HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

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Treatment of Multiple Myeloma: current challenges and future perspectives

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What should be the treatment goal in Symptomatic MM patients?

To search for an appropriate balance between treatment efficacy, toxicity & costs

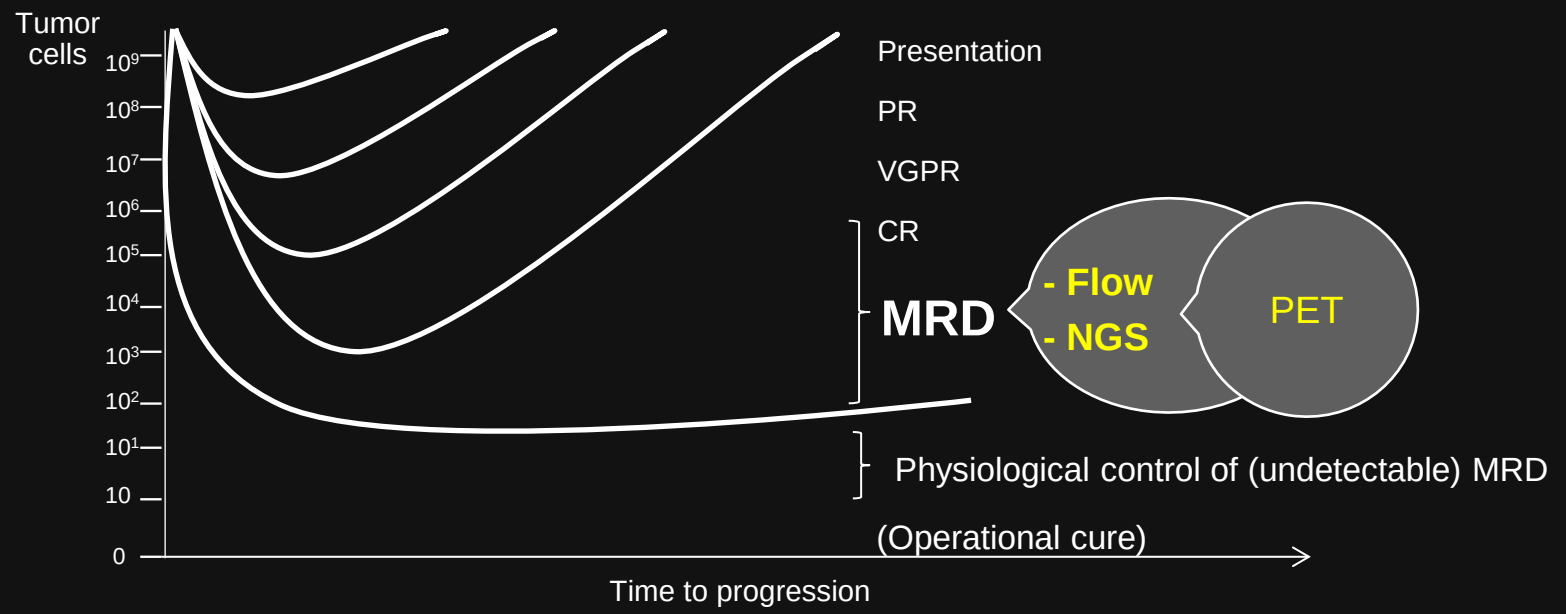
- **In frail patients (> 85y)**
  …….to ensure QoL & avoid additional costs of expensive treatments

- **In fit elderly patients (65-85y) & young ones with severe co-morbidities ……**
  treatment goal should be to prolong survival and ensure QoL

- **In young patients (<65y) …**In reference centers & large cooperative groups
  ……to investigate therapeutic schemes with a cure in the horizon

Optimizing Treatment Monitoring in MM

MRD techniques will contribute to both a better definition of response and to monitoring the efficacy of intensification and maintenance therapies… to tailor treatment & to avoid both under & over treatments



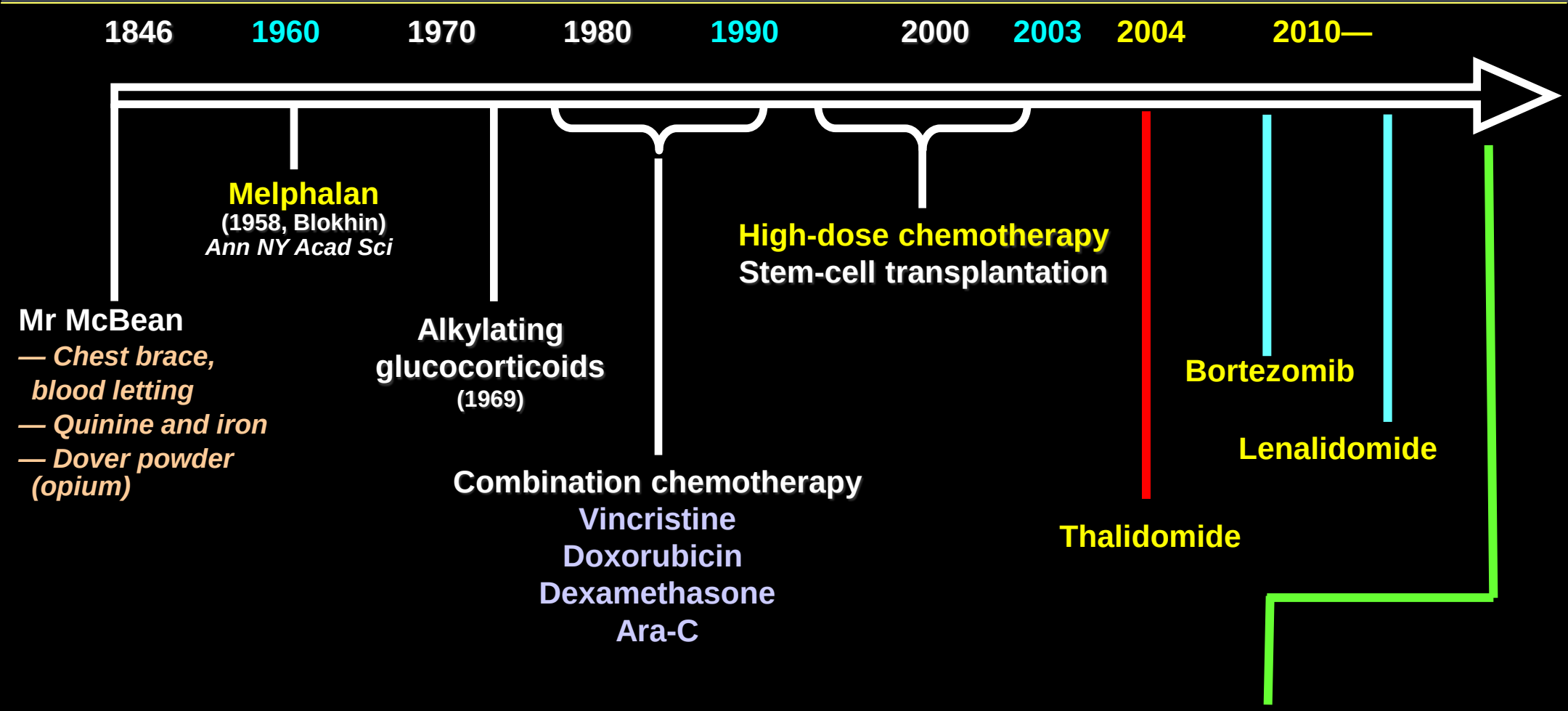
IMWG criteria for MRD in multiple myeloma

Response subcategory		Response criteria
IMWG MRD negativity criteria (Requires CR as defined below)	Sustained MRD-negative	MRD negative in the bone marrow (by next-generation flow cytometry or next-generation sequencing) and by imaging as defined below, confirmed 1 year apart; subsequent evaluations can be used to further specify the duration of negativity (e.g. MRD negative at 5 years)
	Imaging MRD-negative	MRD negative as defined below (by next-generation flow cytometry or next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or a validated equivalent method), with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD-negative	Absence of clonal plasma cells by next-generation sequencing on bone marrow aspirates in which the presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or a validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher

IMWG, International Myeloma Working Group

Kumar SK, et al. *Lancet Oncology* 2016

Myeloma treatment in the last century



HDACs, Histone deacetylases; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors

Young "Symptomatic/active" MM Patients:

"Old" Transplant candidate approach

Induction (VAD or TD)

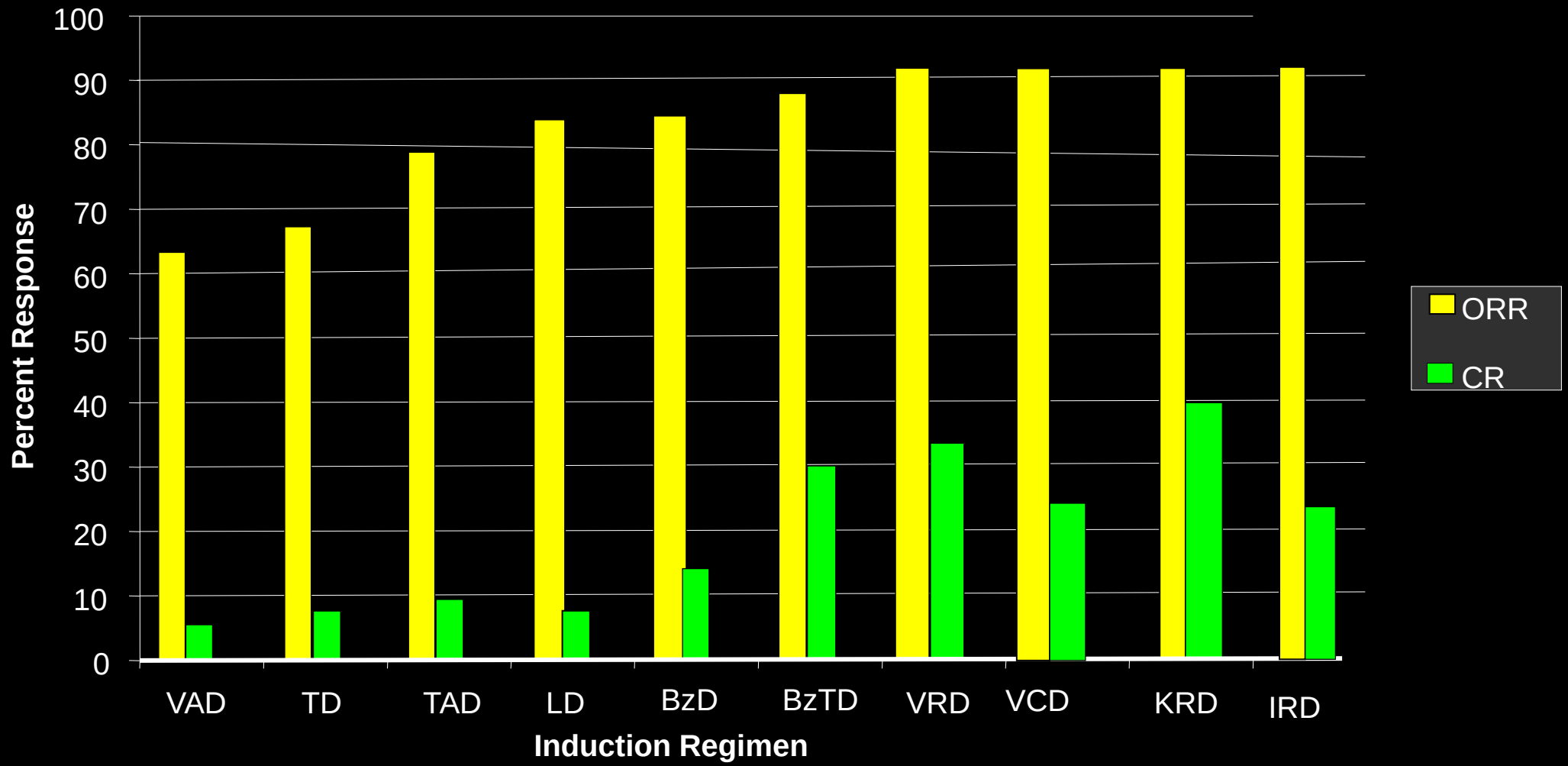
↓

ASCT (Mel 200)

↓

Maintenance (IFN +/- Predn)

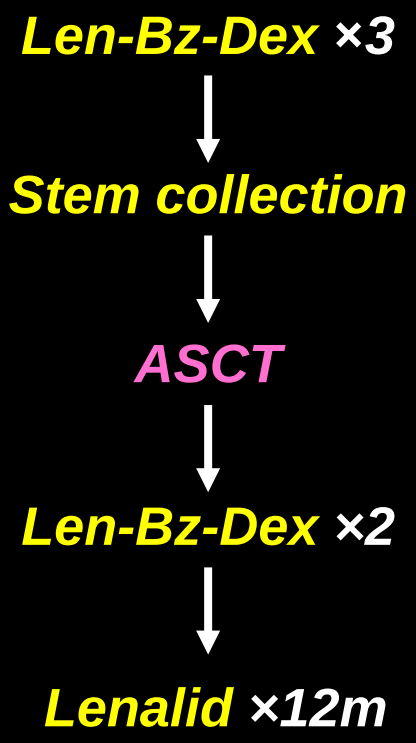
Have the new induction regimens improved outcome as compared to VAD or TD?: *Response to induction*

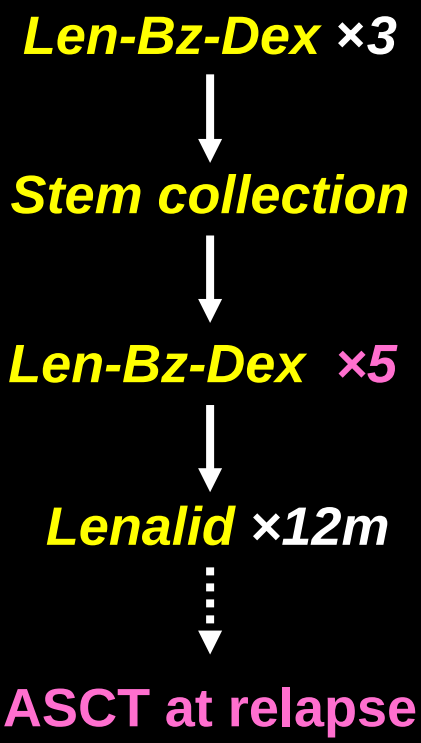


This translates into prolonged PFS: VTD or PAD >VAD or TD

- *Adapted from: How I treat MM in younger patients by Stewart K, Richardson P , San Miguel JF . Blood 2009; 114: 5436-43*

The Debate…ASCT: Up-Front or at Relapse



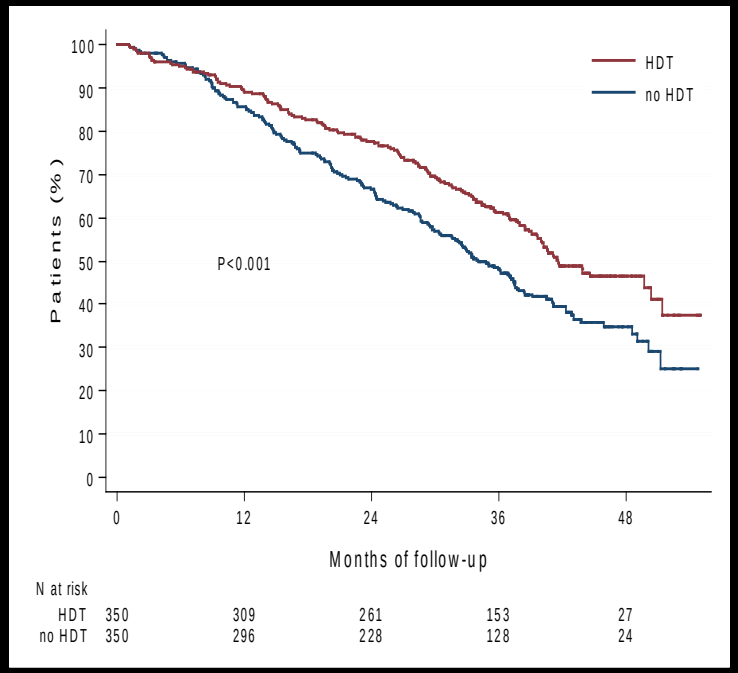


NCI Clinical Trial Identifier NCT01191060.

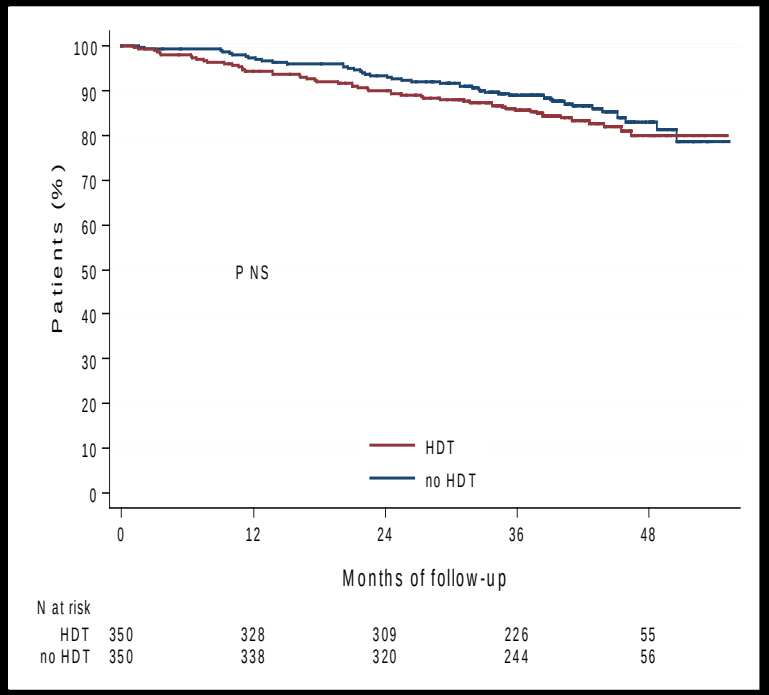
IFM 2009: PFS and OS

	RVD arm	vs	Transplant arm
• CR:	49%		59%
• ≥ VGPR:	78%		88%

PFS

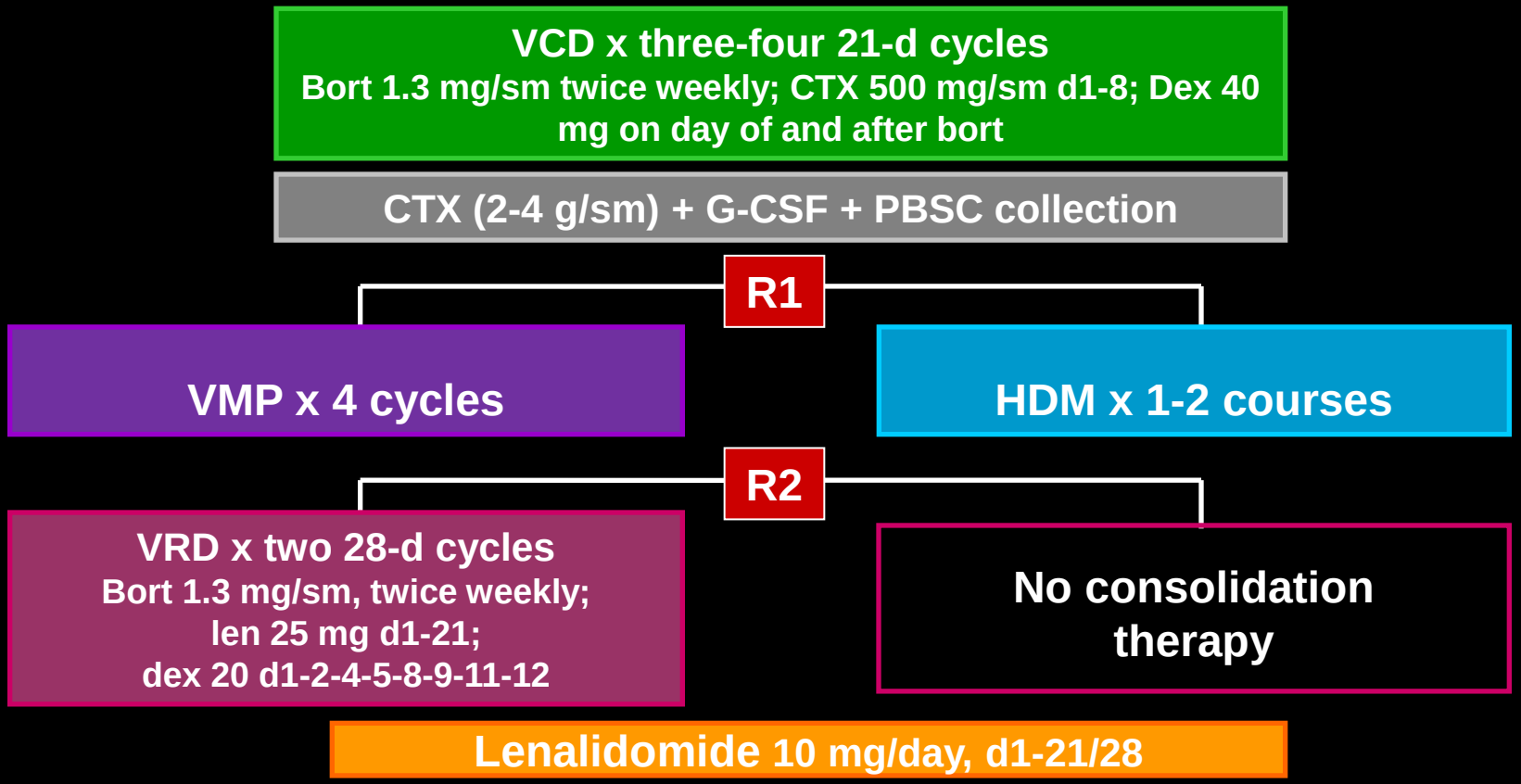


OS



Attal M. ASH 2015

EMN02/HO95 MM trial: study design (n= 1192)



- Upfront ASCT was associated with a significant improvement in PFS vs VMP in the overall patient population (Median PFS: NR vs 46m)
- Superior PFS with ASCT vs VMP was retained across prespecified subgroups of patients at low (NR vs 46m) and high risk (42 vs 32m)

Cavo ASCO 2016)

Comparison of early vs. late ASCT

Pooled analysis of two trials (n=529)

- **GIMEMA MM-RV-209……. Rd-MPR vs. Rd-Mel200** (2nd rand: +/- maintenance)
- **EMN MM-RV-441……..... Rd-CRD vs. Rd-Mel200** (2nd rand: R vs RP Maint.)

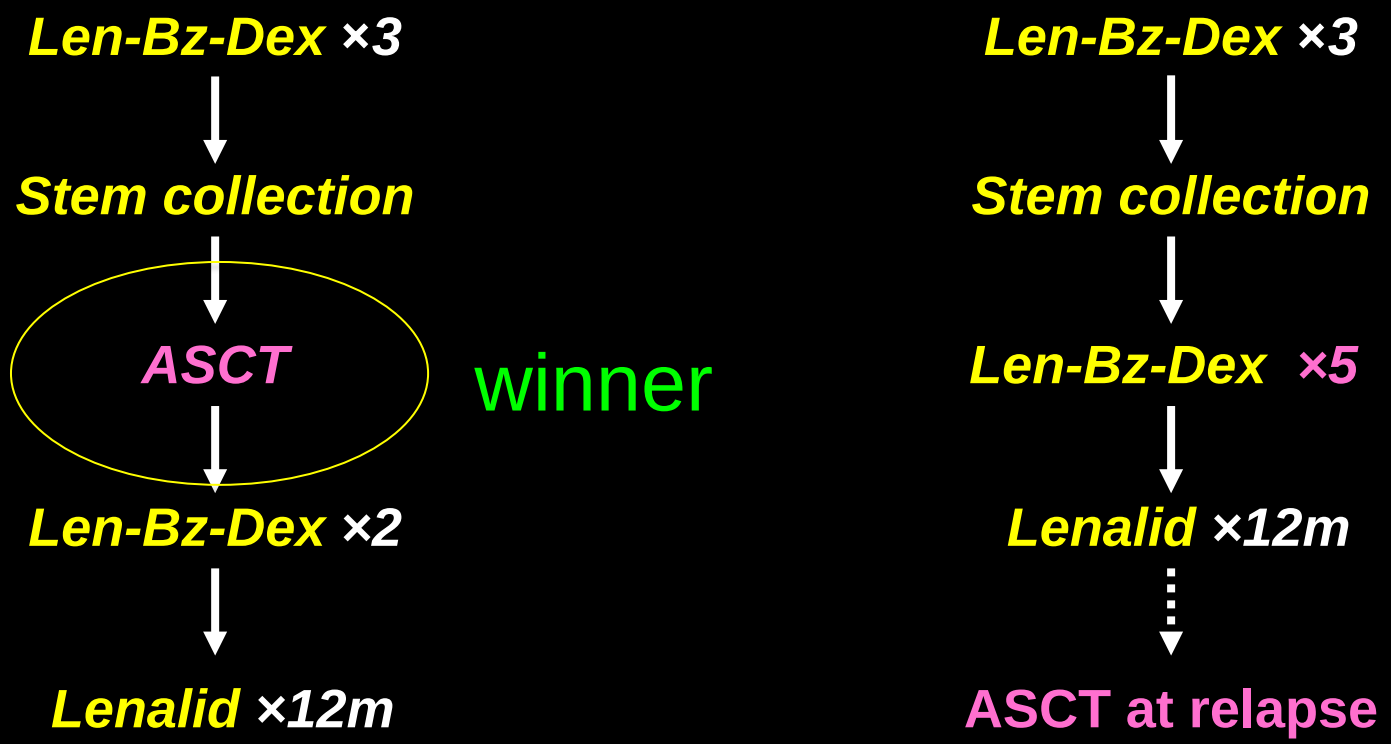
	Early ASCT	Late ASCT	P
PFS (months)	**42**	**24**	**< 0.001**
4-year OS	**84%**	**70%**	**<0.001**

only 53% of CCT patients received ASCT at relapse

Gay et al et al. EHA 2016;
Palumbo et al NEJM 371:895-905, 2014;

Gay (EHA 2016): (benefit in all subgoups, but higher in good prognosis (Stage I and low risk cytog)

The Debate…ASCT: Up-Front or at Relapse



NCI Clinical Trial Identifier NCT01191060.

Options after ASCT

Consolidation

- **Improve response/deeper following therapy**
  - *By administration of treatment for a limited period*

VTD: Upgrade to CR post-consolidation by 30% (molecular and PFS)

Cavo et al Blood 2012

Maintenance

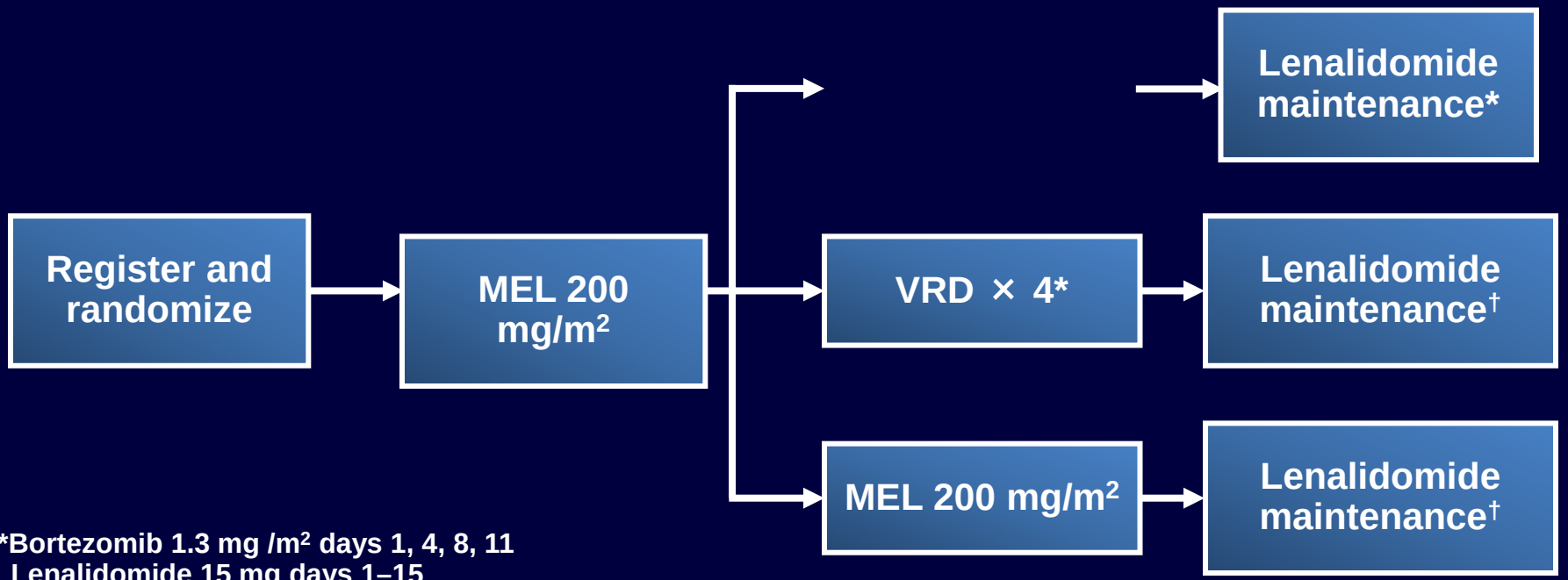
- **Maintain response achieved following therapy**
  - *By administration of treatment for prolonged period*

- *Thalidomide (6 trials)… PFS: + 6/6 OS: +3/6*
- *Bortezomib (2 Trials)…. PFS: + 2/2 OS: +1/2*
- *Lenalidomide (3 trials)… PFS: +3/3 OS: + 1/3*

Morgan et al. Blood 2012;119(1):7-15; Kagoya et al. Leuk Res 2012;36(8):1016-21; Attal et al. ASH 2013 (Abstract 406) 2013, Gay et al. ASH 2013 (Abstract 2089), Sonneveld et al. ASH 2013 (Abstract 404), Rosinol et al. ASH 2012 ;

Attal M. NEJM 2012, 366: 1782-91 *McCarthy P, NEJM 2012, 366: 1770-81* *Palumbo et al NEJM 371:895-905, 2014*

BMT CTN 0702: SCHEMA



*Bortezomib 1.3 mg /m² days 1, 4, 8, 11
Lenalidomide 15 mg days 1–15
Dexamethasone 40 mg days 1, 8, 15
†Lenalidomide 15 mg daily × 3 years

https://clinicaltrials.gov/ct2/show/NCT01109004.

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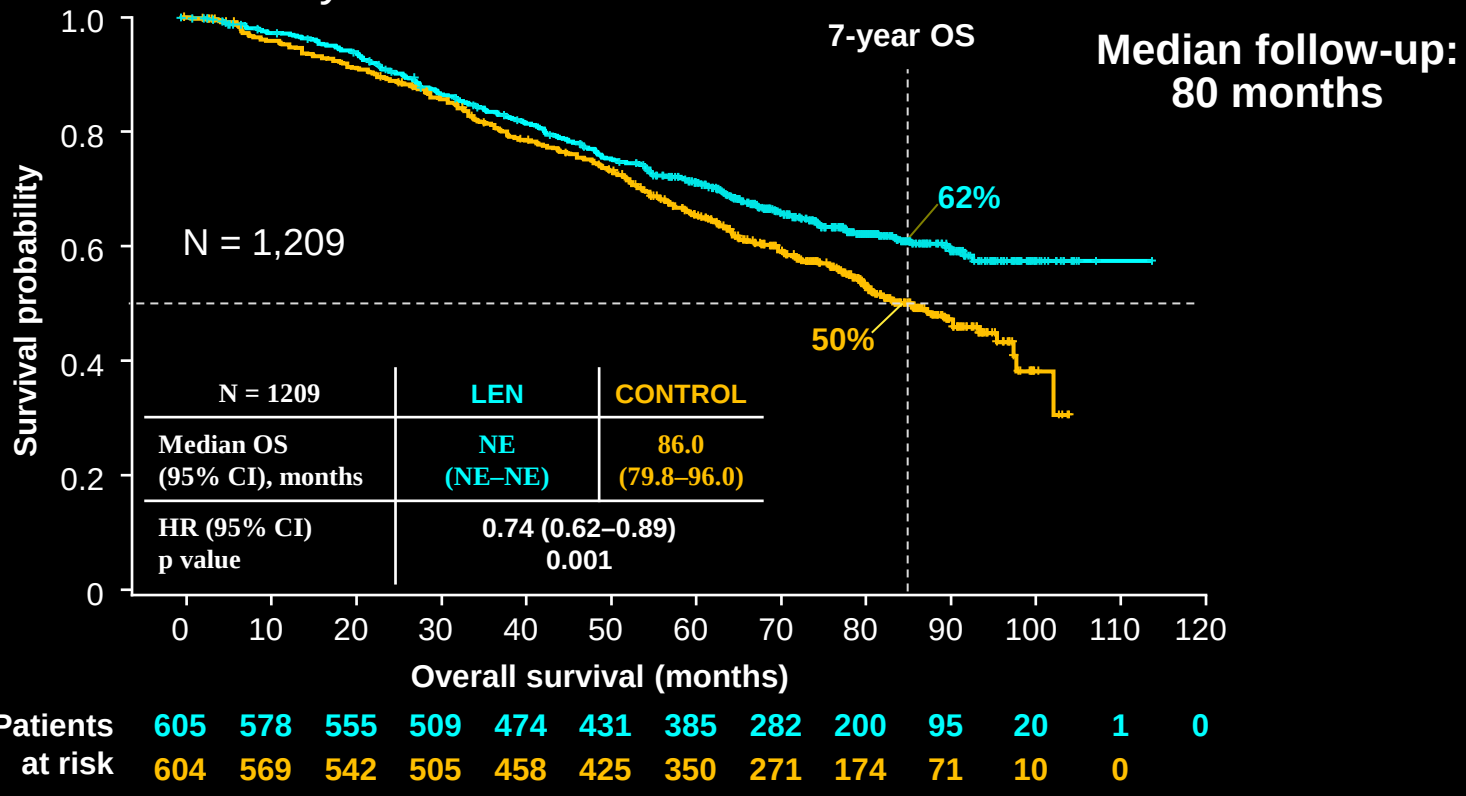
Attal M. NEJM 2012, 366: 1782-91 *McCarthy P, NEJM 2012, 366: 1770-81* *Palumbo et al NEJM 371:895-905, 2014*

Lenalidomide maintenance: OS meta-analysis

26% reduction in risk of death, representing an estimated 2.5-year increase in median survival[a]



The OS benefit was observed in all investigated subgroups of patients (except high-risk CA and ISS stage III)

LEN maintenance after ASCT can be considered a standard of care

[a] Median for LEN treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median 86 months; HR = 0.74) .

CA, cytogenetic abnormality; ISS, International Staging System; NE, not estimable.

Attal M, et al. J Clin Oncol. 2016;34 Suppl:abstract 8001.

Bortezomib maintenance therapy

Study details	n	Treatment	Outcome	
			PFS	OS
HOVON 65 MM/ GMMG-HD4[1]	413	PAD x 3 → HDM → bortezomib every 2 weeks for 2 years	34 months	90
Median follow-up: 91 months	414	VAD x 3 → HDM → thalidomide daily for 2 years	28 months p = 0.001	83 months RMS_{8y} (4.8 months) p = 0.04
PETHEMA/GEM[2]	89	VT (1 cycle bortezomib every 3 months, thalidomide daily) for 3 years	Significant PFS benefit for VT p < 0.0009	OS not significantly different between arms
Median follow-up: 34.9 months	87	Thalidomide (daily for 3 years)		
	90	Interferon-α2b (3 x per week for 3 years)		

HOVON 65 MM → PAD x3 → tandem HDM → bortezomib maintenance: benefit for patients with del(17p)

Bortezomib maintenance after double ASCT is effective in patients with del(17p)

Bortezomib administered at 1.3 mg/m^2 i.v. in both studies

HDM, high-dose melphalan; i.v., intravenous; PAD, bortezomib, doxorubicin, dexamethasone; RMS_{8y}, restricted mean survival time at 8 years; VAD, vincristine, doxorubicin, dexamethasone.

1. Sonneveld P, et al. Blood. 2015;126:abstract 27. Presented at ASH 2015.
2. Rosinol L, et al. Blood. 2012;120:334. Presented at ASH 2012.

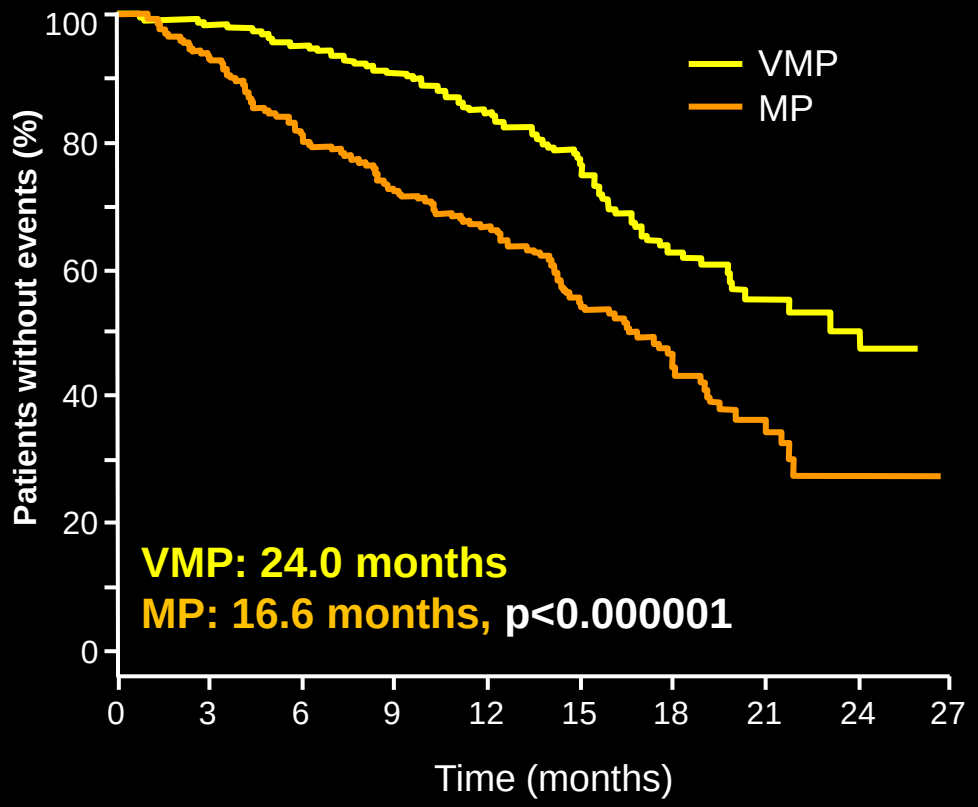
Maintenance therapy after ASCT: future

Sponsor/cooperative group	Treatment
	Lenalidomide-based
IFM/DFCI 2009	Lenalidomide x 1 year vs lenalidomide until DP
Myeloma XI	Lenalidomide vs lenalidomide + vorinostat vs no maintenance
GEM14MAIN	Lenalidomide vs lenalidomide + ixazomib for up to 2 years Patients with MRD will continue 3 additional years
GMMHD6	Lenalidomide-dexamethasone vs lenalidomide-dexamethasone + elotuzumab
GIMEMA	Lenalidomide vs lenalidomide + carfilzomib
SWOG	Lenalidomide vs lenalidomide + ixazomib until DP
US Cooperative group trials (pick the winner)	Lenalidomide vs lenalidomide + vaccination/lenalidomide x 2 years vs lenalidomide until DP Lenalidomide vs lenalidomide + ixazomib
AFT-40	Lenalidomide vs lenalidomide + durvalumab vs lenalidomide + daratumumab vs lenalidomide + ACY241
	Other
C16019 Takeda Millennium	Ixazomib for up to 2 years vs placebo
HOVON-IFM	Daratumumab vs placebo
CCT-PNK-004-mmy001	Human cord blood derived, cultured and expanded NK cells

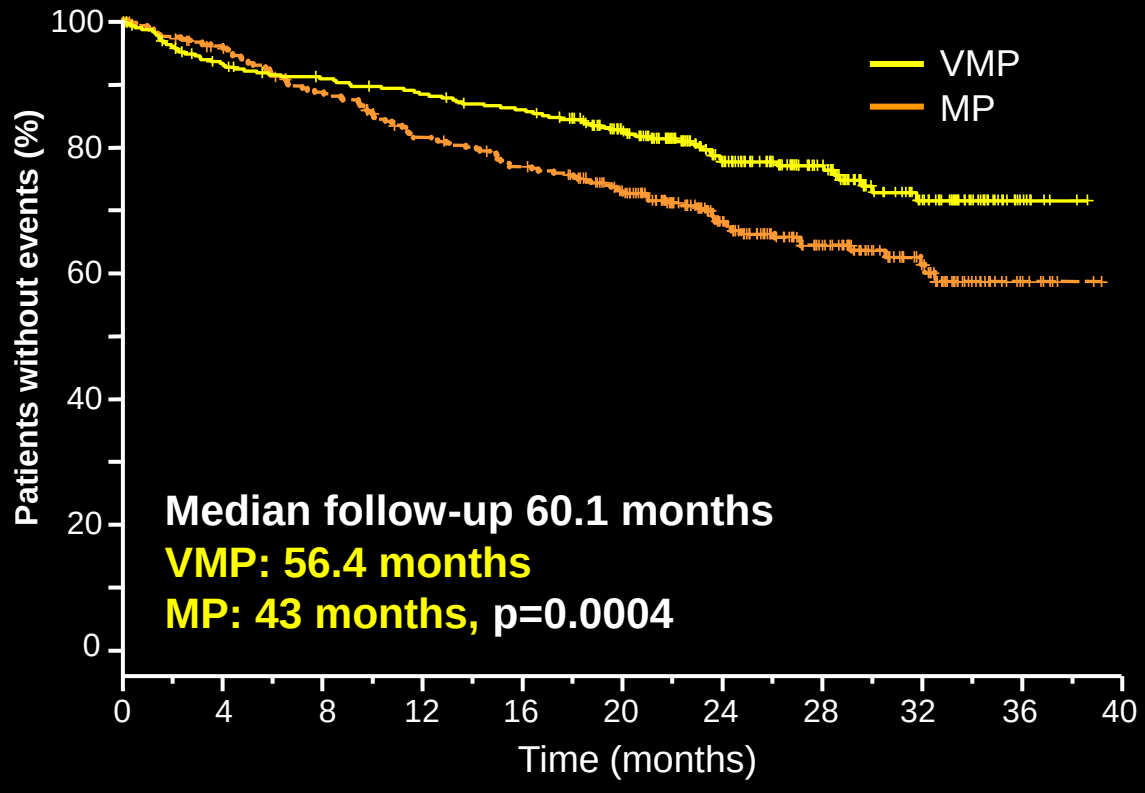
Developing early endpoints as surrogate markers for long-term outcomes and OS is critically important; otherwise, trials may continue for 10 years or longer

Elderly MM: bortezomib + MP (VMP) vs. MP (682 patients)

TTP[1]



OS: 13.3 months benefit[2]



*** Weekly and/or subcutaneous administration reduced PN (grade 3) from 14% to 5–3%[3]**

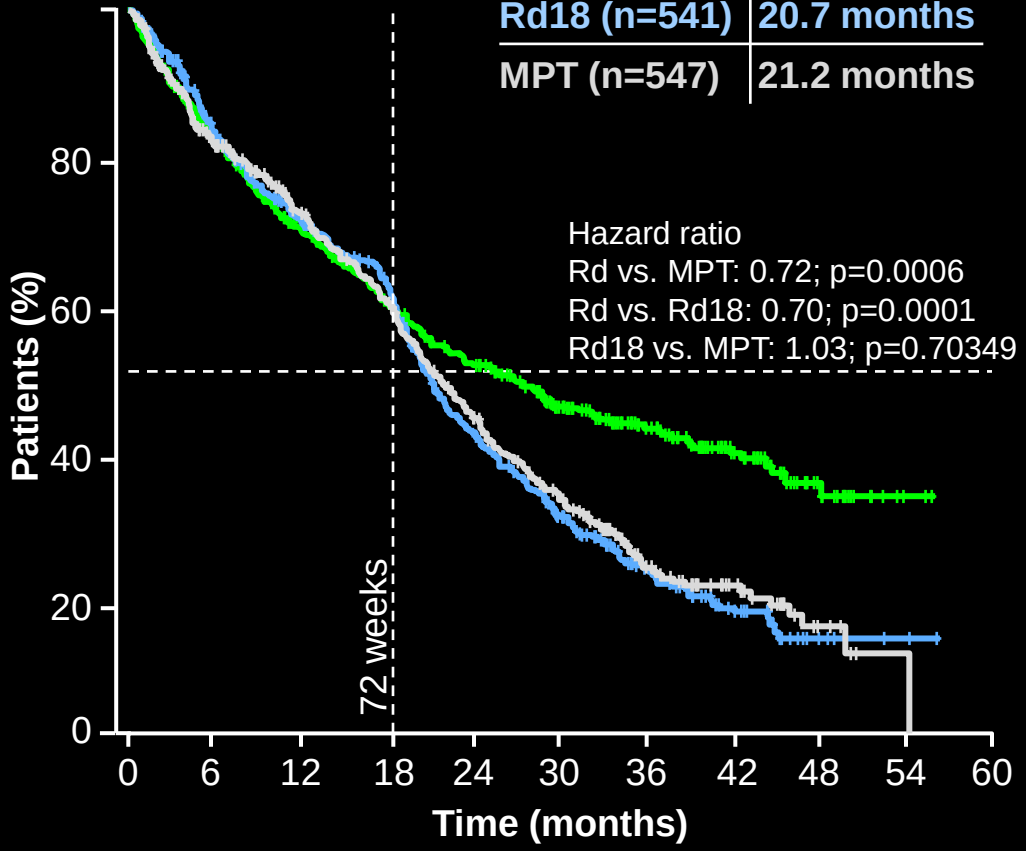
MP, melphalan and prednisone; PN, peripheral neuropathy; VMP, bortezomib, melphalan, and prednisone

1. Mateos MV, et al. *Lancet Oncol* 2010; 10: 934-942; (Palumbo A, et al. *J Clin Oncol* 2010; 28: 5101-5109.)
2. San Miguel J, et al. *N Engl J Med* 2008; 359: 906-917; 3. San Miguel J, et al. *Clin Oncol* 2013,31:448-455.

FIRST trial: LEN–DEX (18 cycles or continuous) vs. MPT

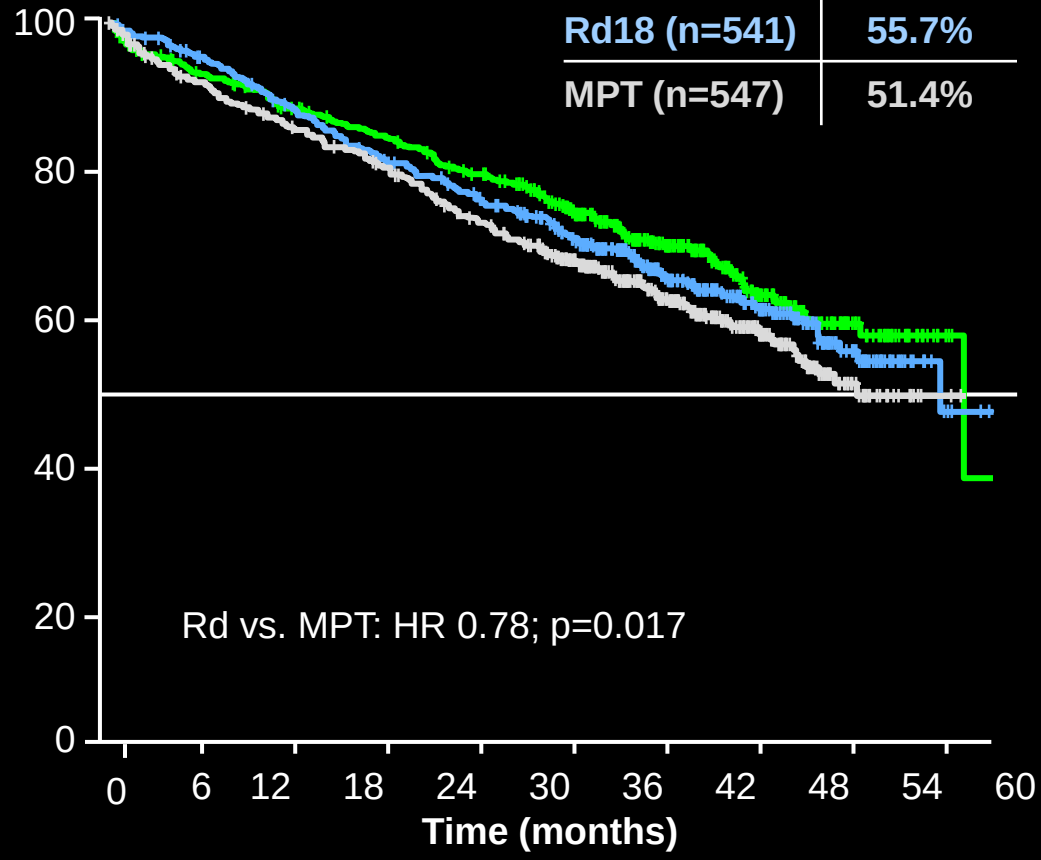
PFS

	Median PFS
Rd (n=535)	25.5 months
Rd18 (n=541)	20.7 months
MPT (n=547)	21.2 months



OS

	4-year OS
Rd (n=535)	59.4%
Rd18 (n=541)	55.7%
MPT (n=547)	51.4%



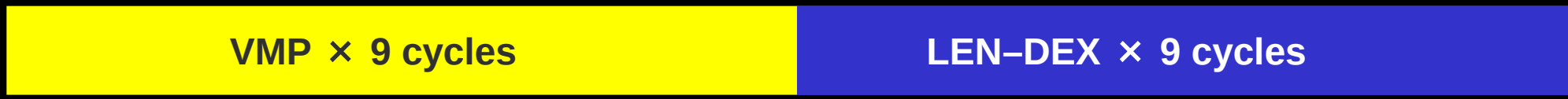
MPT, melphalan+prednisone+thalidomide; Rd, continuous lenalidomide+dexamethasone; Rd18, 18 cycleslenalidomide+dexamethasone

Benboubker L, et al. *N Engl J Med* 2014; 371: 906-917.

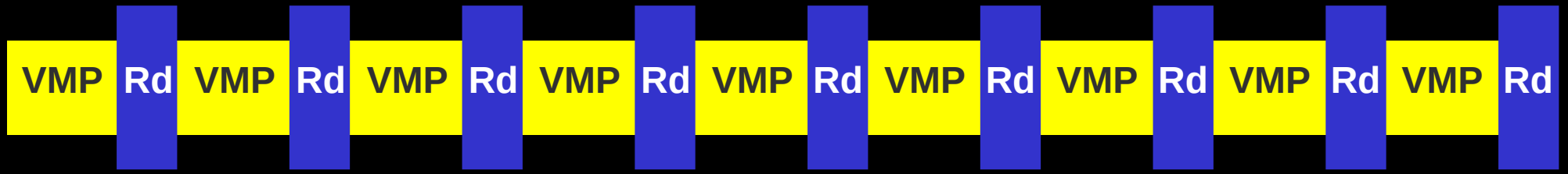
PETHEMA/GEM and GEM2010 trials

Symptomatic newly diagnosed MM patients >65 years

Sequential scheme



Alternating scheme*



Hypothesis:
— higher efficacy for the alternating scheme
— less probability of cell scape
— lower cumulative toxicity

74 weeks

**Half of the patients will start with VMP and half with Rd*

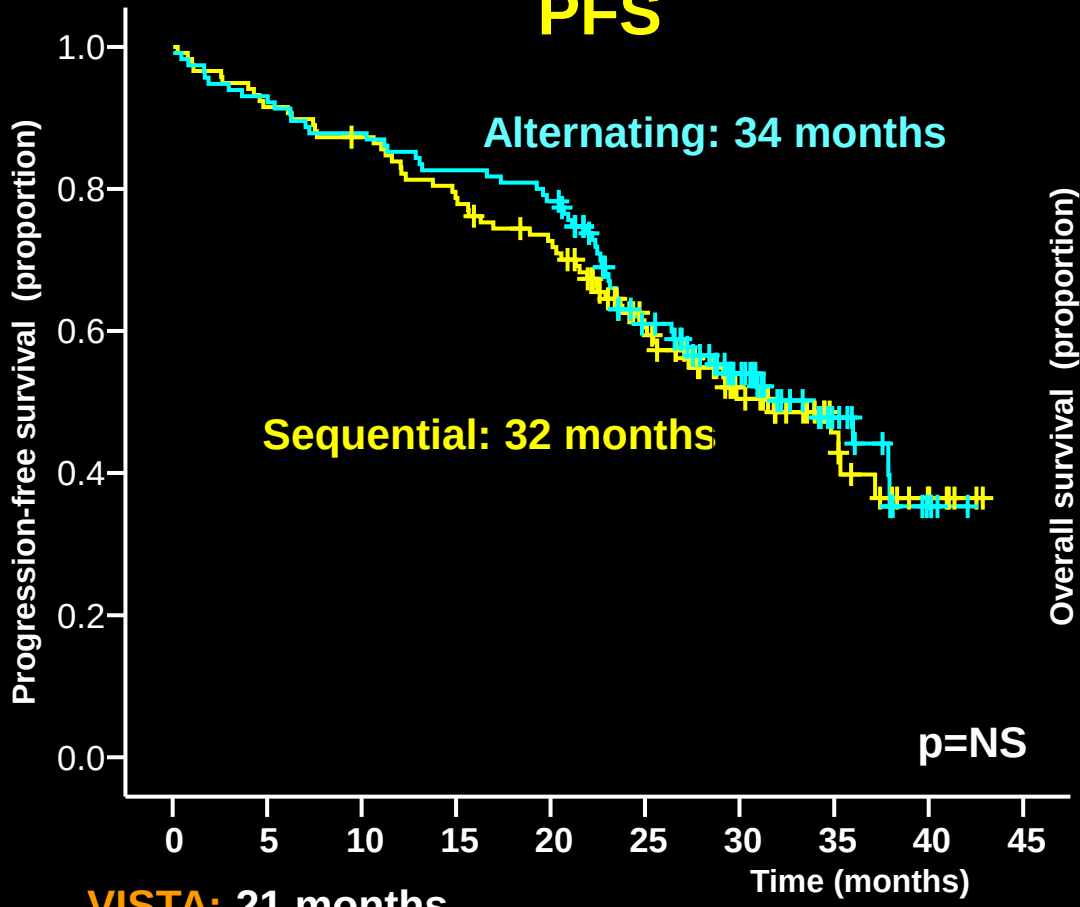
N=240 patients

VMP, bortezomib+melphalan+prednisone

Outcomes in terms of PFS and OS

Median follow-up: 30 months (9–43 months)

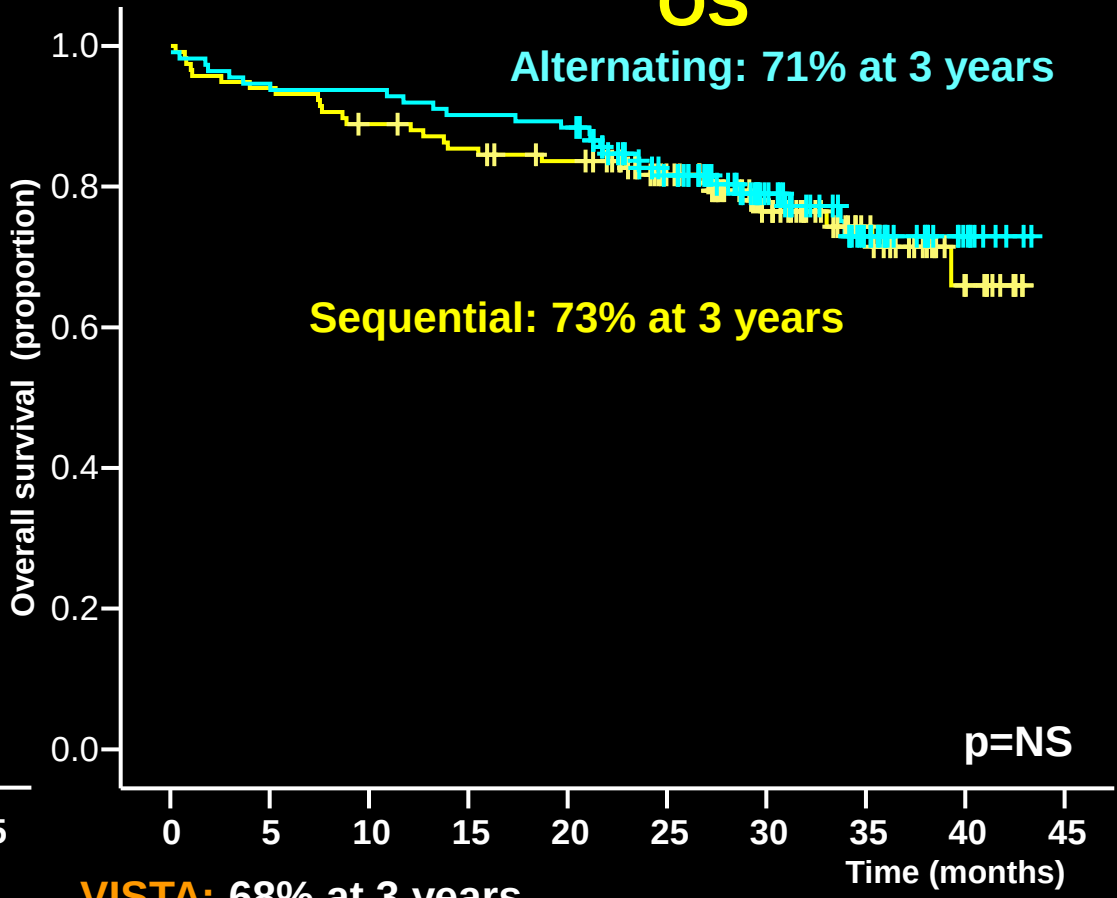
PFS



VISTA: 21 months

FIRST: 25 months (cont Rd); 21 months (Rd18)

OS



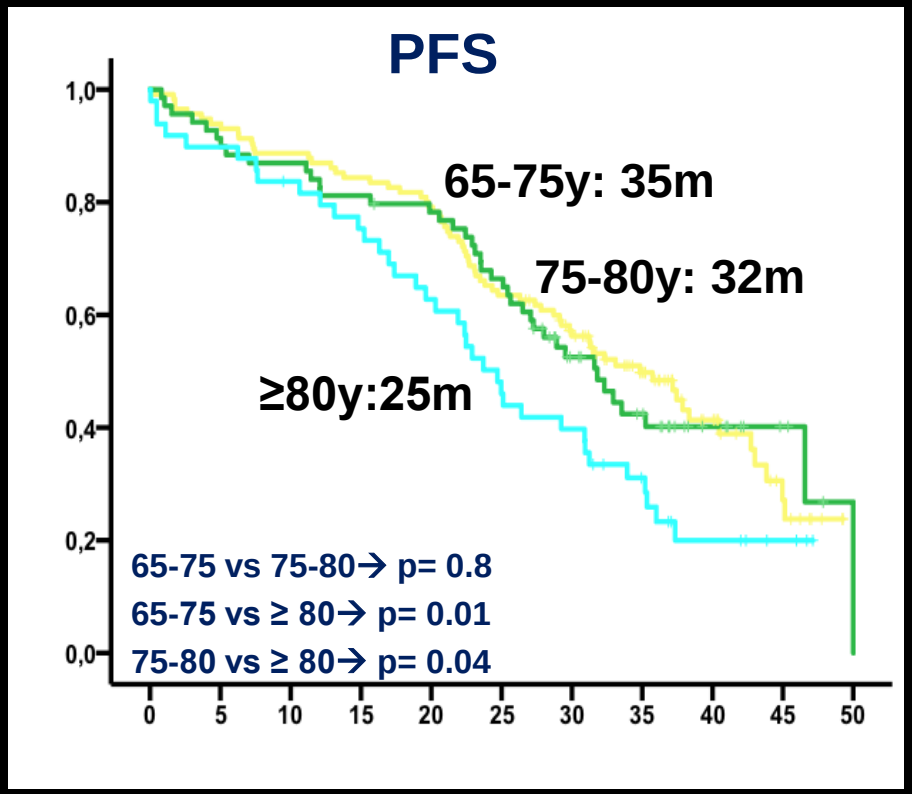
VISTA: 68% at 3 years

FIRST: 59% (cont Rd) and 56% (Rd18) at 4 years

Mateos MV, Blood 2016

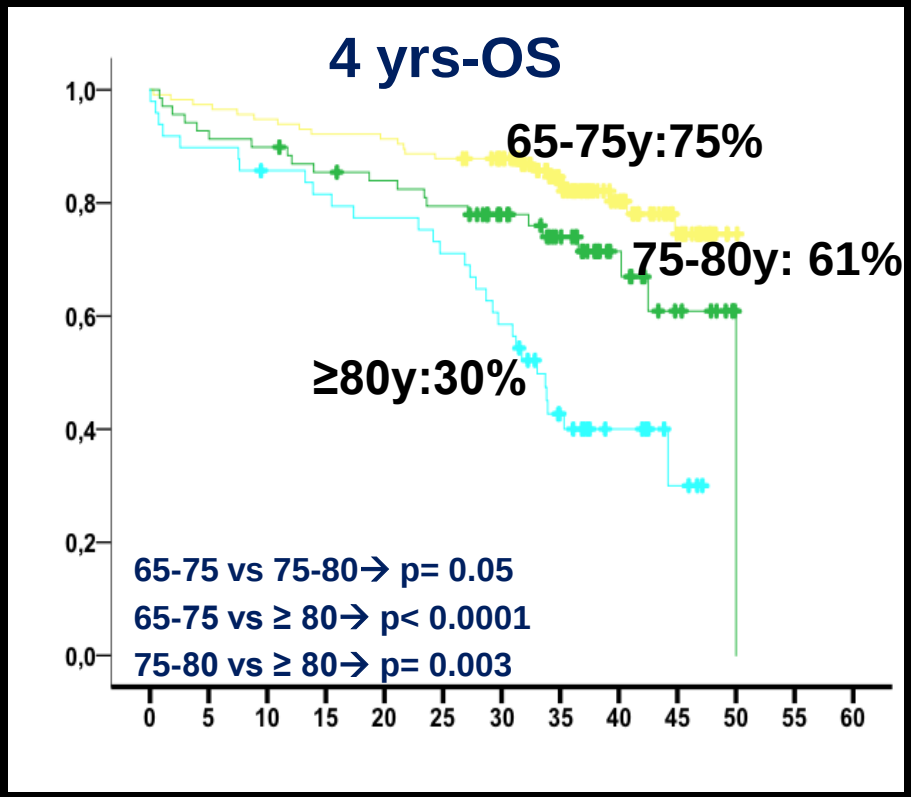
Outcome in terms of PFS and OS on ITT analysis (n=233)

Median follow-up: 37 (9-50)



VISTA: 21m

FIRST: 25m (cont Rd); 21m (Rd18)



VISTA: 68% at 3 yrs

FIRST: 70% at 3 yrs (cont Rd); 66% at 3yrs (Rd18)

Mateos MV et al. ASH2015

Future of the treatment for elderly MM patients

Alkylators-based regimens

MP

Alkylators-free regimens

IMiD's

VMP | Len-dex

Spanish standard of care for "fit" elderly NDMM patients

It is necessary to individualize the treatment in elderly patients according to the frailty

Future of the treatment for elderly MM patients

Alkylators-based regimens

MP

~~MPT~~

Six randomized trials: Benefit in PFS&OS...6m

VMP

One randomized trial: Benefit in PFS&OS

KMP = VMP
VMP-Dara vs VMP
CyBorD-SAR

Alkylators-free regimens

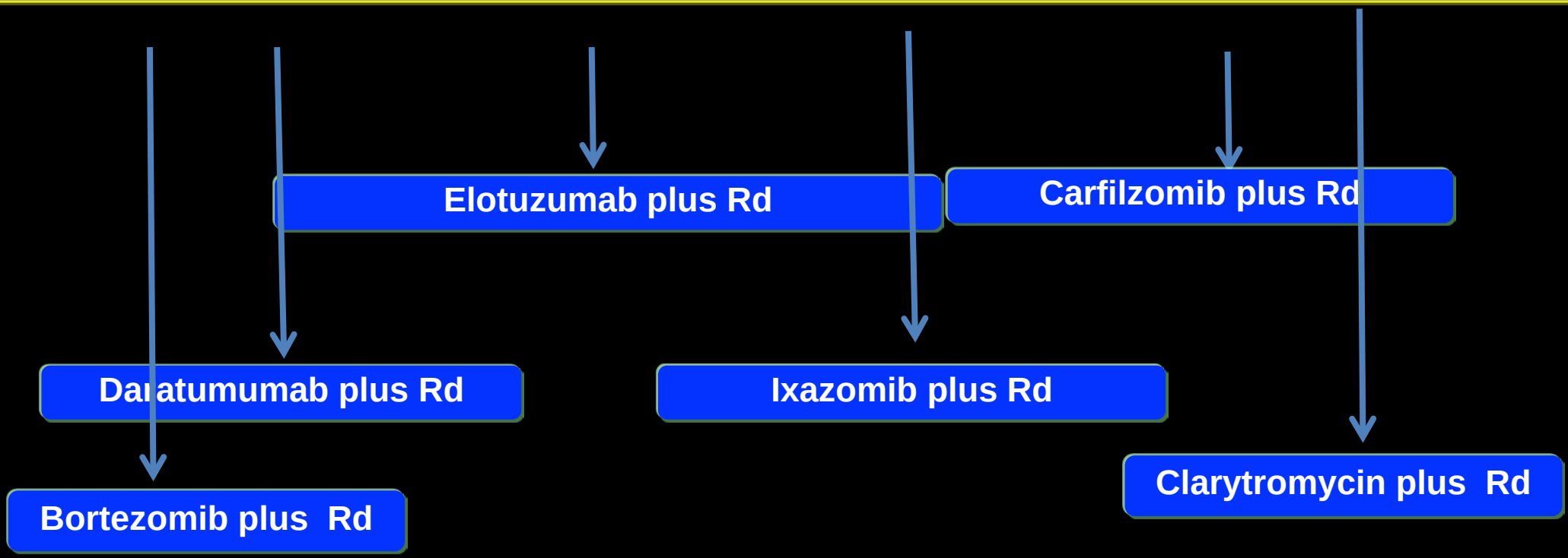
IMiD's

Len-dex

One randomized trial: Benefit in PFS&OS vs MPT

Benboubker L, et al. NEJM 2014; 371: 906-17

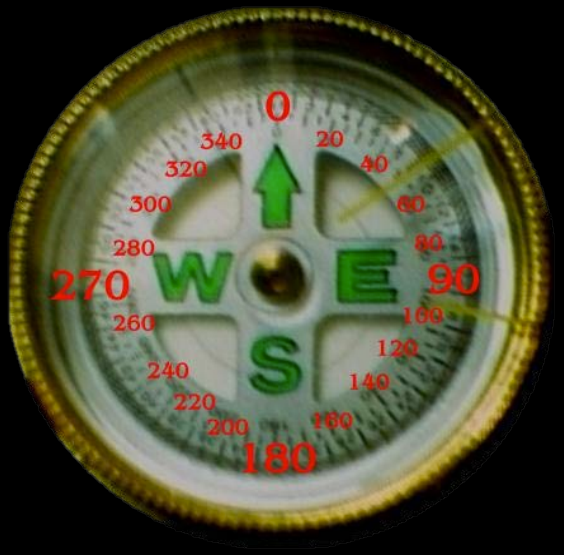
Rd as continuous therapy as backbone for different new regimens for elderly NDMM



Strategies at relapse: How to make the right choice?

Type of relapse

Efficacy of previous treatments

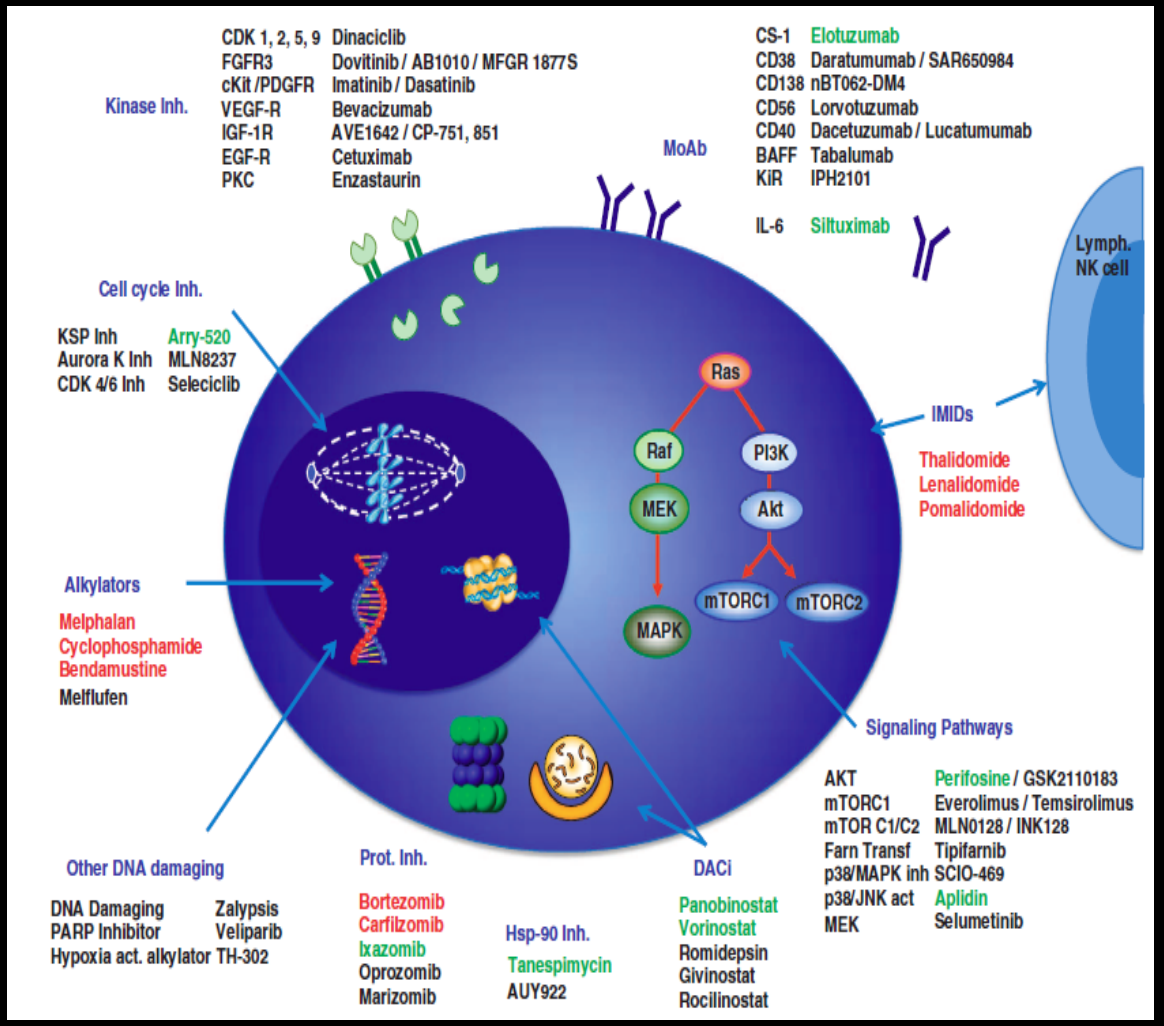


Toxicity of previous treatments

Further options

Novel drugs in MM

- **Derivatives from already approved**
  - Novel PIs
  - Novel IMiDs
- **Immuno-oncologic approaches**
- **Novel drugs with different MoA**
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors



CDK, cyclin-dependent kinase

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

Doublets & Triplets with new Proteasome inhibitors in relapsed MM: survival on Phase III trials

- **ASPIRE trial (KRd vs. Rd)[1]:**
  - PFS 26.3 vs. 17.6 months (HR 0.69, p=0.0001) …… ▲ 9 months
  - OS at 2 years: 73% vs. 65% (HR 0.79, p=0.01)

- **ENDEAVOR trial (Kd vs. Vd)[2]:**
  - PFS 18.7 vs. 9.4 months (HR 0.53, p=0.0001) …… ▲ 9.3 months
  - OS NE vs. 24 months (HR 0.79, p=0.06)

- **TOURMALINE–MM1 trial (IRd vs. Rd)[3]:**
  - PFS 20.6 vs. 14.7 months (HR 0.74, p=0.01) …… ▲ 5.9 months

KRd/Kd/IRd are new standards of care for patients after 1 prior line of therapy

IRd, ixazomib+lenalidomide+dexamethasone; Kd, carfilzomib+dexamethasone; KRd, carfilzomib+lenalidomide+dexamethasone; Vd, bortezomib+dexamethasone

1. Stewart AK, et al. *N Engl J Med* 2015; 372: 142-152; 2. Dimopoulos MA, et al. *Lancet Oncol* 2016; 17: 27-38;
3. Moreau P, *N Engl J Med* 2016; 374: 1621-1634;

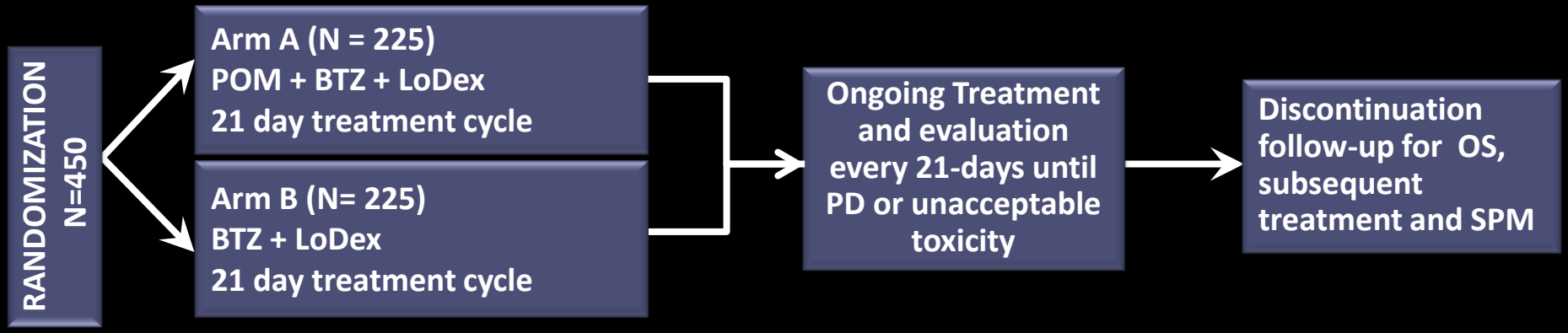
Pomalidomide-Dex in Refractory MM (& combinations)

	MM-003[1]	STRATUS (MM-010)[2]	Pom-Dex vs Pom-Cyclo-Dex[3]		Pom-Btz-Dex[4]
Treatment	**PD**	**PD**	**PD**	**PCD**	**PVD**
n	*302*	*604*	*36*	*34*	*34*
Population	*Failed Bort & Len & refr to last line*		*At least 2 prior lines & Len-refractory*		*1-4 prior lines & Len-refractory*
ORR, %	31	35	39	65	85
≥ VGPR, %			14	12	45
PFS, months	4.0	4.2	4.4	9.5	-
OS, months	13.1	11.9	16.8	NR	-

*EFS at 12 months

1. *San Miguel, Lancet Oncology 2013; 2. Dimopoulos MA, et al. ASH 2014. Abstract 80; 3. Baz et al. ASH 2014. Abstract 303; 4. Richardson et al. ASH 2015. Abstract 3036*

OPTIMISMM (MM-007) Phase 3 study:Pom+Btz+Dex vs Btz+Dex
1 – 3 prior treatments

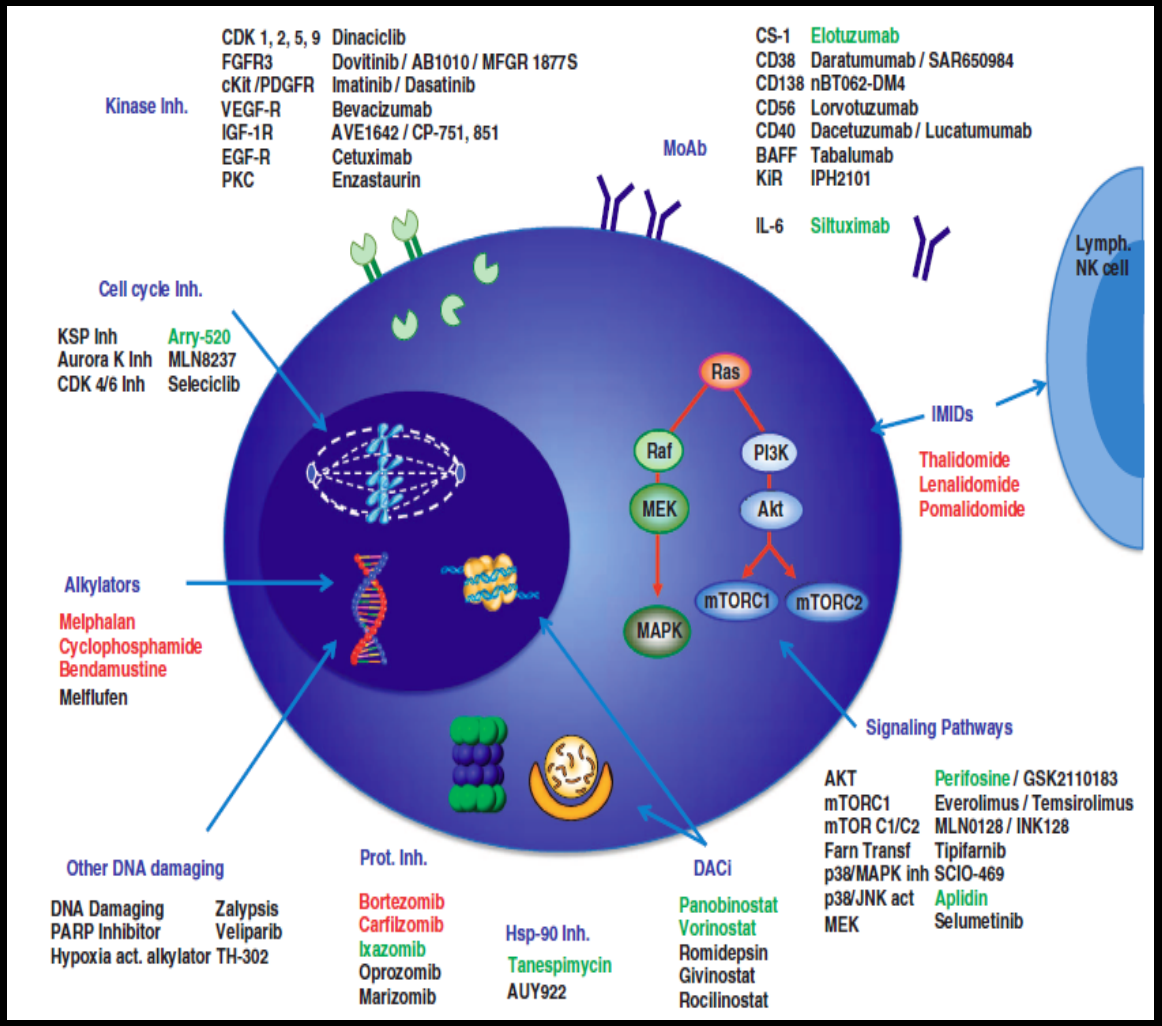


End Points	1: PFS 2: OS, ORR, duration of response
I/E Criteria	• At least 1 but no greater than 3 prior anti-myeloma regimens • All subjects must have received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles • Pts with BTZ exposure are eligible but BTZ exposure not required. Must not be BTZ refractory
N	450

1. Richardson PG et al. Poster presented at ASCO 2015 (Abstract TPS8610).

Novel drugs in MM

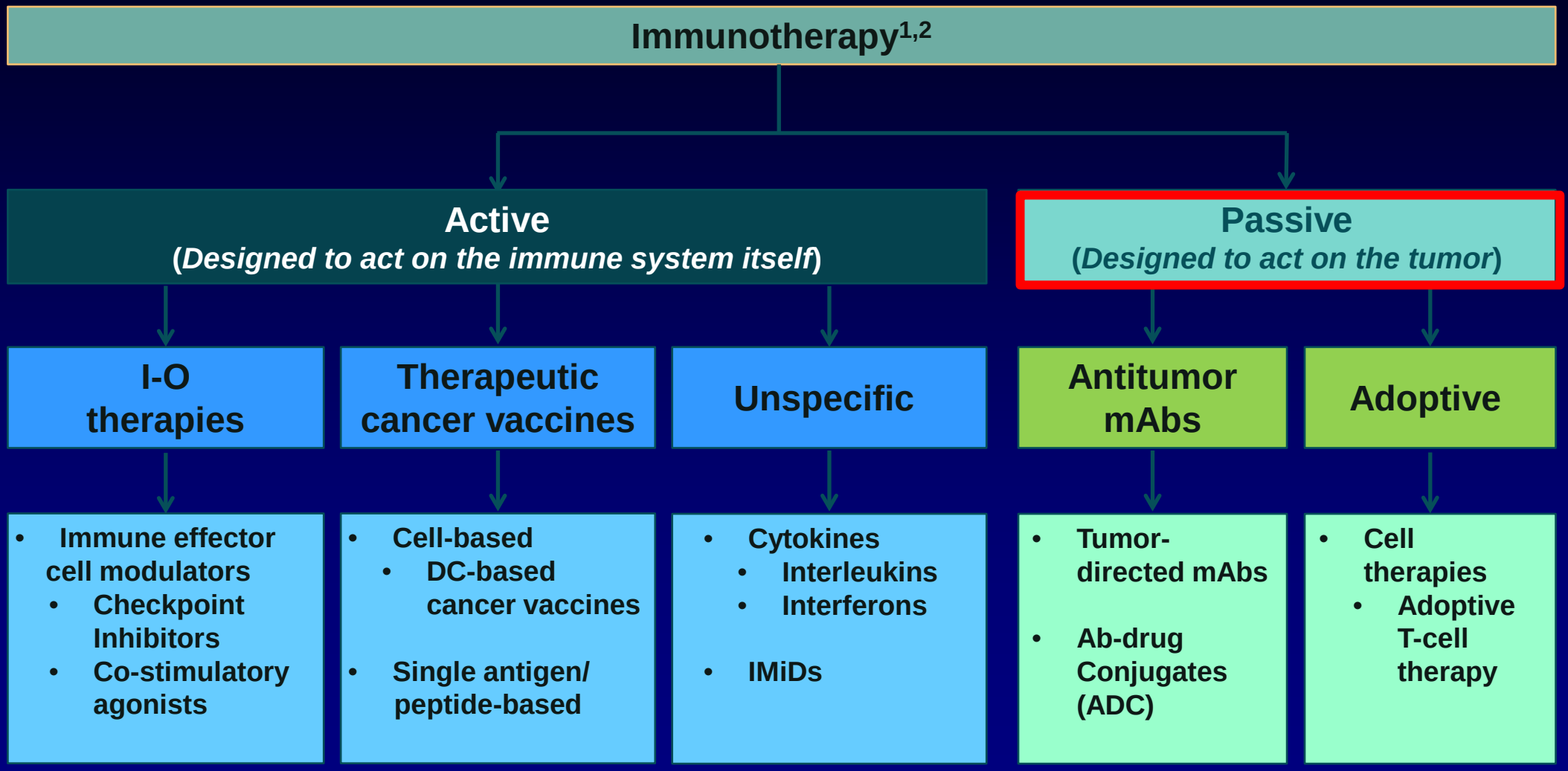
- **Derivatives from already approved**
  - Novel PIs
  - Novel IMiDs
- **Immuno-oncologic approaches**
- **Novel drugs with different MoA**
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors



CDK, cyclin-dependent kinase

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

Immune-therapies under investigation in MM



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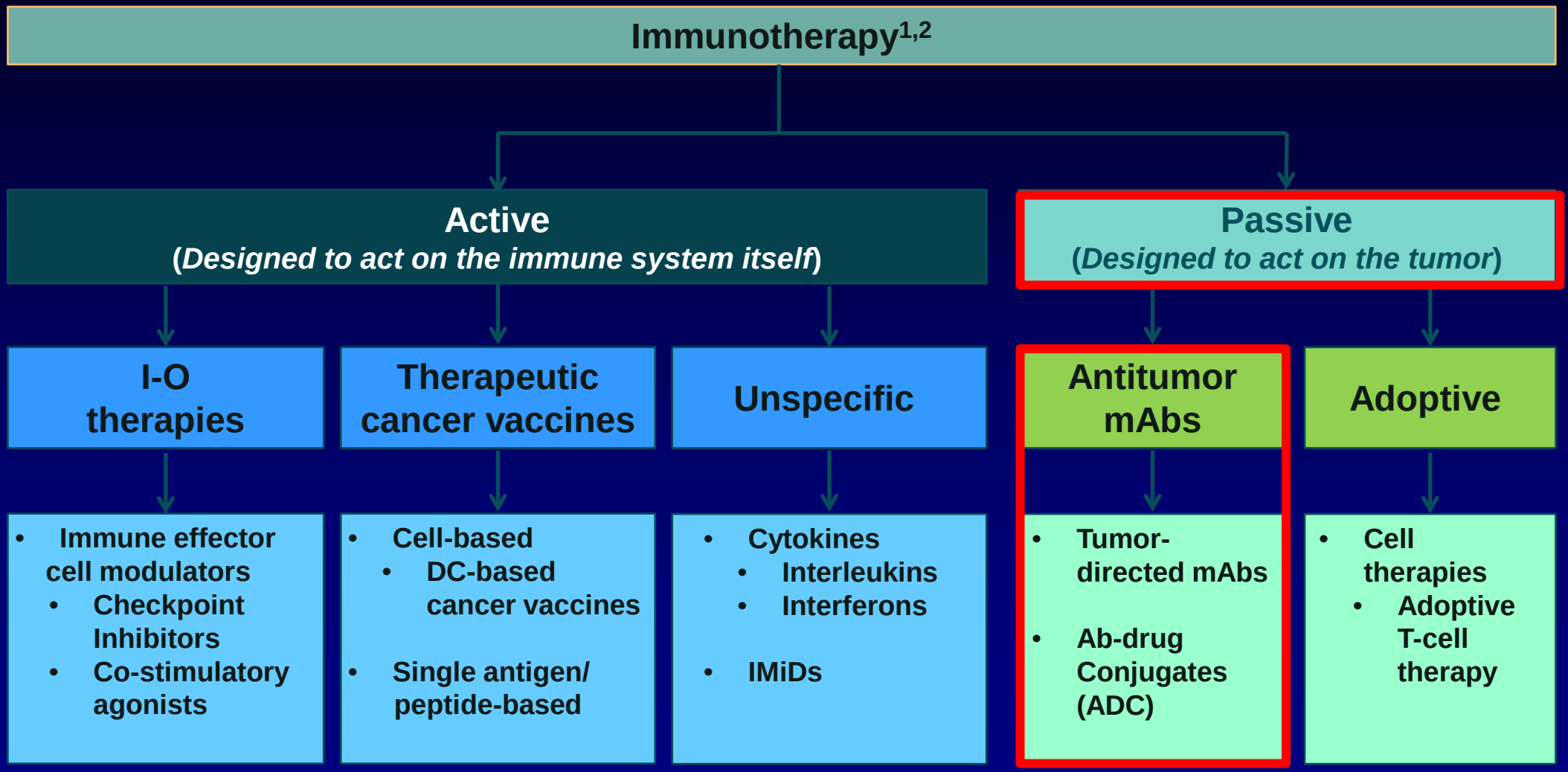

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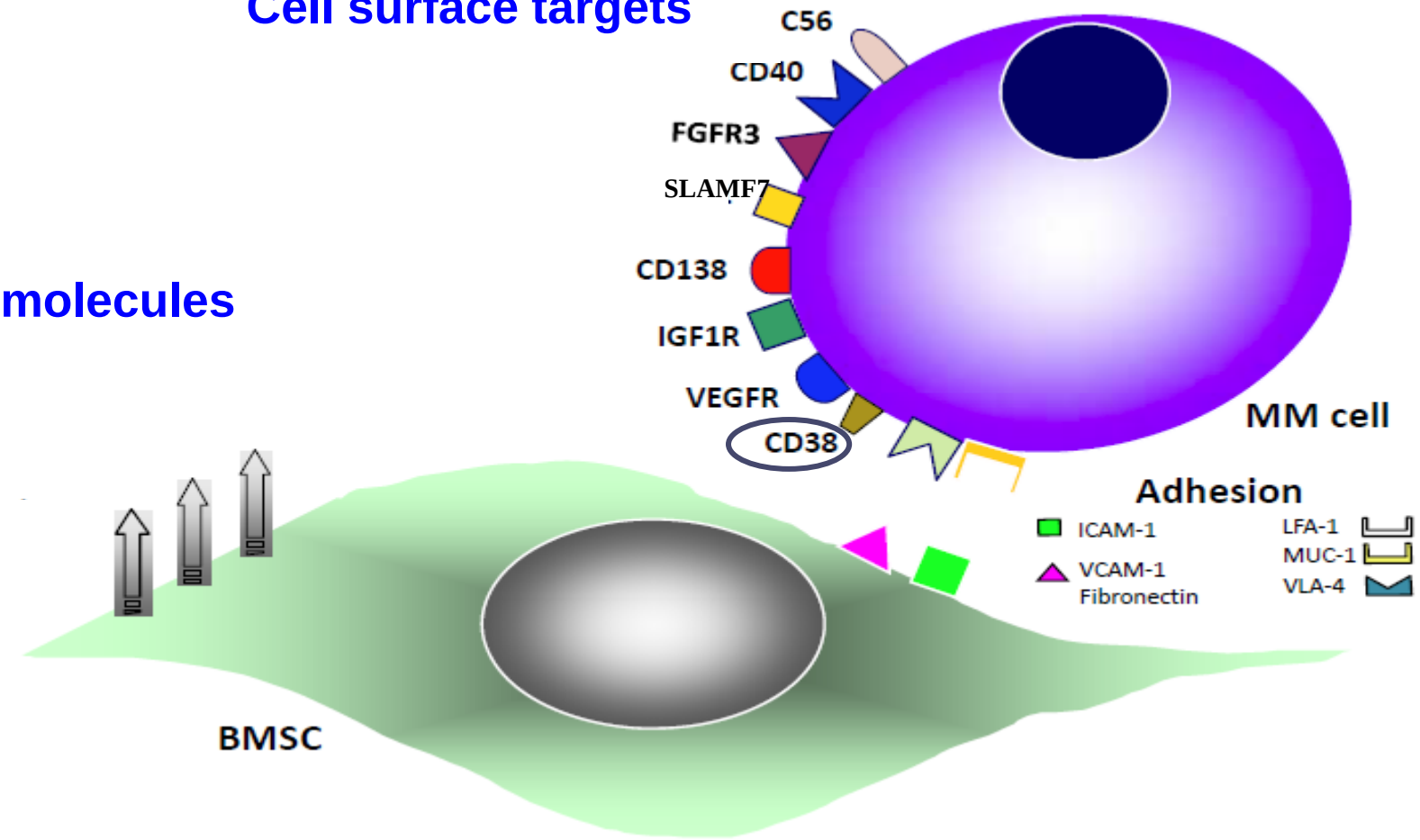
Targets for monoclonal antibody therapy in MM

Cell surface targets

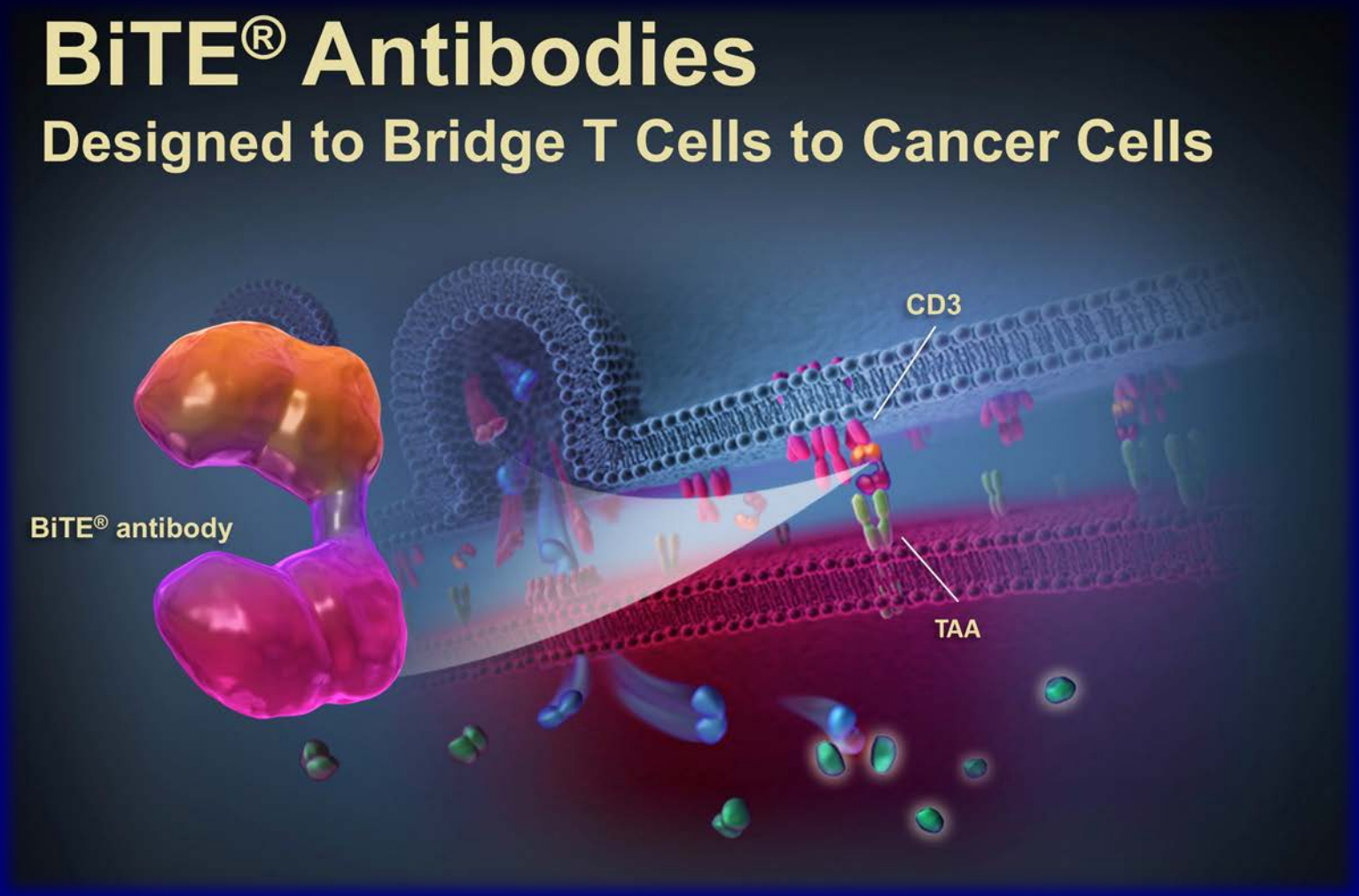
Signaling molecules

- IL-6
- RANKL
- DKK1
- VEGF
- IGF-1
- SDF-1α
- BAFF, APRIL

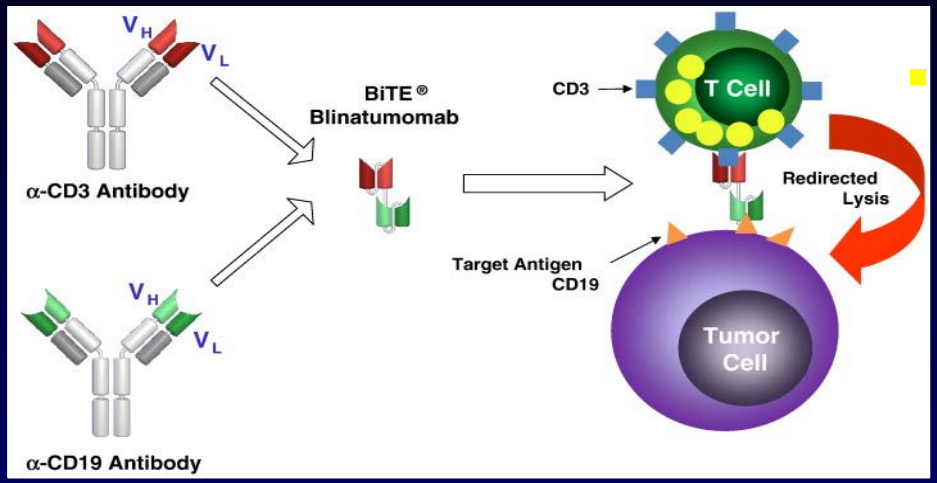


Adapted from: Anderson KC. J Clin Oncol 2012;30:445-452

Future for mAbs: Bispecific Antibodies

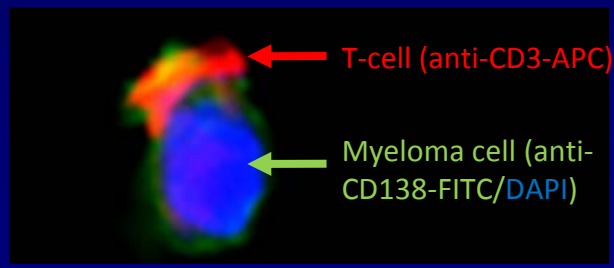


Bispecific T cell engagers (BiTEs)



Double specificity by targeting: the tumor cell & T-cell (CD3). Overcome the limitations of an immunosuppresive tumor microenvironment by linking CTLs with the tumor cell.

- **B-Cell Maturation Antigen (BCMA) expression was observed in malignant PCs in 99.5% MGUS and MM patients, and also in normal PC and plasmablasts.**

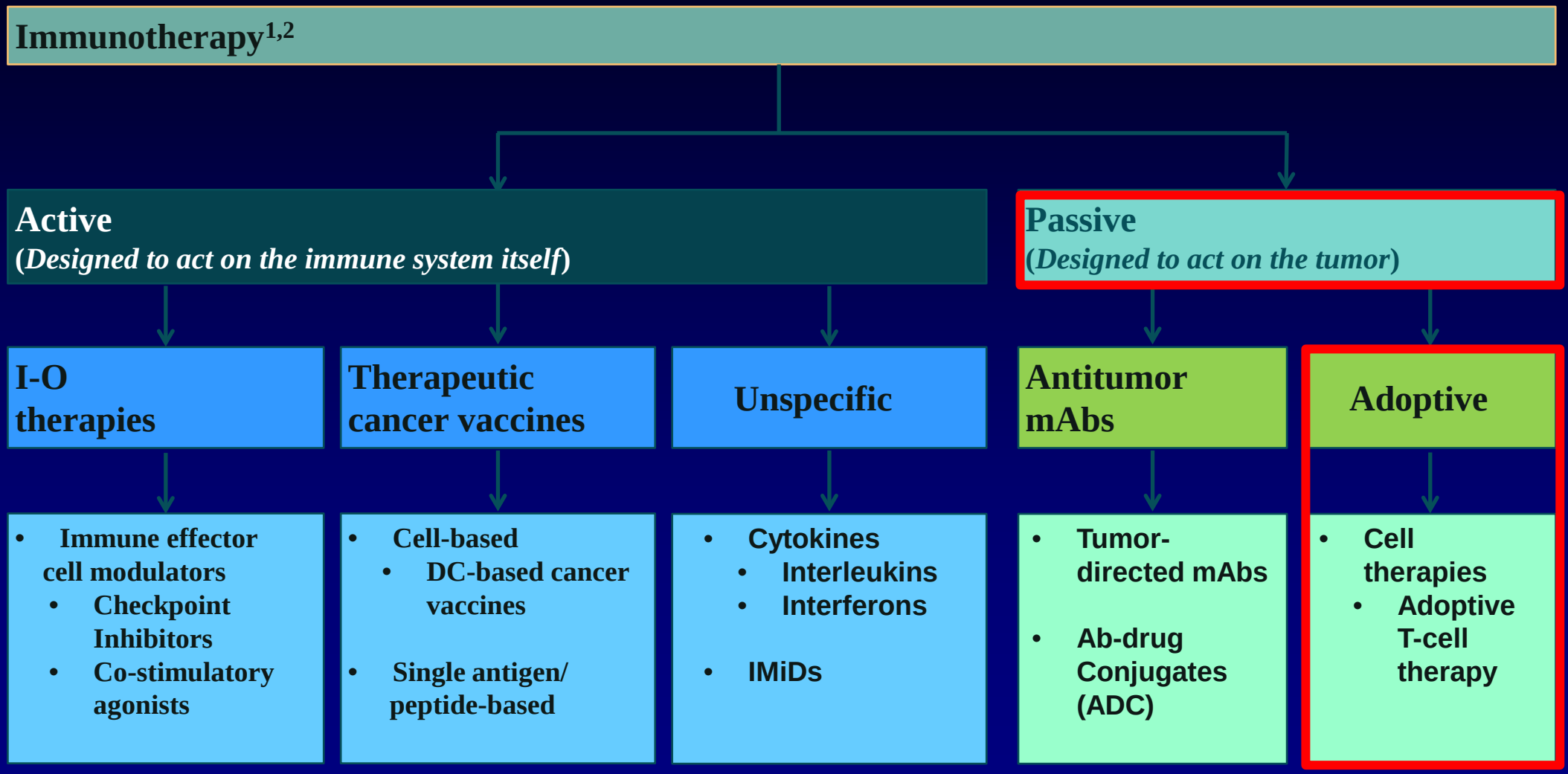


- **EM801 effectively binds myeloma cells and T-cells**

- **In vitro, EM801 induced concentration dependent cell death in mPCs in prmary BM-samples of NDMM (75%) and RRMM (80%) & tumor regression in a Xenograft model**

Seckinger A et al, ASH 2015 oral presentation 117

Immune-therapies under investigation in MM



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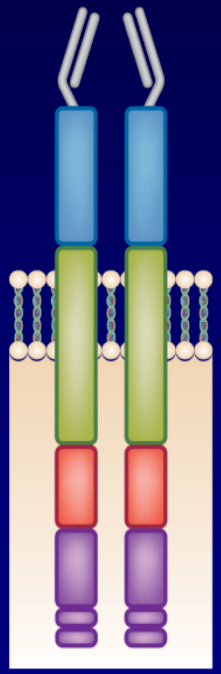
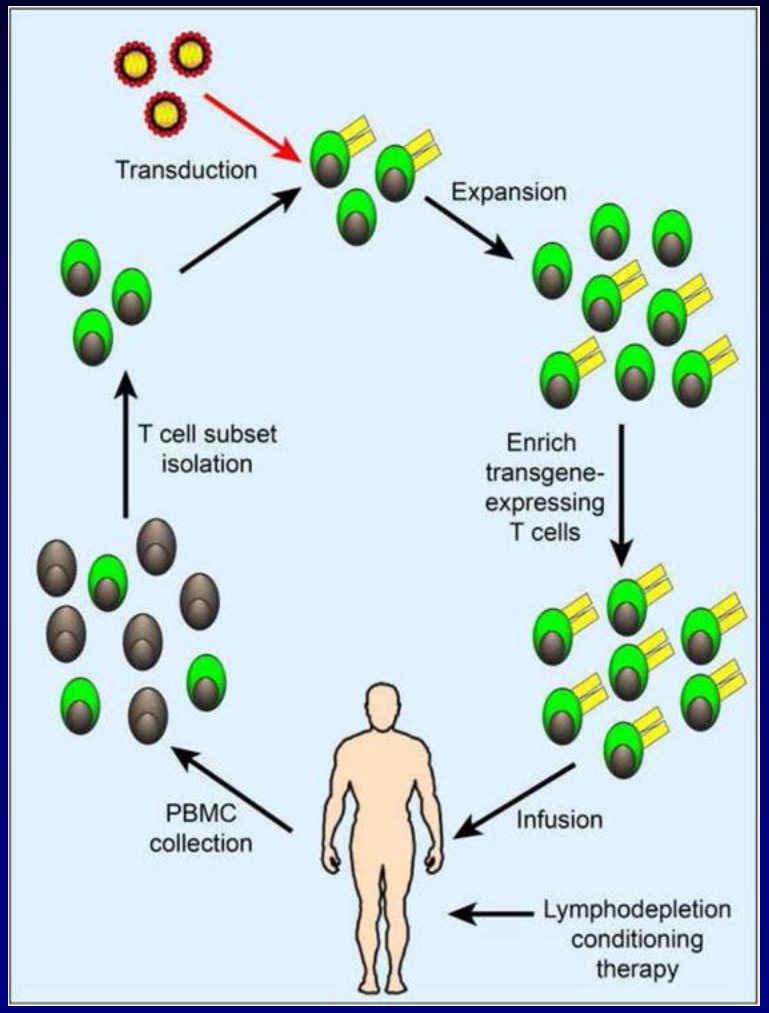
Adoptive T cell therapy: CAR-T cells

- CAR T or NK cells are engineered anti-tumor immune cells with high affinity chimeric antigen receptors specific for tumor antigens[1]

Chimeric Antigen Receptor Structure[1]



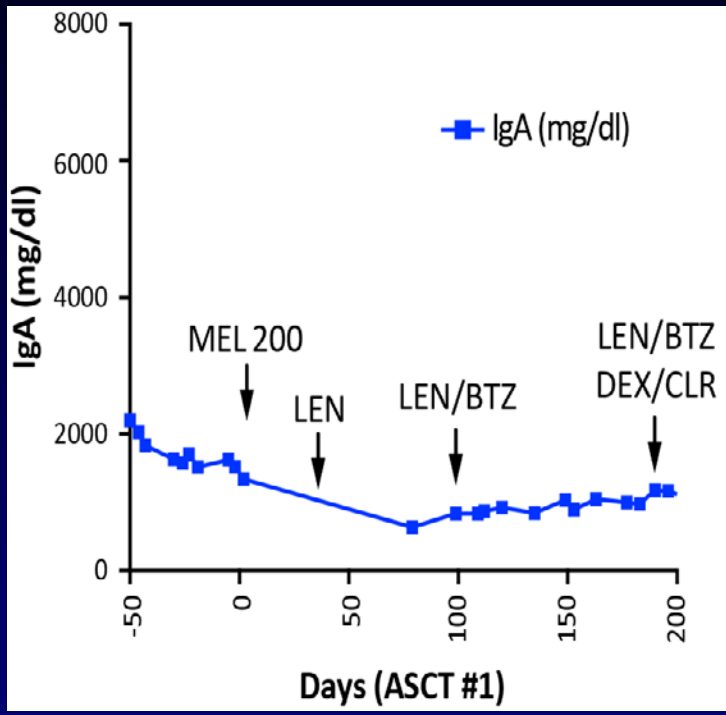
- Single-chain antibody able to recognize tumor-associated antigens in a non-MHC–specific manner
- Molecular hinge region derived from CD8 to provide flexibility to allow reorientation to bind antigen
- Cytoplasmic domain of CD28 and additional signaling domains, including CD137, were added to later generation CARs to enhance cytokine secretion and tumor growth inhibition
- Cytoplasmic signaling domain of CD3ζ



1. Kershaw MH et al. Nat Rev Cancer. 2013;13:525-541.

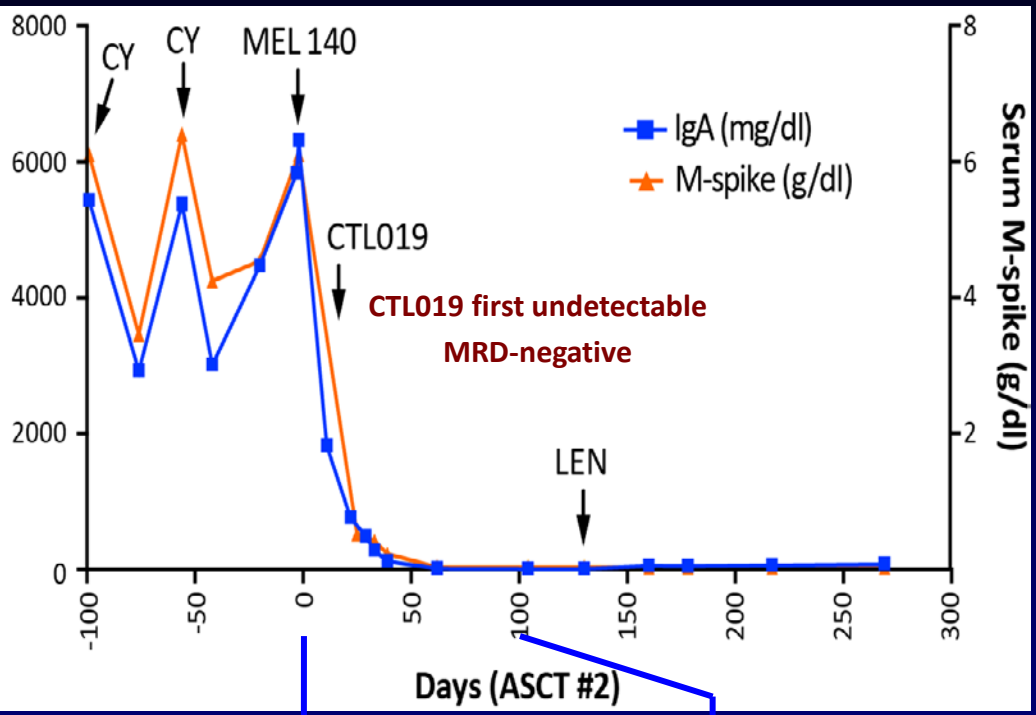
Turtle CJ, Hudecek M, Curr Opin Immunol, 2012

Adoptive T cell therapy: CAR-T cells in MM (CD19)



Additional regimens including…

- **carfilzomib**
- **pomalidomide**
- **vorinostat**
- **elotuzomab**

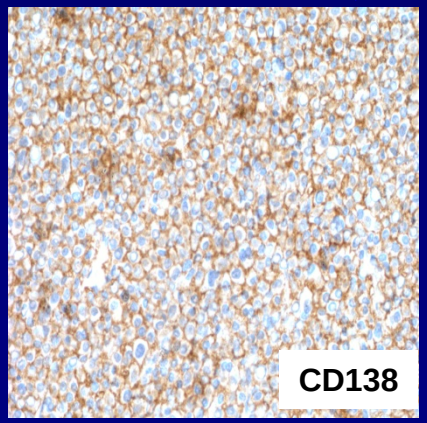


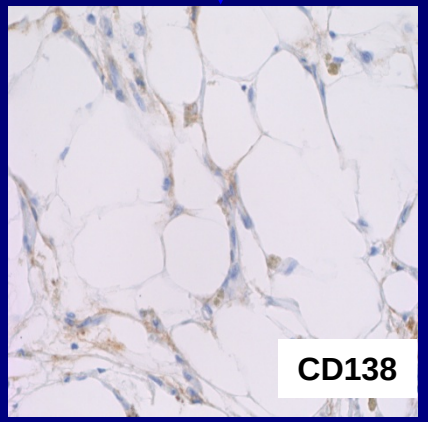
sCR, MRD neg

Now d +307

TTP after ASCT #1 d190

Remission inversion

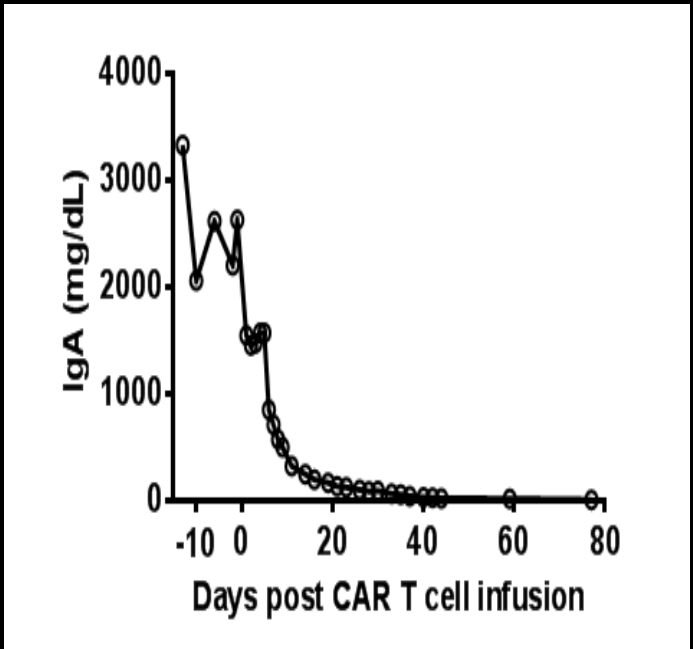


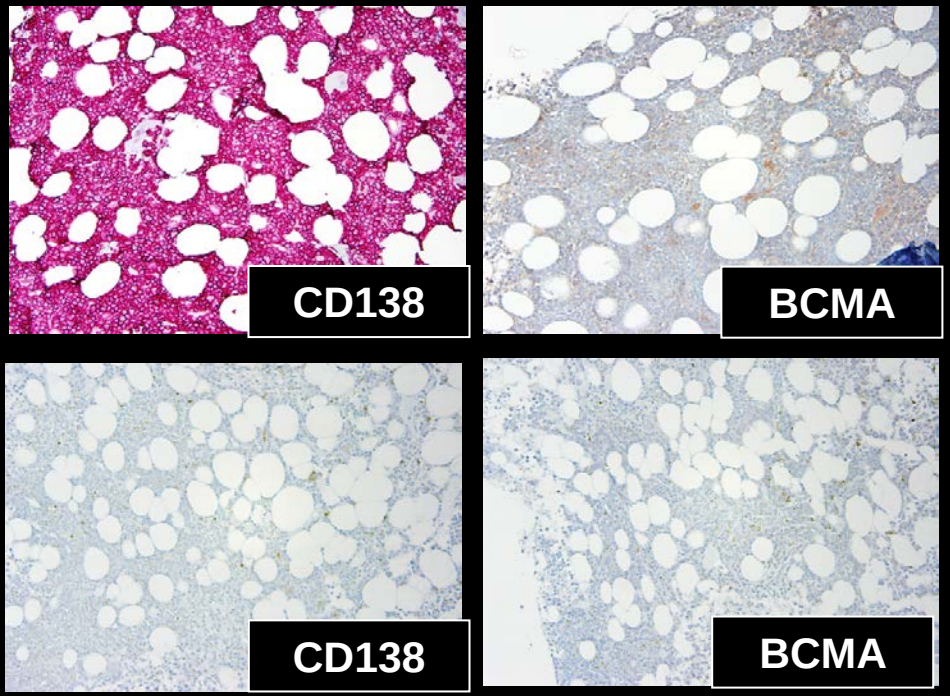


Stadtmauer, NEJM 2015

First-in-human clinical trial of T cells expressing an anti-B-cell maturation antigen chimeric antigen recepto: *4/12 Pts (2PR, 1 VGPR; 1sCR)*

Patient 10 obtained SCR of chemotherapy-resistant IgA myeloma after **CAR-BCMA T**-cell infusion





- Serum and urine IFE-negative

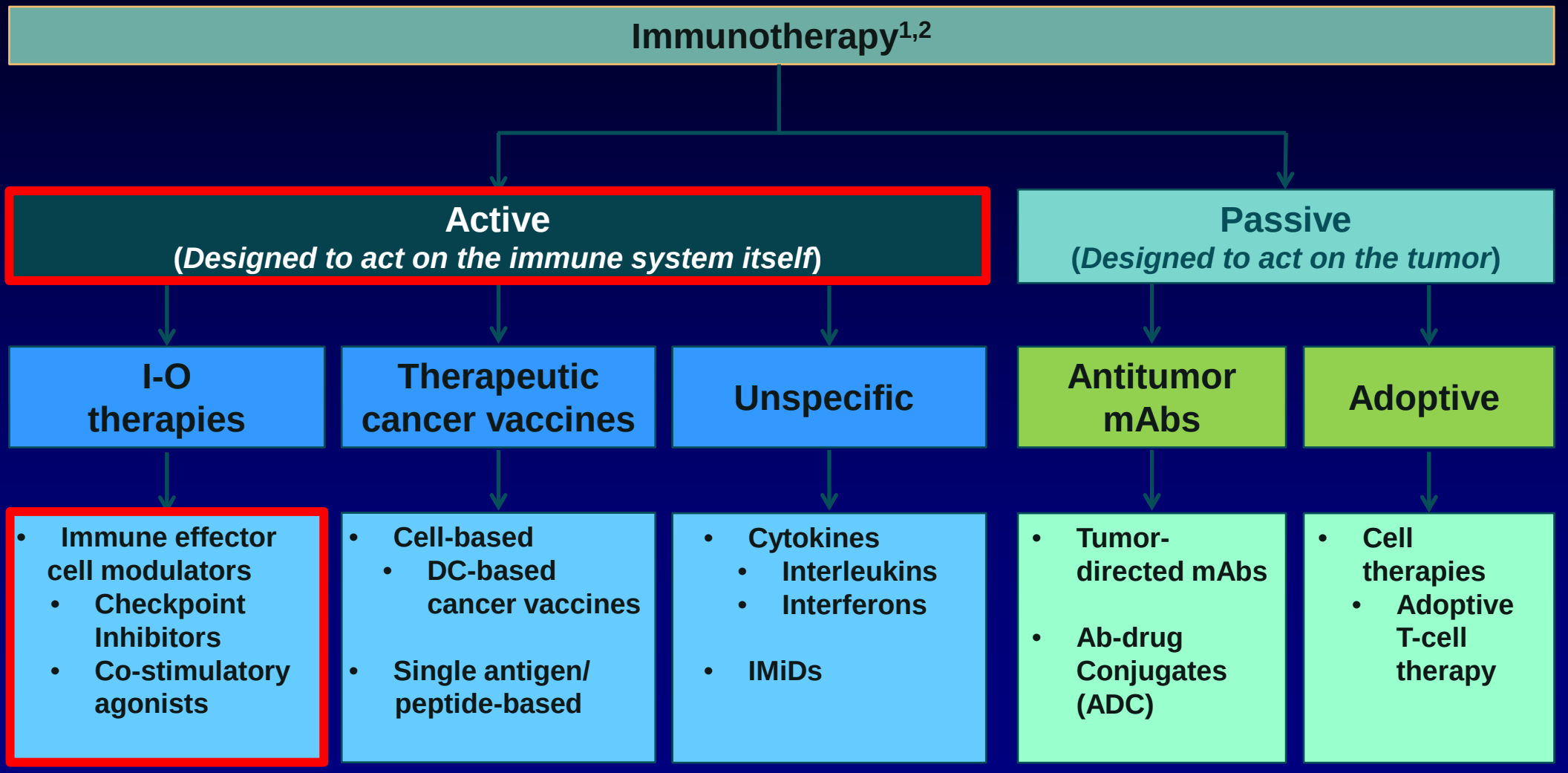
Bone marrow flow cytometry-negative

BCMA: B-cell maturation Ag
a member of the TNF superfamily

Abbas, & Kochenderfer, ASH 2015 (LBA1)

- *Patient 10 experienced cytokine release syndrome including fever, tachycardia, hypotension, elevated liver enzymes, and elevated creatinine kinase-all resolved in 2 weeks or less*

Immune-therapies under investigation in Cancer



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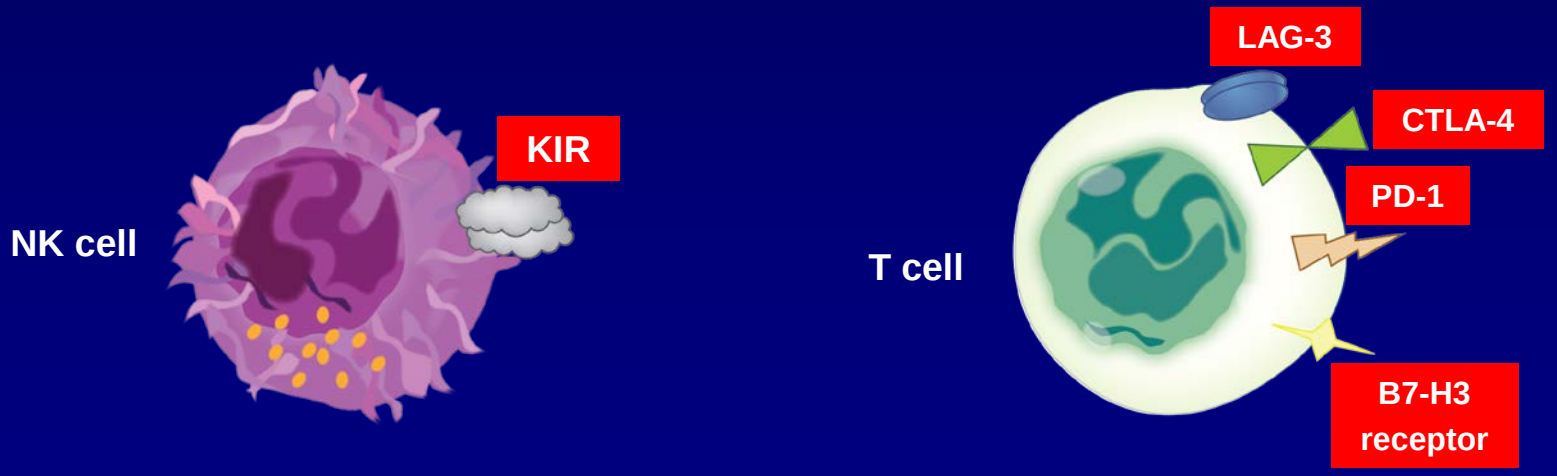
1. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6-viii9. 2. Mellman I et al. *Nature*. 2011;480:480-489.

Immuno-oncology Activating/Inhibitory Pathways

Activating

SLAMF7, signaling lymphocytic activation molecule family member 7.

Inhibitory

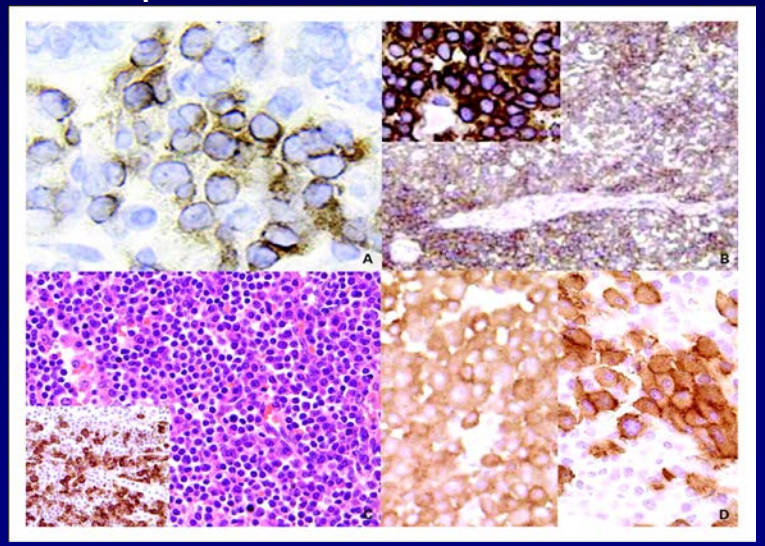


KIR, killer cell immunoglobulin-like receptor;
CTLA-4, cytotoxic T-lymphocyte-associated protein 4;
LAG-3, lymphocyte-activation gene 3;
PD-1, programmed cell death protein 1.

Elotuzumab (Anti-SLAM F7 MoAb) in MM

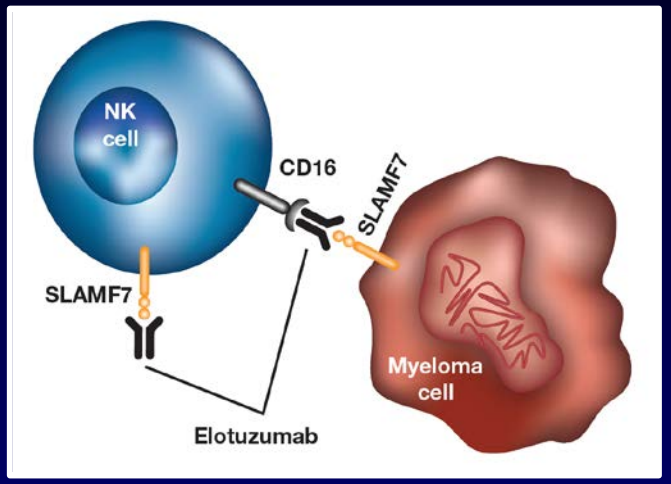
- **SLAMF7**: Signaling Lymphocyte Activation Molecule-1. Also called CS1
- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is **highly expressed on >95% of MM cells**[1-3]
  - Also on NK cells
  - Little to no expression on normal tissues

Normal plasma cells | Plasmacytoma



Lymphoplasmacytic lymphoma | MM cells in bone marrow

Dual mechanism of action



Binding to SLAMF7 directly activates Natural Killer cells,[4] but not myeloma cells[5]

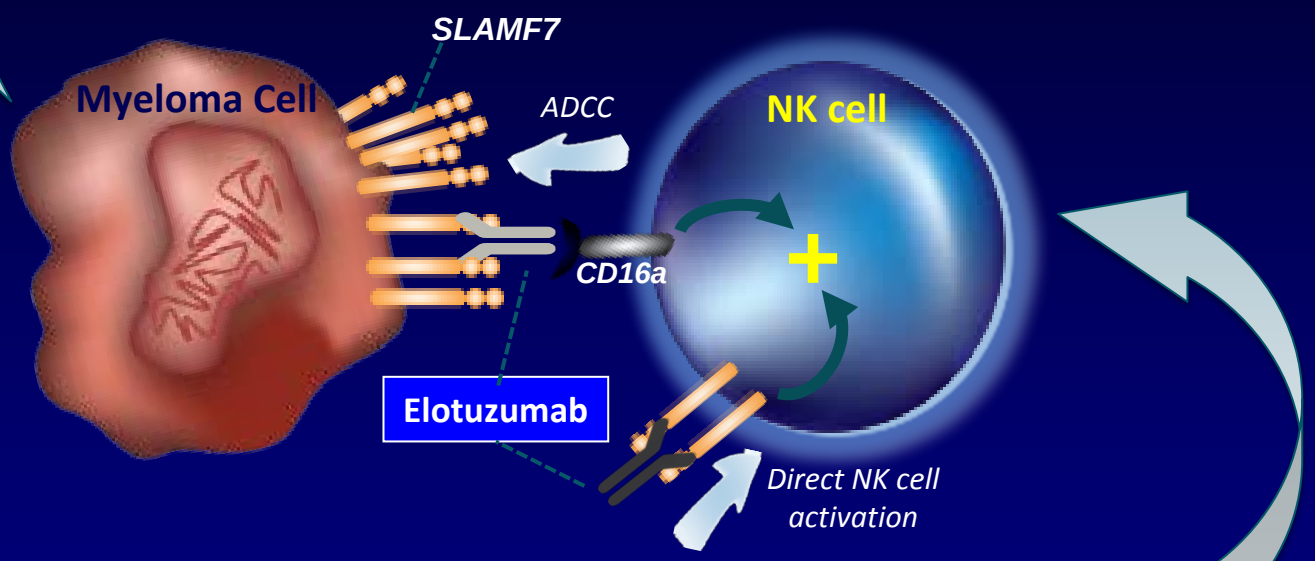
When bound to myeloma via SLAMF7, Elo activates Natural Killer cells via a CD16 mediated pathway, enabling selective killing via antibody-dependent cellular cytotoxicity (**ADCC**) with minimal effects on normal tissue

• **Phase I**	n=25 → *26% SD*

1. Hsi ED et al. Clin Cancer Res. 2008;1; *2. Tai YT et al. Blood. 2008*
3. Van Rhee F et al. Mol Cancer Ther. 2009; *4. Collins SM et al. Cancer Imm. Immunother. 2013*
5. Guo H et al. Mol Cell Biol. 2014; *6. Zonder et al Blood 2012*

Elotuzumab synergizes with Lenalidomide in MM

Lenalidomide
Induces myeloma cell injury and lowers threshold for NK cell–mediated killing of myeloma cells by elotuzumab

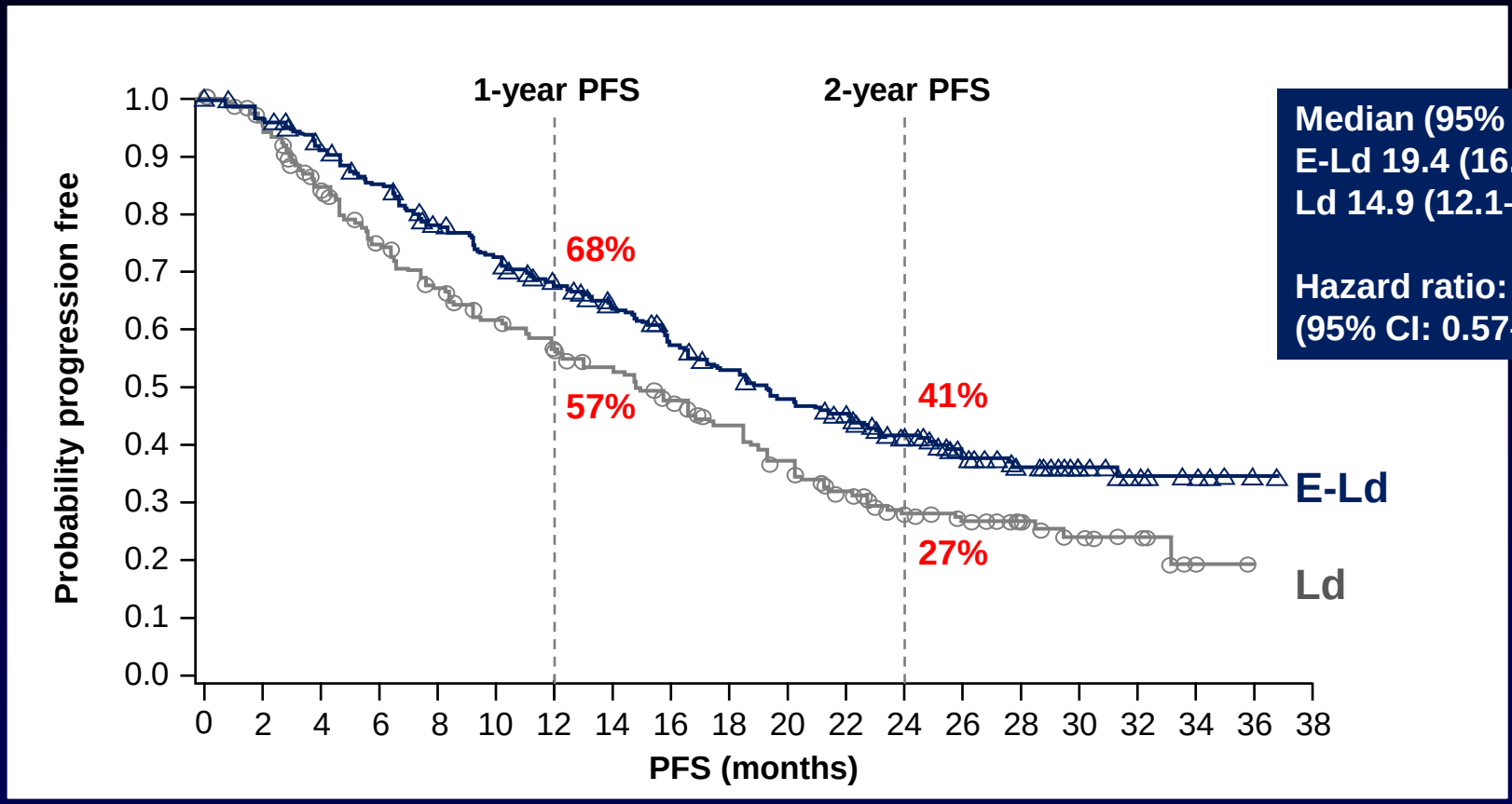


Lenalidomide
Enhances adaptive and innate immune system, including production of IL-2, to increase NK cell activity

ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; SLAMF7, signaling lymphocytic activation molecule family member 7

1. Balasa B et al. *Cancer Immunol Immunother.* 2015;64:61-73.

Eloquent-2: Elo + Ld vs Ld
Co-Primary End Point: PFS



Median (95% CI) PFS:
E-Ld 19.4 (16.6–22.2) months
Ld 14.9 (12.1–17.2) months

Hazard ratio: 0.70
(95% CI: 0.57–0.85; P=0.0004)

E-Ld-treated patients had a 30% reduction in the hazard of PFS; treatment difference at 1 and 2 years was 11% and 14%, respectively

Lonial et al. NEJM 2015

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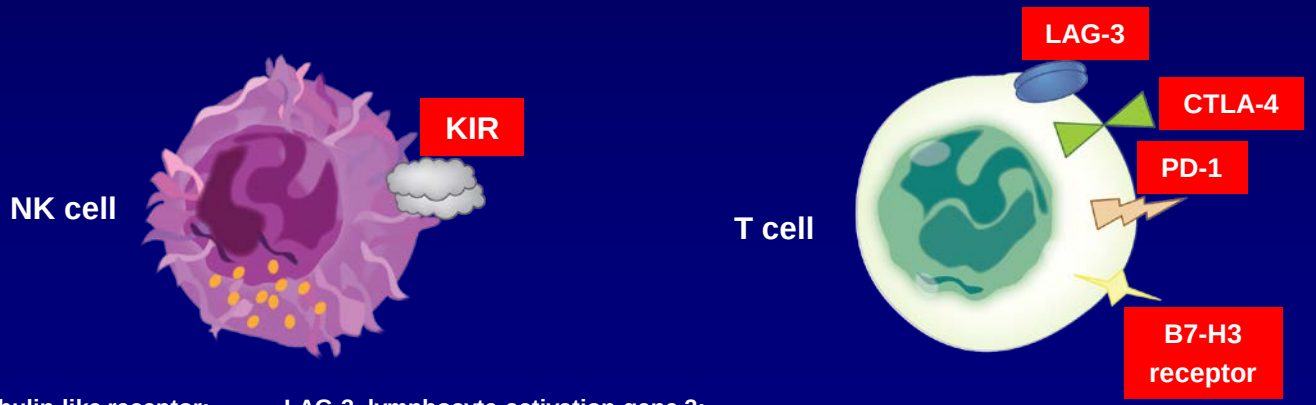

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Check-Point Inhibitors

RR of Nivolumab (Anti-PD1) in Haem Malignancies

Tumor Type	# pts	ORR	CR	PR	SD
Multiple Myeloma	27	1 (4)	1 (4)	0	17 (63)
B-Cell Non-Hodgkin Lymphoma	31	8 (26)	3 (10)	5 (16)	16 (52)
Diffuse Large B-Cell	11	4 (36)	2 (18)	2 (18)	3 (27)
Follicular NHL	10	4 (40)	1 (10)	3 (30)	6 (60)
Mantle Cell Lymphoma	4	0	0	0	3 (75)
Primary Mediastinal B-Cell	2	0	0	0	2 (100)
Other B-NHL	4	0	0	0	2 (50)
T-Cell Non-Hodgkin Lymphoma	23	4 (17)	0	4 (17)	10 (43)
CTCL/MF	13	2 (15)	0	2 (15)	9 (69)
Peripheral T-Cell	5	2 (40)	0	2 (40)	0
Other T-NHL	5	0	0	0	1 (20)
Hodgkin Lymphoma	23	20 (87)	6 (26)	14 (61)	3 (13)

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

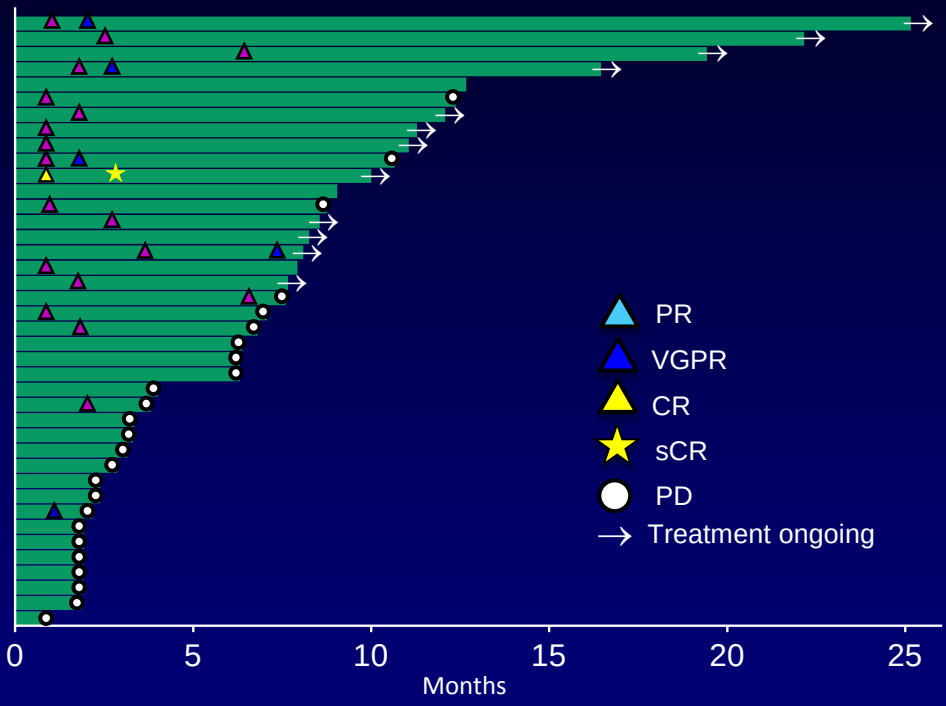
Lesokhin. EHA 2015

Pembrolizumab + LD Antitumor Activity in RRMM patients

Best Response (n (%))

	Efficacy Population† (n = 40)	Len-Refr (n = 29)
ORR	20 (50)	11 (38)
sCR	1 (3)	1 (3)
VGPR	5 (13)	3 (10)
PR	14 (35)	7 (24)
SD	19 (48)	17 (59)
PD	1 (3)	1 (3)

Treatment Exposure & Response Duration

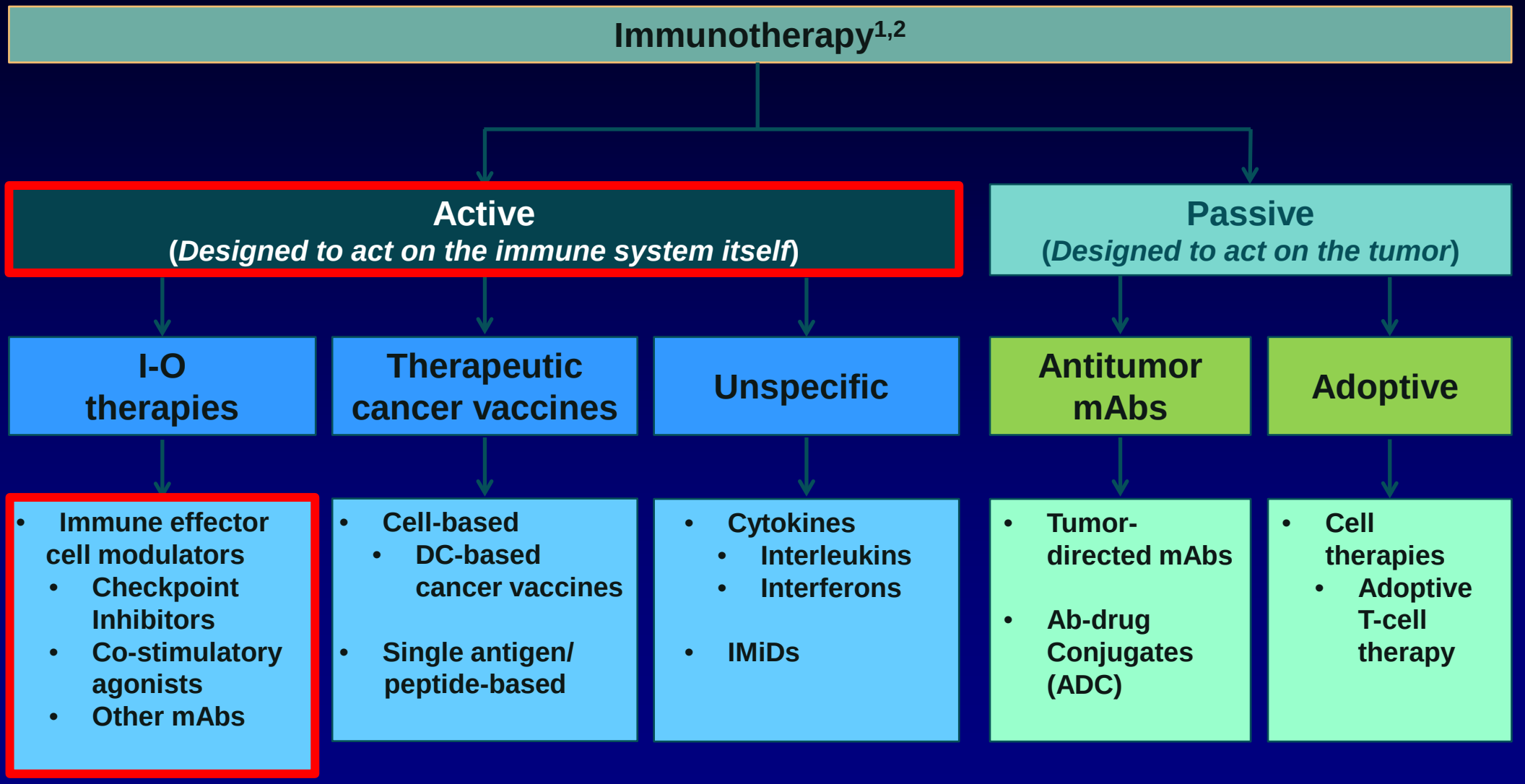


Median follow-up: 9 months (range, 1-25)
Median DOR: 11.3 months
Median time to achieve first objective response: 1.5 months (range, 1.0-6.6)
4 patients who responded (20%) upgraded the quality of response
75% of patients were still alive

Pembro plus Pom-dex has shown also significant activity in RRMM patients (Badros, ASH 2015)

†11 patients NE by central review
3 discontinued within cycle 1 for reasons other than PD (2 no treatment assessments and 1 SD by investigator)
8 inadequate myeloma data for response assessment (5 PD and 3 SD by investigator)

Immune-therapies under investigation in Cancer



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Signaling molecules

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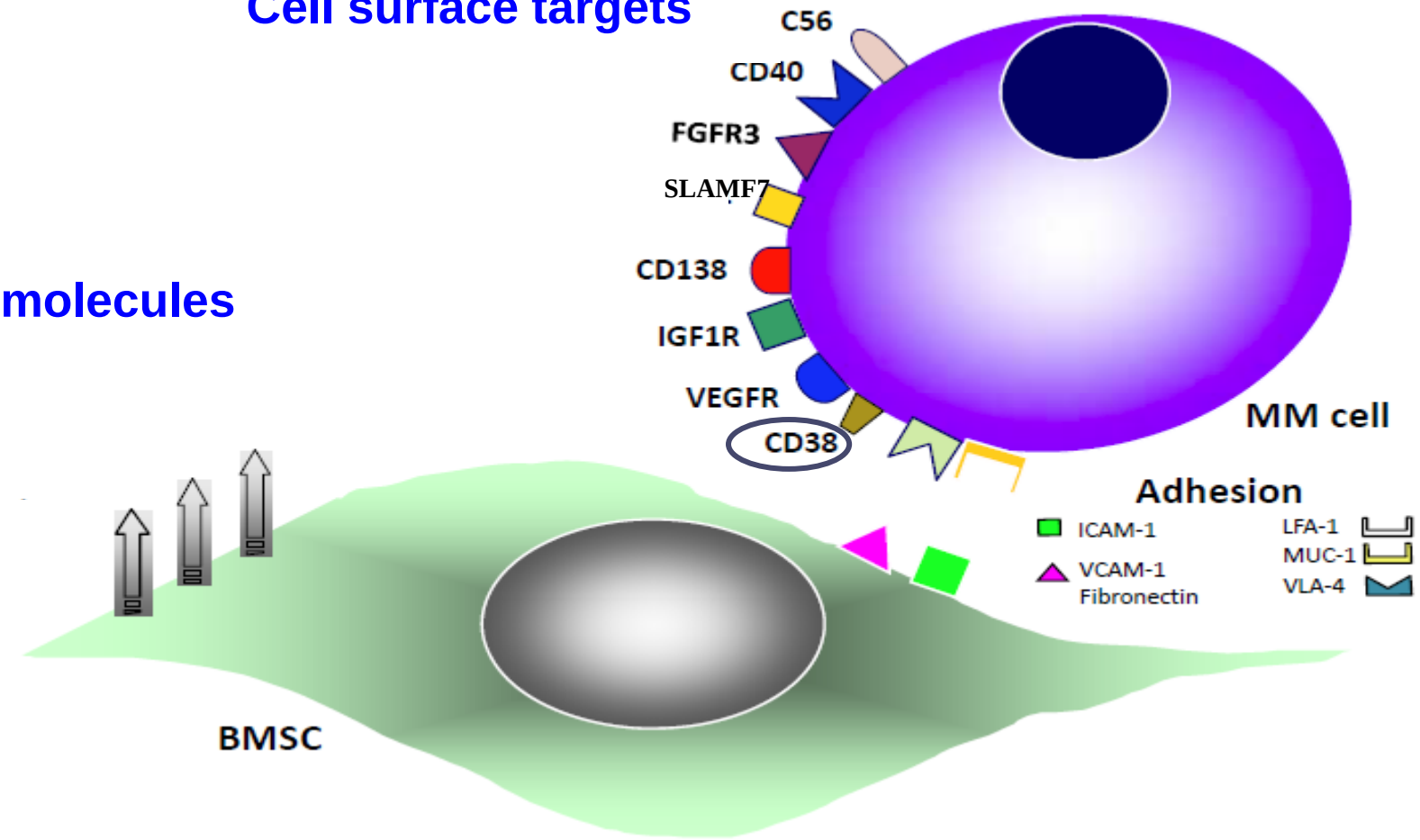
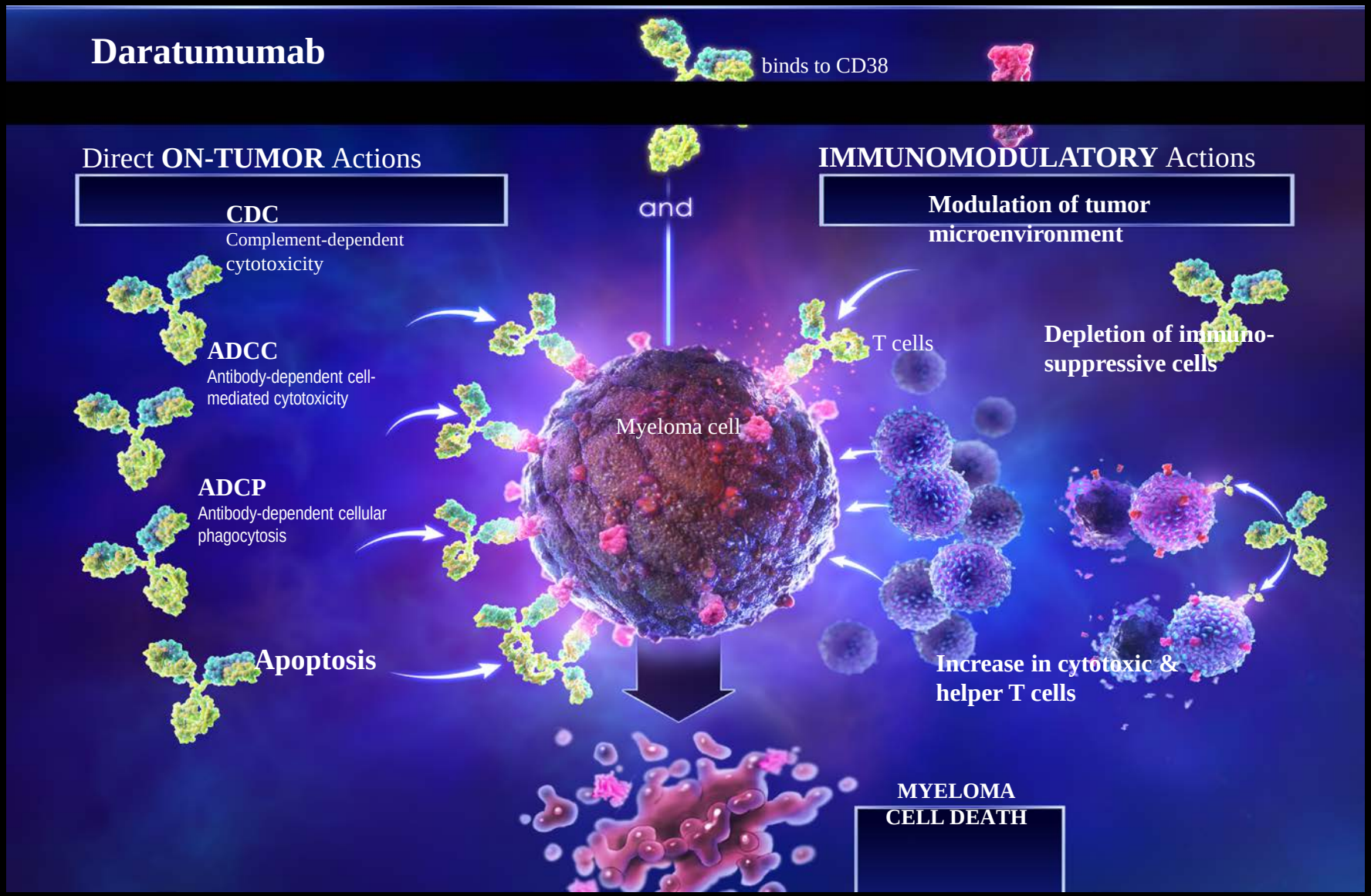


Adapted from: Anderson KC. J Clin Oncol 2012;30:445-452

Anti CD38 antibodies : Mechanisms of Action



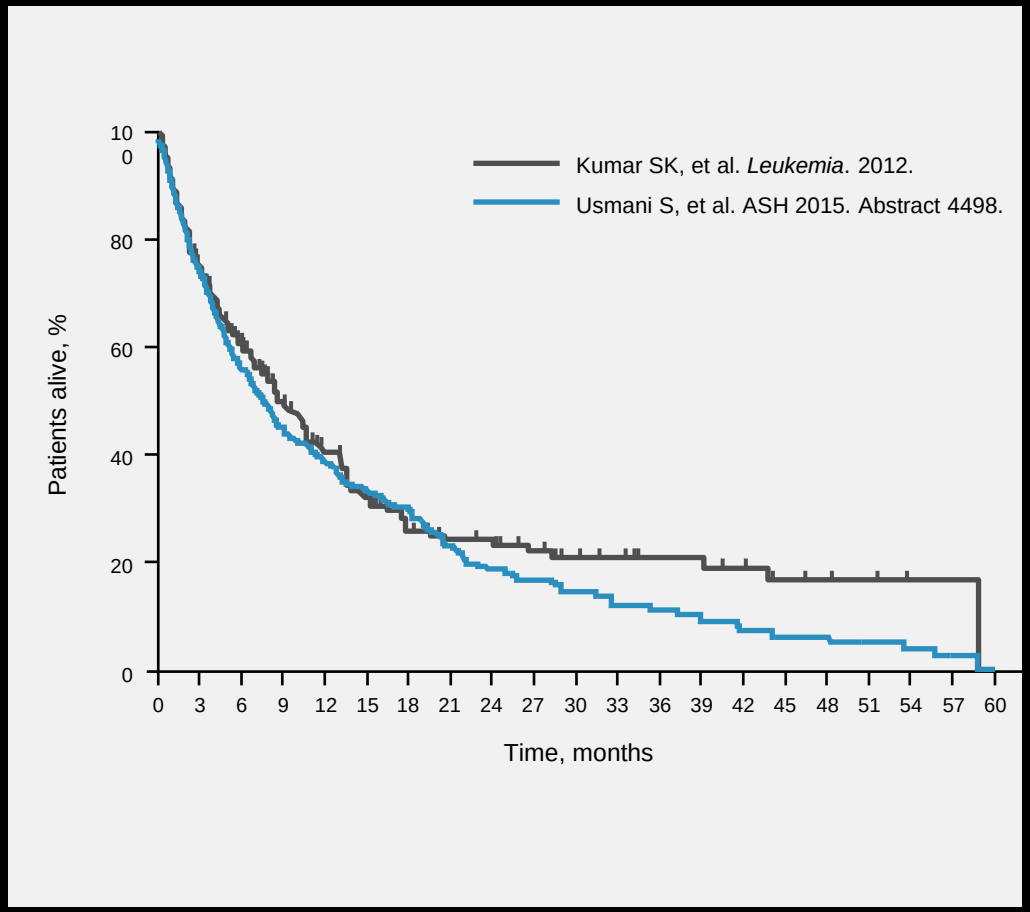
Anti CD38 in MM: single agent activity in RRMM

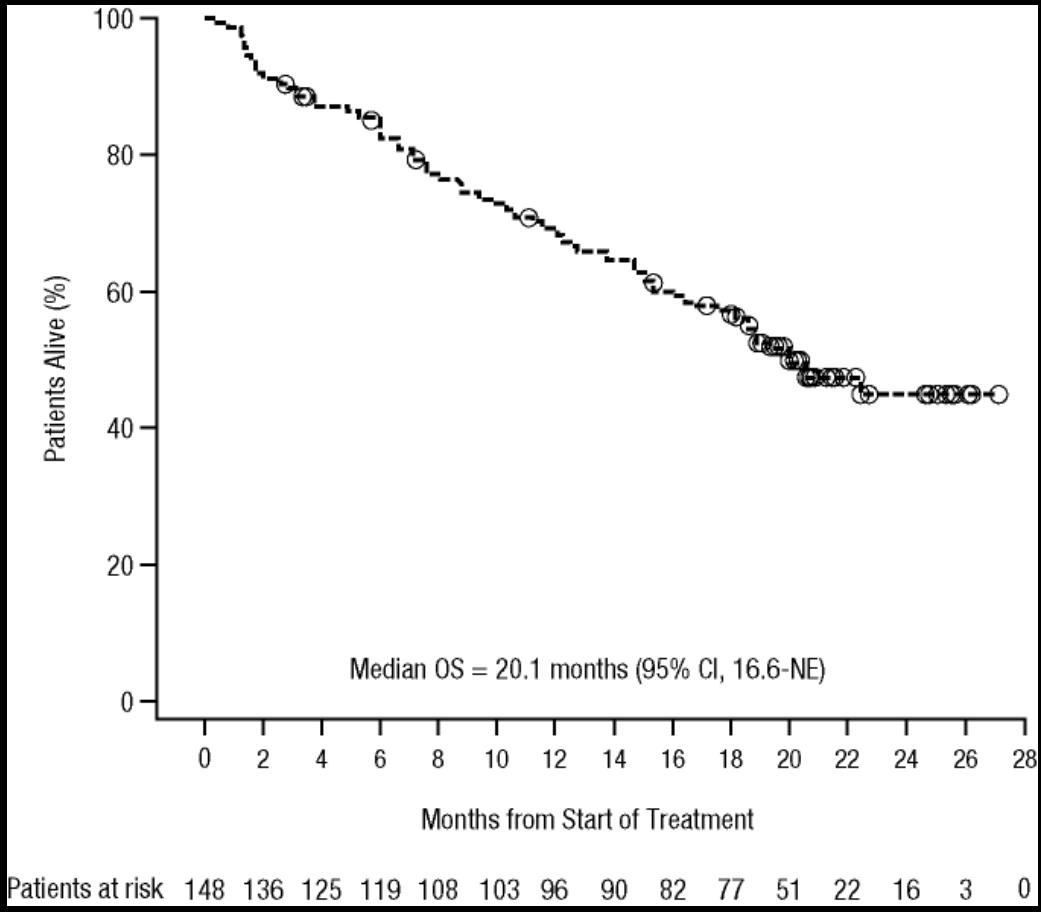
	Daratumumab	Isatuximab
Study details	3 studies: GEN501[1], SIRIUS[2] & combined analysis[4]	First in-human, phase 1 dose escalation[3]
Patients	Pts with rel/ref MM n=148 (SIRIUS n=42 and GEN501 n=106)	Pts with rel/ref MM n=40
Dose	16 mg/kg	Dose is not yet defined
Results	• **ORR 31%** ***(36% GEN501 & 29% SIRIUS)*** • **Median DOR: 7.6 m** • **Median OS: 20 months** • Median PFS: 4m, Infusion-related reactions gr 1-2	• At ≥ 10 mg/kg: **29%** • At 20 mg/kg: **24%**[5] • Infusion-reactions mainly grade 1/2, only with first dose

Dara/SAAR are CD38 MoAB showing activity as single agents in RRMM patients

[1]Lokhorst HM et al, NEJM 2015, 363:8; [1]Lokhorst et al. ASCO 2014; Abstract 8513; Lonial S JCO 2015, [3]Martin et al. ASCO 2014; Abstract 8532; [4]Usmani S, et al ASH 2015 oral presentation 29, [5]Martin T, ASH 2015 oral presentation 509

GEN501 and SIRIUS (MMY2002) Combined Analysis: OS





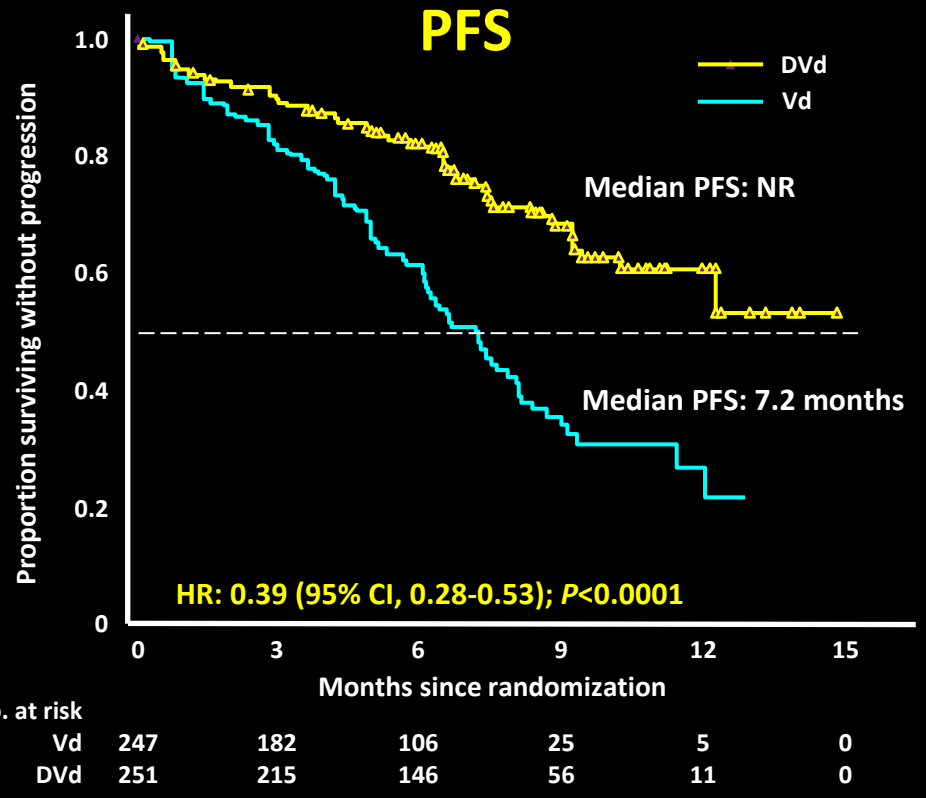
The 18-month and 24-month OS rates were 56.5% (95% CI, 47.9%-64.2%) and 45.0% (95% CI, 35.5%-54.1%), respectively

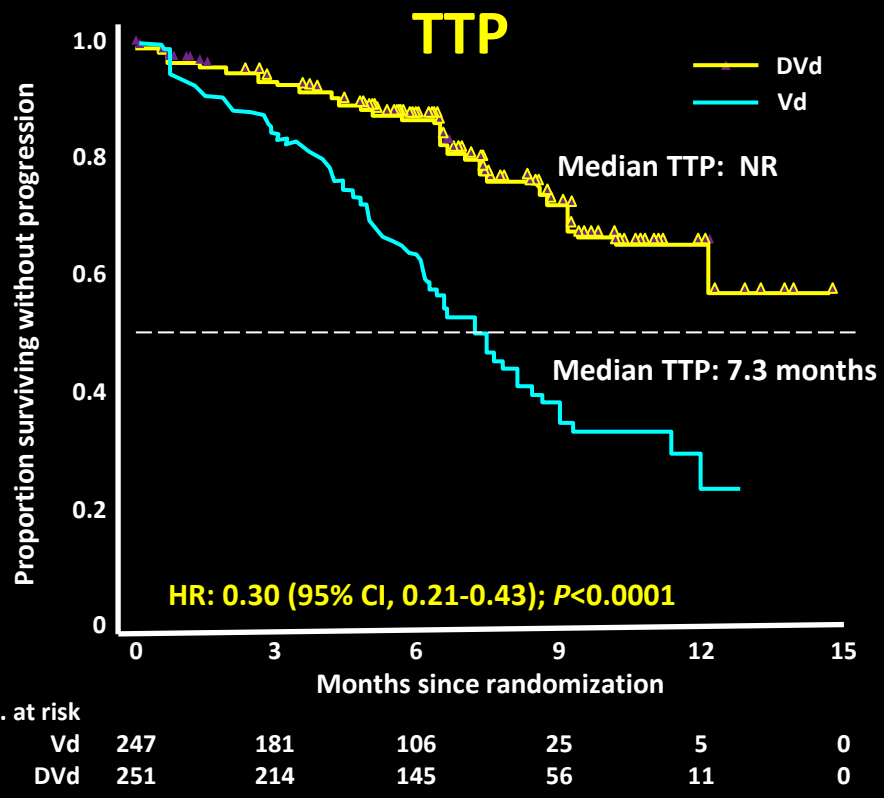
1. Kumar SK, et al. Leukemia. 2012;26(1):149-157.
2. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 4498.

Usmani S, et al. Blood 2016. May 23 [Epub ahead of print].

DVd vs Vd in Relapsed MM - *Phase III CASTOR trial*
Efficacy data: ORR, PFS and TTP

ORR (DVd vs Vd): 83% vs 63% | **CR (DVd vs Vd): 20% vs 9%**





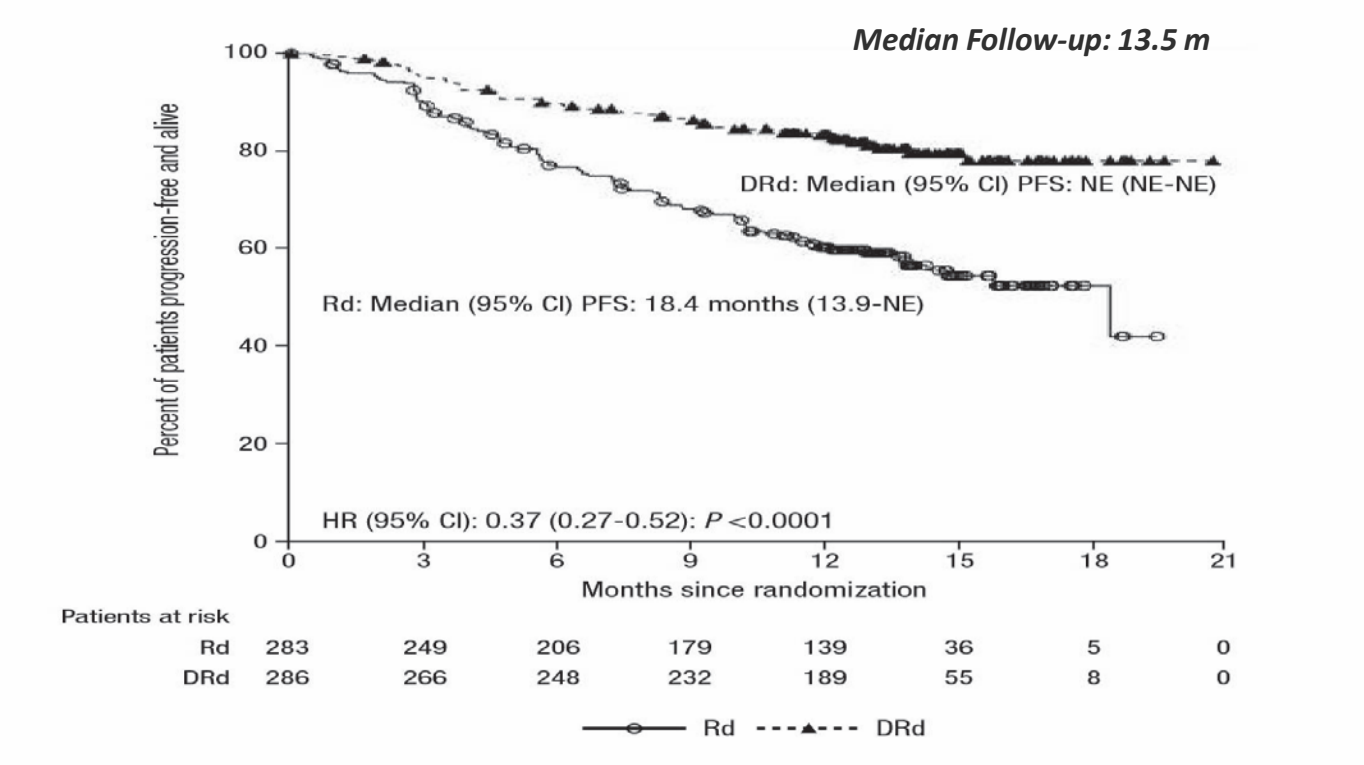
AE: 45% infusion reations (most during the first & Gr ½); PN : 4,5 vs 6,8%
Treatment discontinuation due to AE 7.4% vs 9.3%

Palumbo A, et col. NEJM 2016

Daratumumab-Len-Dex (DRd) vs Len-Dex (Rd) in Relapsed MM - *Phase III POLLUX trial (569 Pts)*

ORR (DRd vs Rd): 93% vs 76% **CR (DRd vs Rd): 43% vs 19%**

TTP (DRd vs Rd): NR vs 18.4 **DOR (DRd vs Rd): NR vs 17.4 m**



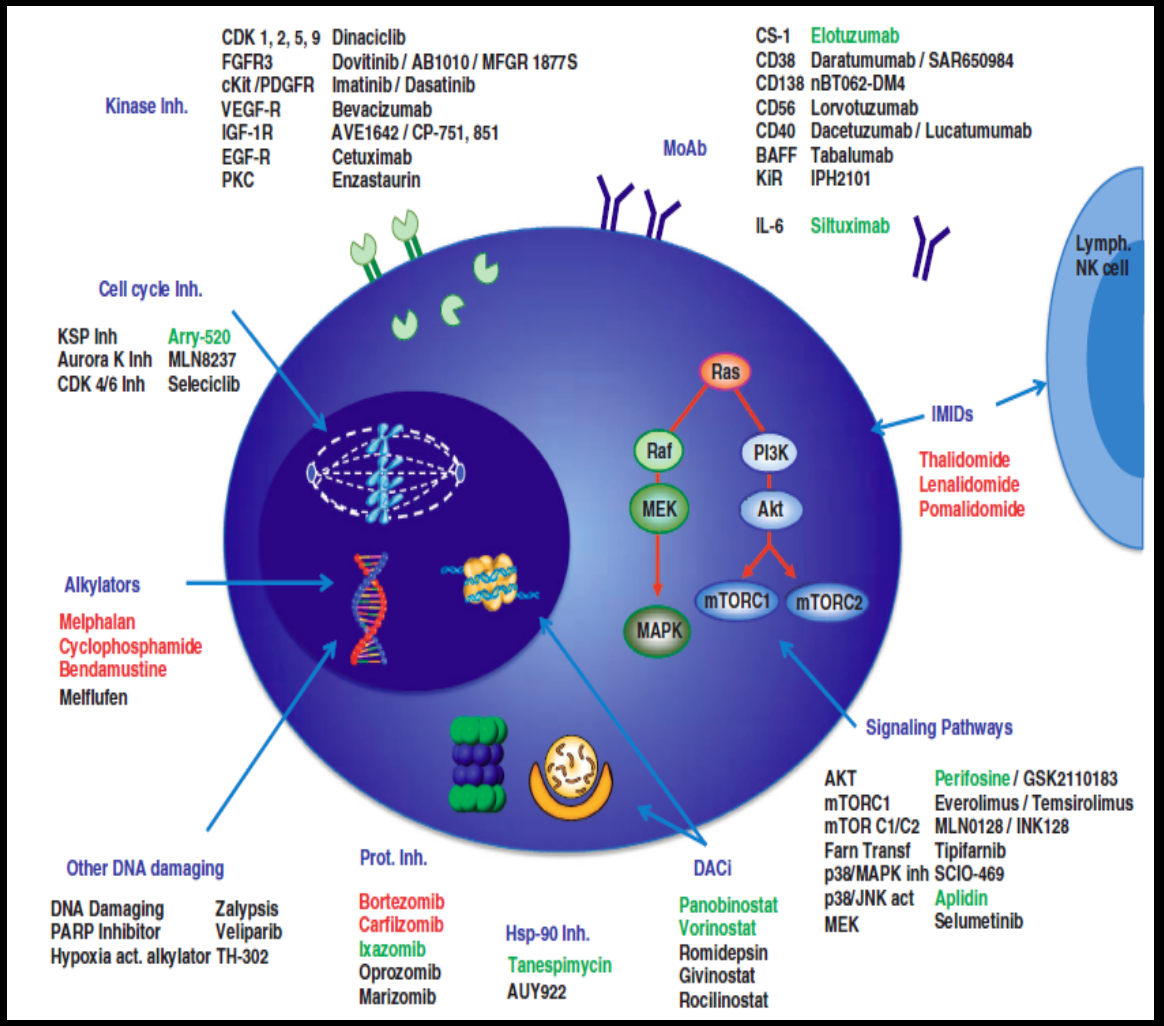
Daratumumab significantly improved PFS (63% reduction in risk of progression/death)

DRd was associated with a manageable safety profile consistent with the profile of D and Rd.

Dimopoulos M, et col. NEJM 2016

Novel drugs in MM

- **Derivatives from already approved**
  - Novel PIs
  - Novel IMiDs
- **Immuno-oncologic approaches**
- **Novel drugs with different MoA**
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors



CDK, cyclin-dependent kinase

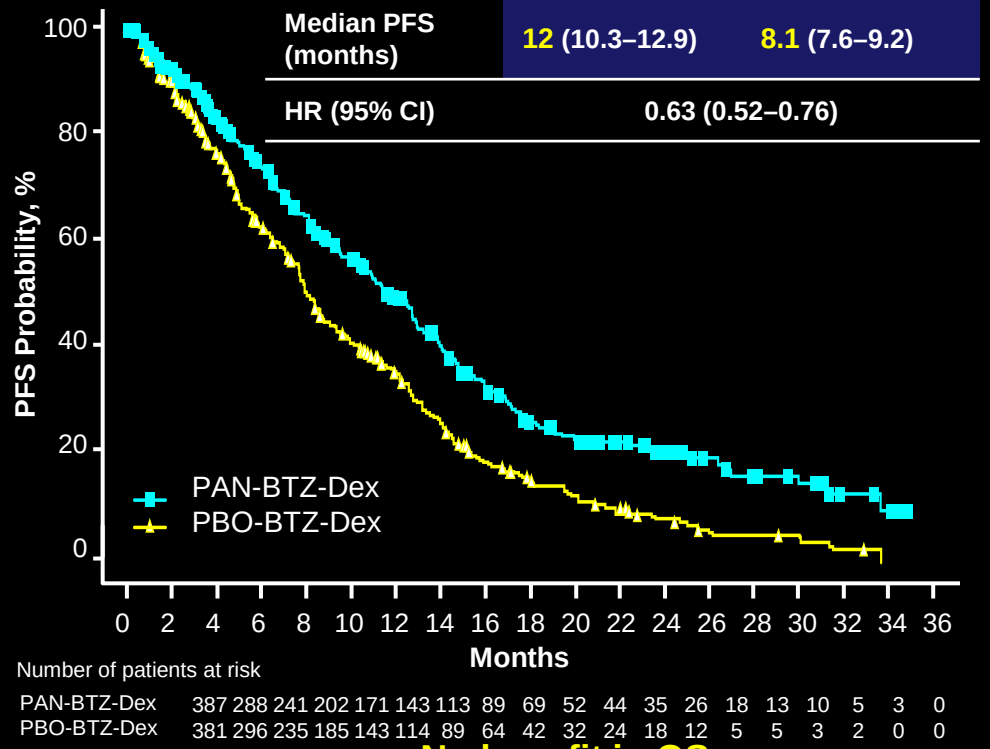
Ocio EM, et al. *Leukemia* 2014; 28: 525-542.

PANORAMA 1: Panobinostat+BTZ+Dex vs. PBO+BTZ+Dex

ORR 60.7% vs. 54.6% | **CR: 27.6% vs. 15.7%**

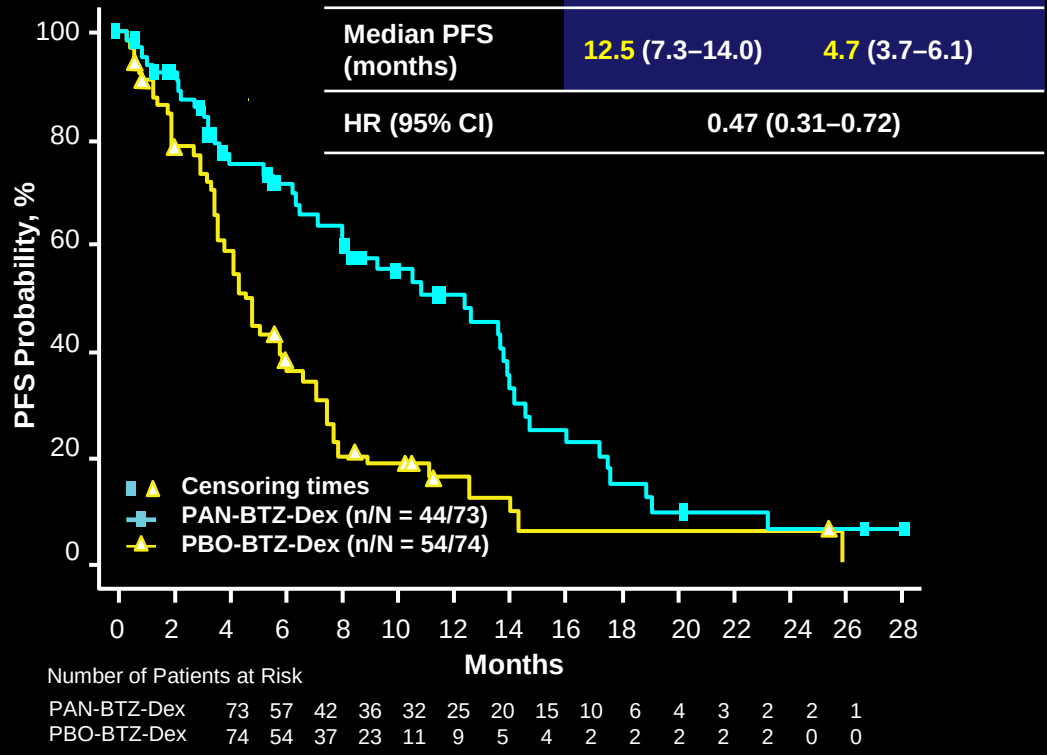
PFS

	PAN-BTZ-Dex	PBO-BTZ-Dex
Median PFS (months)	12 (10.3–12.9)	8.1 (7.6–9.2)
HR (95% CI)	0.63 (0.52–0.76)	



No benefit in OS

	PAN-BTZ-Dex	PBO-BTZ-Dex
Median PFS (months)	12.5 (7.3–14.0)	4.7 (3.7–6.1)
HR (95% CI)	0.47 (0.31–0.72)	



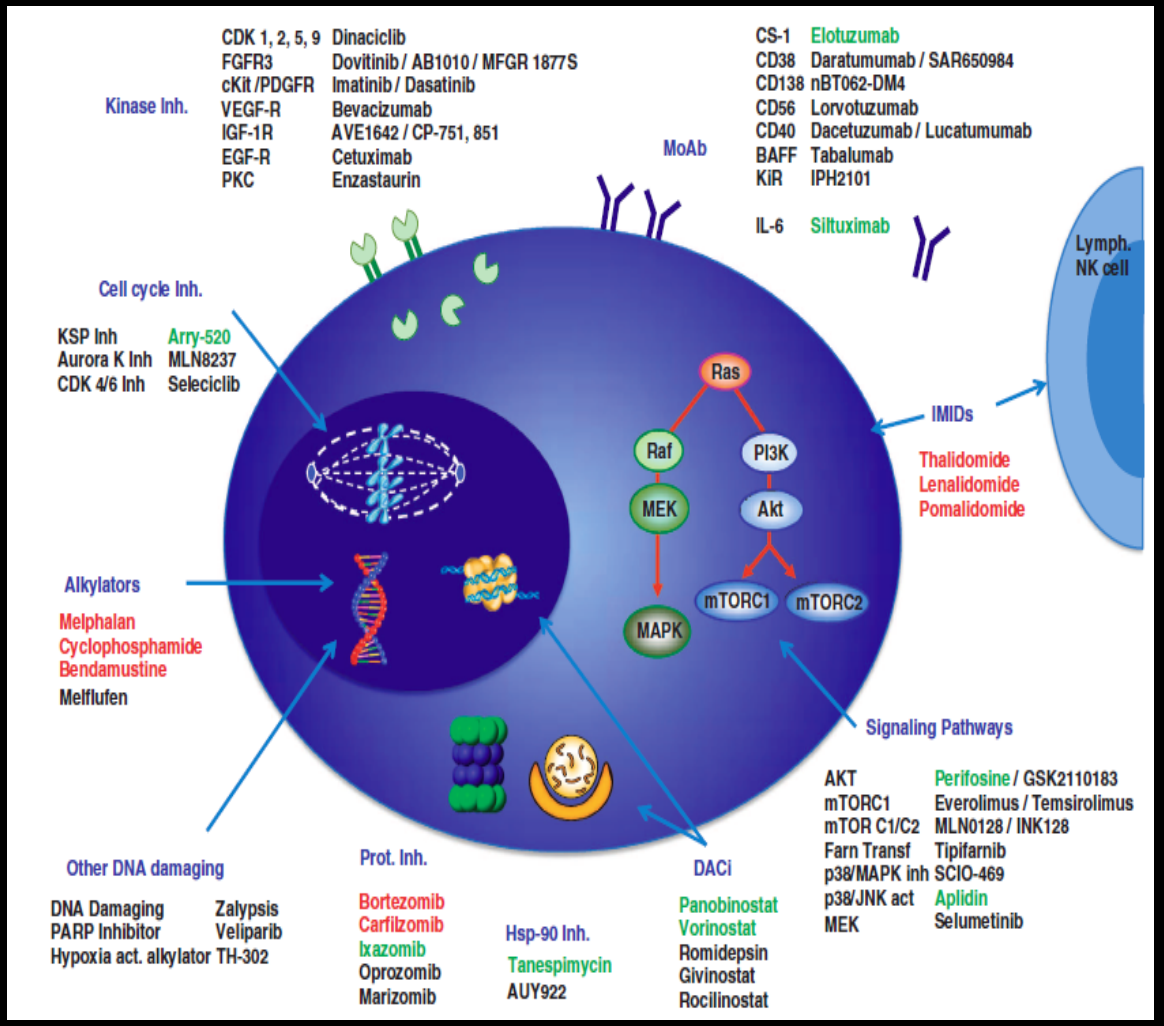
Subgroup analysis by prior treatment: PFS prior BTZ + IMiDs with ≥2 prior lines

BTZ, bortezomib; Dex, dexamethosone; PAN, Panobinostat; PBO, placebo.

San Miguel JF, et al. *Lancet Oncol* 2014; 15: 1195-1206.

Novel drugs in MM

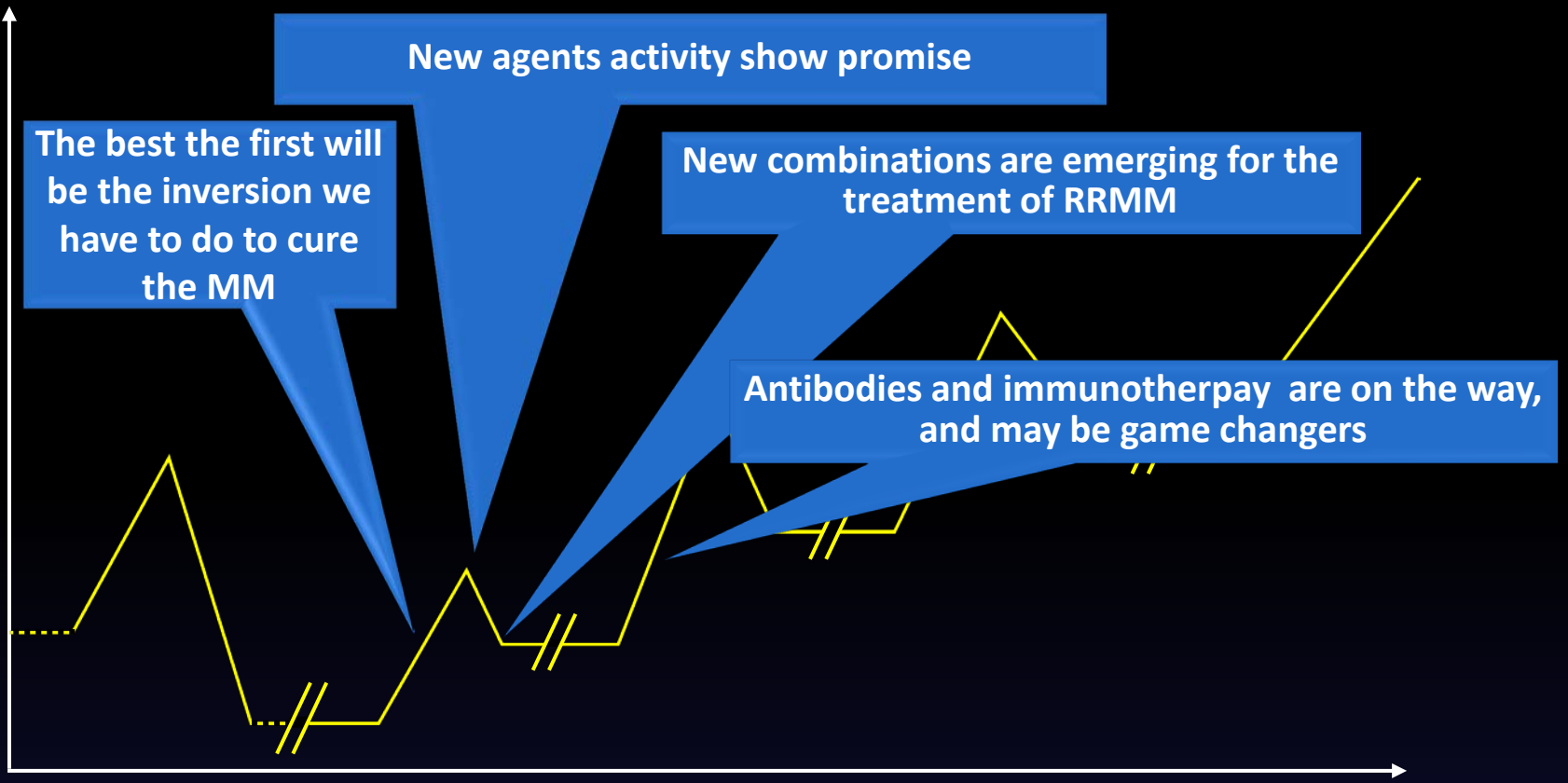
- **Derivatives from already approved**
  - Novel PIs
  - Novel IMiDs
- **Immuno-oncologic approaches**
- **Novel drugs with different MoA**
  - Deacetylase inhibitors
  - CDK inhibitors
  - Akt inhibitors
  - Kinesin spindle protein inhibitors
  - Exportin-1 inhibitor: selinexor



CDK, cyclin-dependent kinase

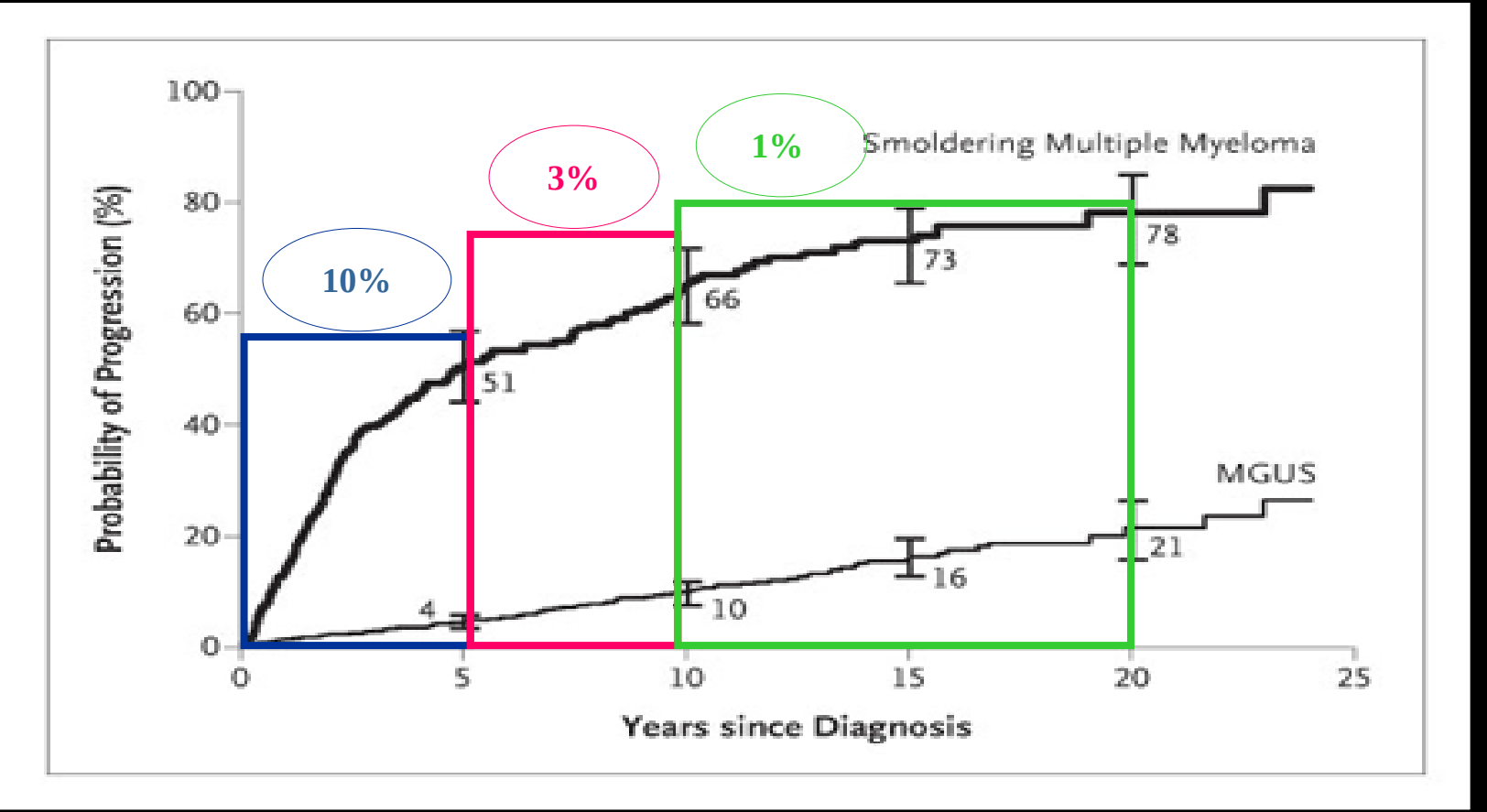
Ocio EM, et al. *Leukemia* 2014; 28: 525-542.

Management of relapsed and refractory MM: Summary



Early Intervention

MGUS/Smouldering Multiple Myeloma: Risk of progression to active disease

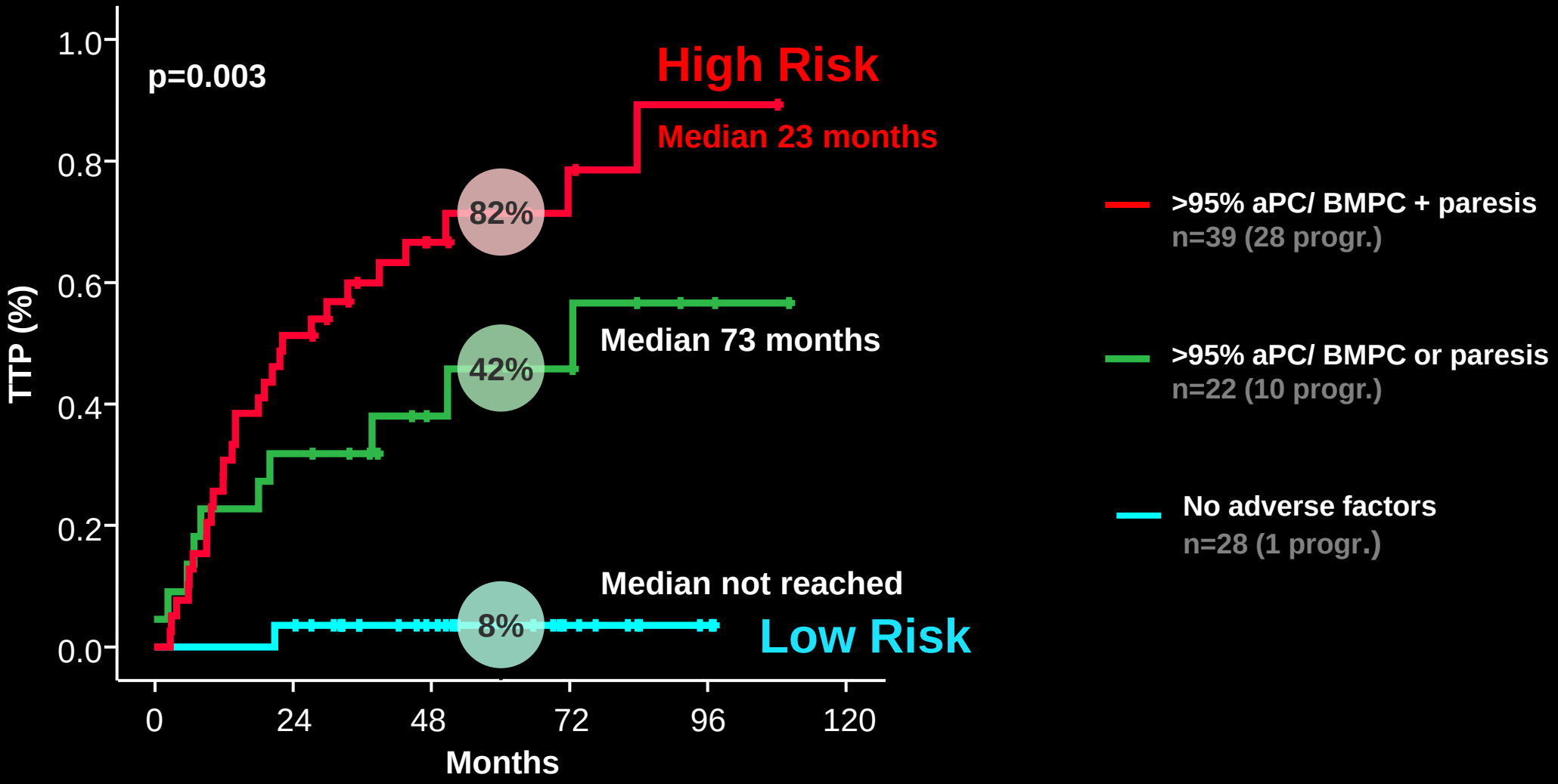


According to the heterogeneity in the risk of progression to MM, we have to identify the individual risk for each new SMM patient.

Kyle R. N Engl J Med 2007; 356:2582-90

Smoldering multiple myeloma: Risk of transformation into symptomatic MM

Based on the % of aberrant PCs by immunophenotype plus immunoparesis

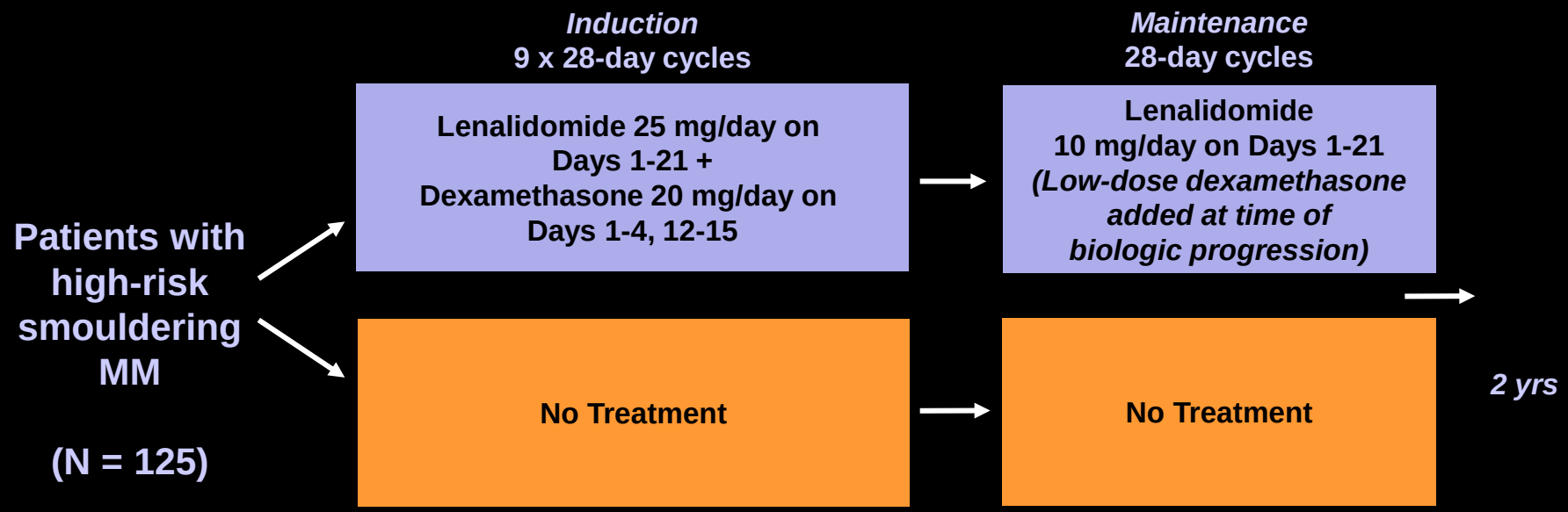


aPC, aberrant plasma cell; prog. progression.

Perez-Persona E, et al. *Blood* 2007;110: 2586-2592.

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial



In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

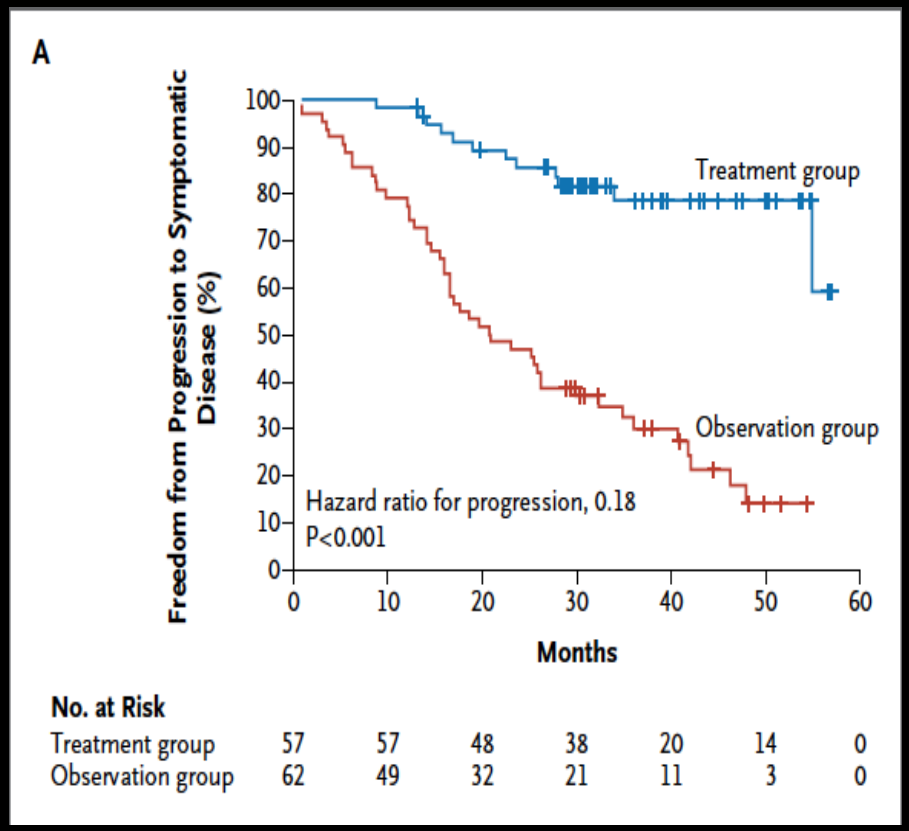
High-risk was defined according to the Mayo and/or Spanish models

Mateos MV, et al. NEJM 2013; 369:438-47

Len-dex vs no treatment: TTP to active disease (n = 119)

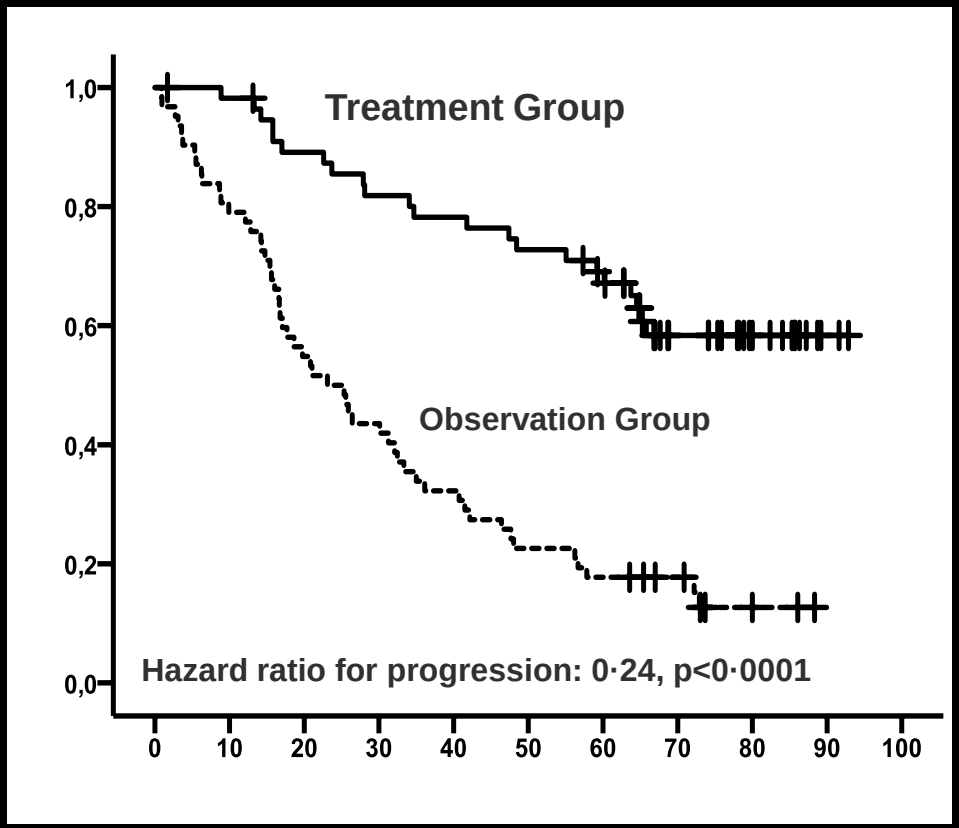
Per-protocol Patients population

Median follow-up: 40 m



Mateos MV, et al. NEJM 2013

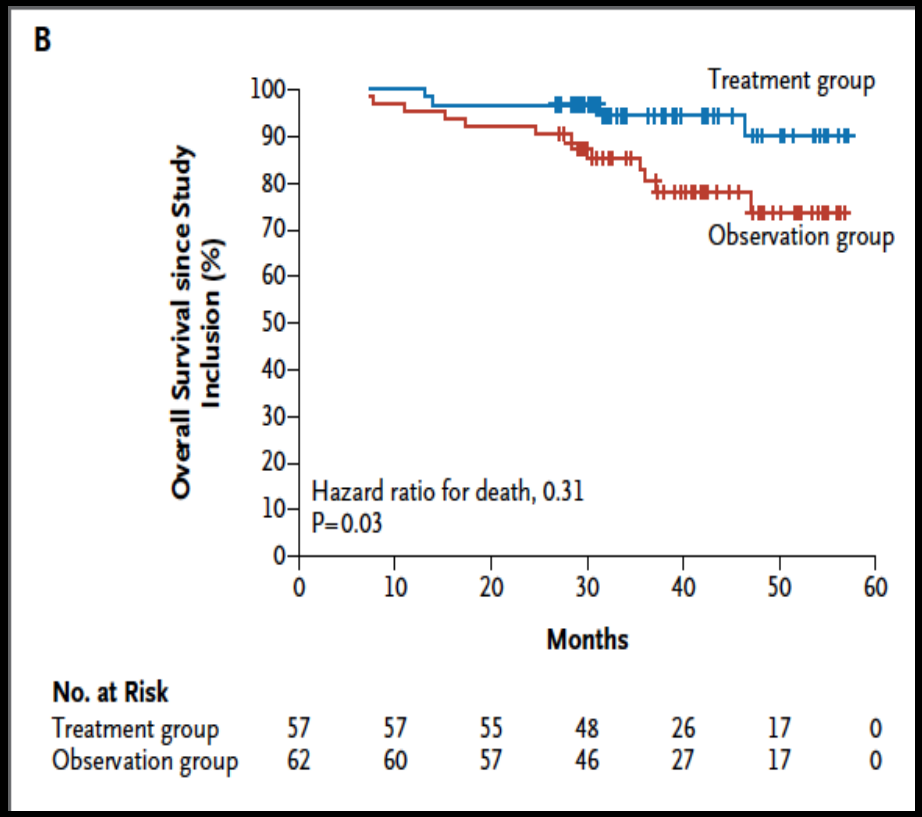
Median follow-up: 75 m



Mateos MV, et al. Lancet Oncology 2016: accepted for publication

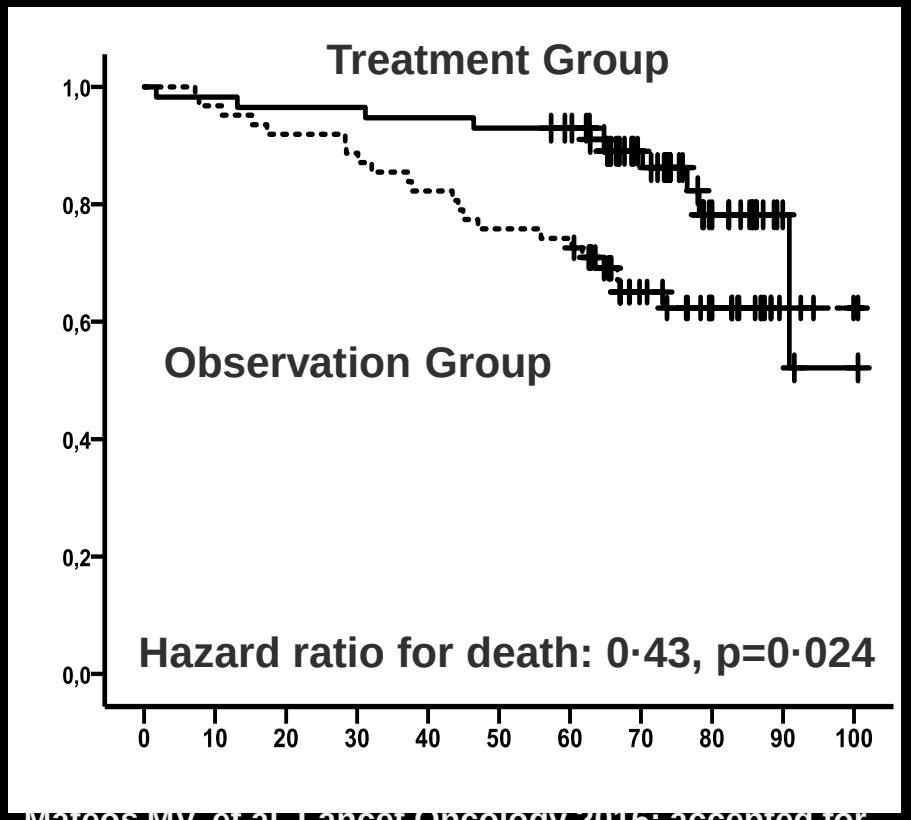
Len-dex vs no treatment: OS from inclusion (n = 119)

Median follow-up: 40 m



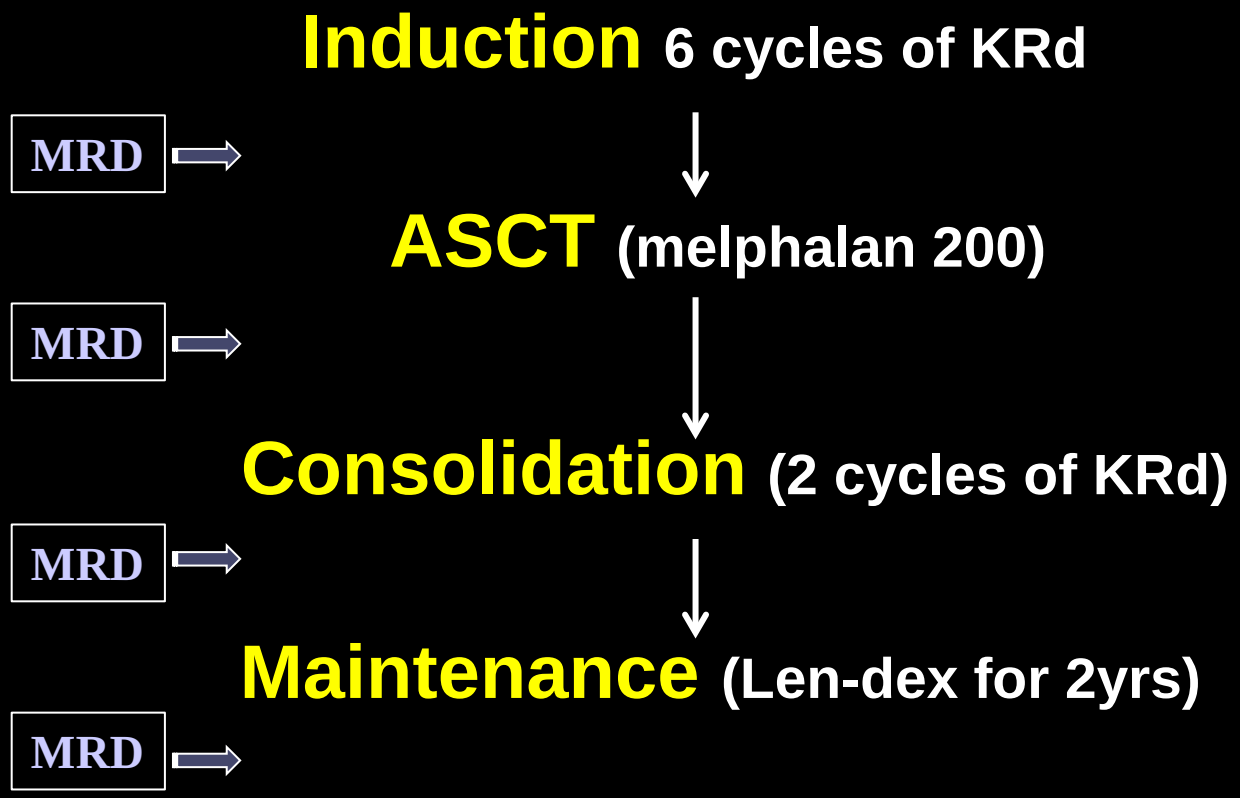
Mateos MV, et al. NEJM 2013

Median follow-up: 75 m



Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Curative Estrategia Smouldering Alto Riesgo (CESAR trial) (n:90)



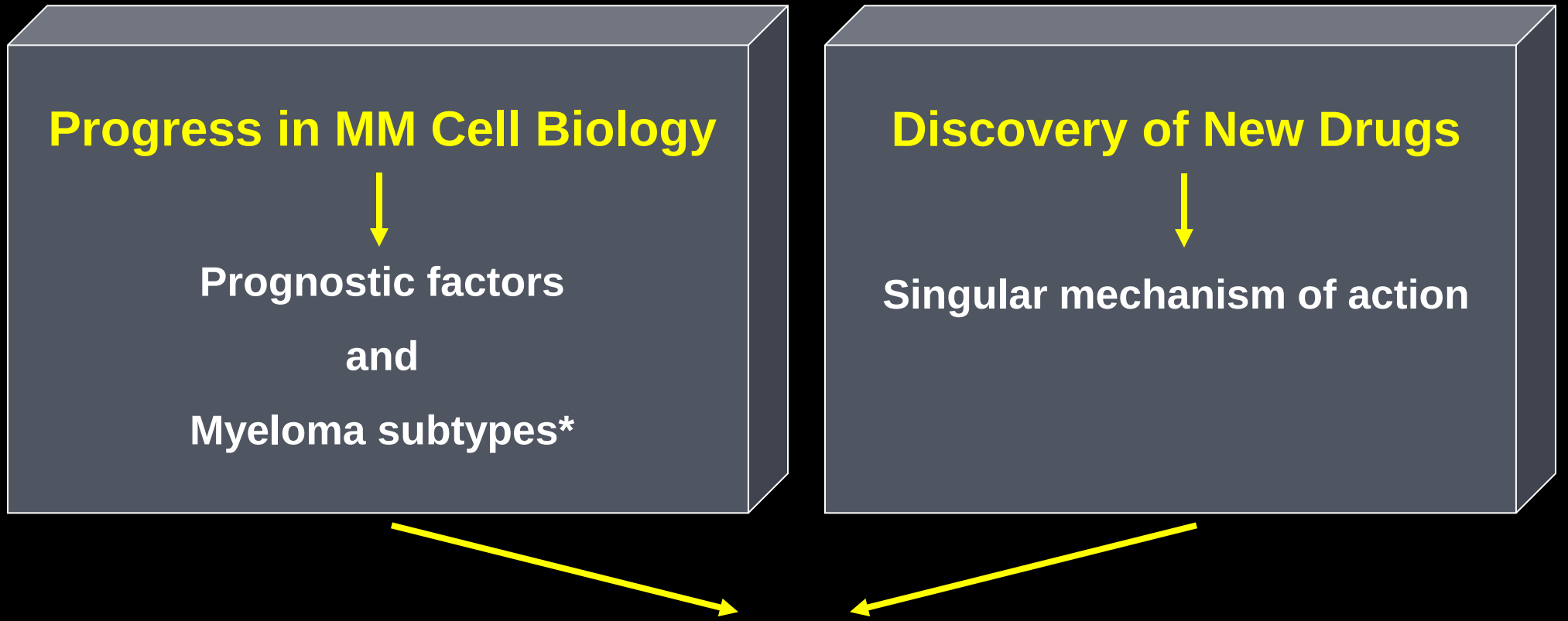
Primary objective: To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

Hypothesis: At least 50% of patients will achieve the objective

20 centers

Multiple myeloma: A model for scientific and clinical progress

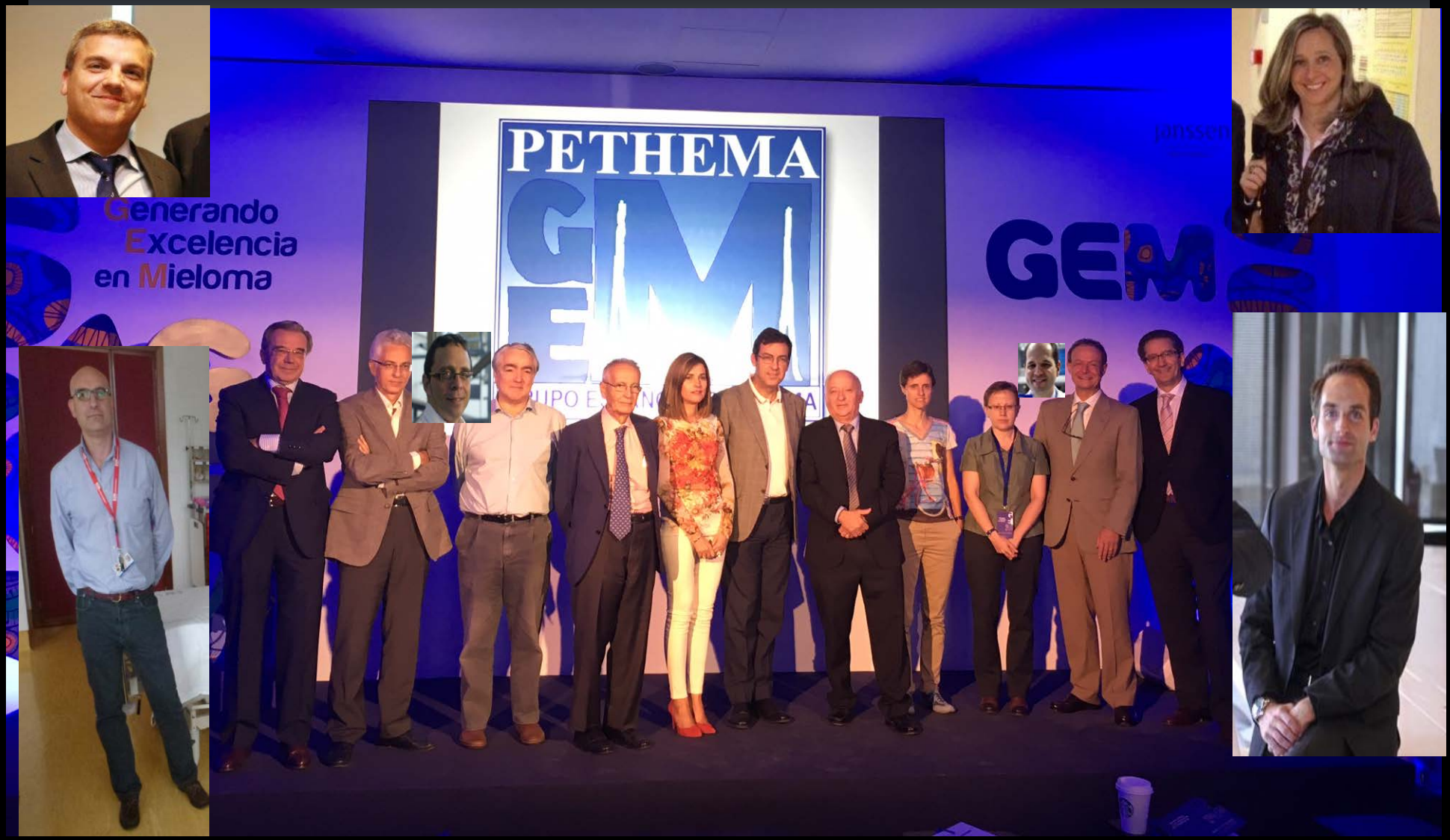
From biology to therapeutics



*MM should not be considered a single entity.

Acknowledgments: Investigators of GEM

Acknowledgments: GEM/Pethema



Support from Arturo Touchard & LLA

Acknowledgments: Patients

Asociaciones locales de cada ciudad/region por el soporte

Acknowledgments: pharmaceutical companies

VELCADE

Genmab
Daratumumab
DARZALEX

SANOFI
SAR650984
Isatuximab

MK-3475
Pembrolizumab
Keytruda

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

SANOFI

MSD

Revlimid

Imnovid (pomalidomide)

AstraZeneca
MEDI4736
Durvalumab

Pharma Mar
Grupo Zeltia

NOVARTIS
Panobinostat
Farydak®

Bristol-Myers Squibb
Elotuzumab
Empliciti™

Bristol-Myers Squibb Company
Nivolumab

Celgene

NOVARTIS

Carfilzomib
Kyprolis

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