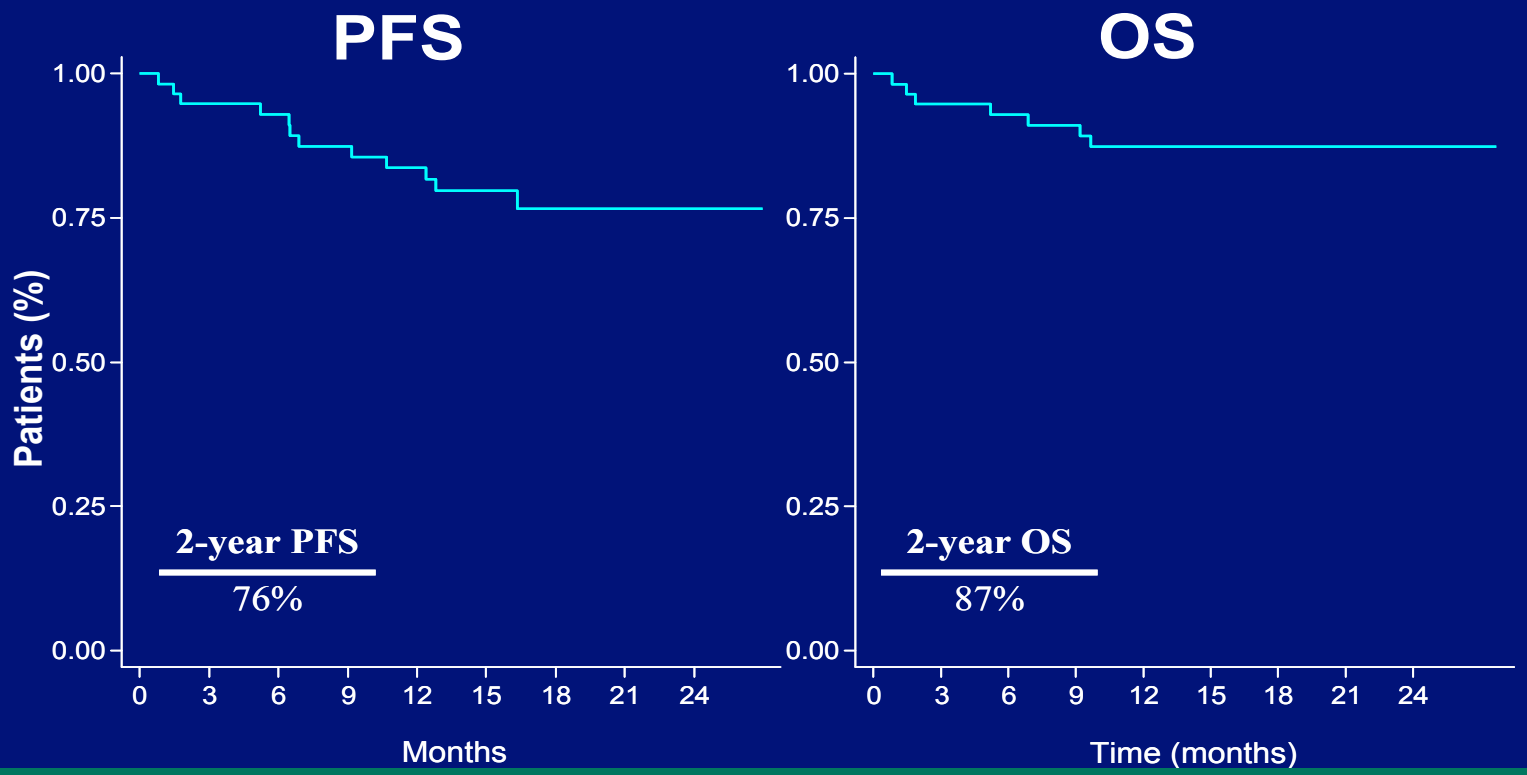
Jakubowiak A et al, EHA 2016

FORTE study design



A Phase II Study with Carfilzomib, Cyclophosphamide and Dexamethasone for NDMM non ASCT candidates

Median follow-up, months (range): 18.1 (2.8-28.3)



	CCyd	MPT	VMP	Rd
Response rates				
≥ VGPR	77%	36%	41%	40%
nCR/CR/sCR	47%	27%	30%*	14%

Bringhen S et al. Blood 2014

Nonhematologic AEs Occurring in ≥20% of Patients in Either Group
Safety Population (n=919)

AE, %	Kd (n=463)		Vd (n=456)	
	All grade	Grade ≥3	All grade	Grade ≥3
Nonhematologic AEs (preferred term)				
Diarrhea	31	4	38	8
Fatigue	29	5	29	7
Dyspnea	29	5	13	2.2
Pyrexia	28	2.4	14	0.7
Constipation	15	0.4	27	2.0
Peripheral neuropathy	9	1.3	27	5
Insomnia	25	1.5	26	2.4
Cough	25	0	14	0.2
Hypertension	25	9	9	3
Peripheral edema	22	0.9	17	0.7
Asthenia	20	4	16	3

AE, adverse event; Kd, carfilzomib and dexamethasone; Vd, bortezomib and dexamethasone.

MARIZOMIB

Metabolita di Actinomicete marino (*Salinospora Tropica*)

E' il primo PI naturale

Non contiene catene peptidiche nella sua struttura

Legame IRREVERSIBILE con CT-L(β5), T-L(β2) e < con C-L(β1)

Inibisce via canonica di NFkB e ↓ secrezione di IL6, TNFα,
Effetto proapoptotico mediato da caspasi 8
Contrasta la resistenza all'apoptosi di cell con overespressione di BCL2 mutato
Effetto antiangiogenetico

Phase 1 Clinical Trial of Marizomib (NPI-0052) in Patients with Advanced Malignancies including Multiple Myeloma: Study NPI-0052-102 Final Results. Harrison et Al. Clinical Cancer Res 2016

INIBITORI ORALI DEL PROTEASOMA

OPROZOMIB

Derivato da Carfilzomib, inibitore IRREVERSIBILE

IXAZOMIB (MLN9708, MLN2238)

Inibitore REVERSIBILE

Conclusion

- PIs changed the therapeutic scenario in MM

-Bortezomib , first in class, demonstrated high activity in R/R MM, newly diagnosed ASCT eligible and ineligible patients

-Route and schedule of administration of bortezomib improved tolerability

-Bortezomib became a backbone for combination therapies with newer agents

-II generation PIs: higher activity and improved tolerability?