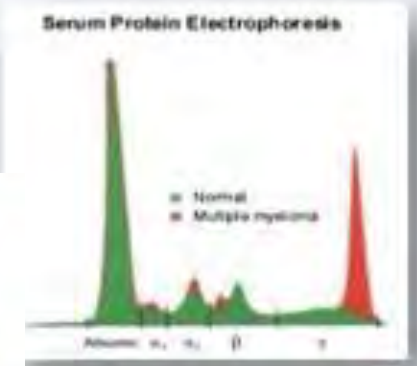
MIELOMA

Multiple Myeloma

Clonal proliferation of malignant plasma cells.



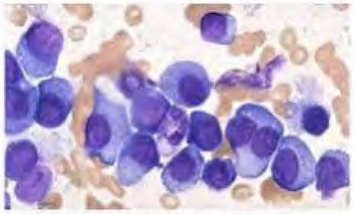


Image 1: Multiple myeloma plasma cells with classic "fried egg" appearance.

- excess bone marrow plasma cells
- monoclonal protein
- osteolytic bone lesions
- renal disease
- anemia
- immunodeficiency

"Punched Out" Lesions

Worldwide ~1% of all new cancer cases.

Raab et al., Lancet, 2009

Diagnostic Criteria for Myeloma

	Monoclonal Gammopathy of uncertain significance (MGUS)	Smouldering Multiple Myeloma (SMM)	Multiple Myeloma
Monoclonal component	< 3 g/dL serum	≥ 3 g/dL serum	Present (*serum/urine*)
	AND	AND/OR	AND
Bone Marrow Plasma Cells (%)	< 10%	10-60%	> 10%[b]
	AND	AND	AND
Mieloma-defining event	Absent	Absent	Present

Rajkumar, S.S. et al. Lancet Oncol 2014; 15: e538–48.

Revised IMWG diagnostic criteria

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

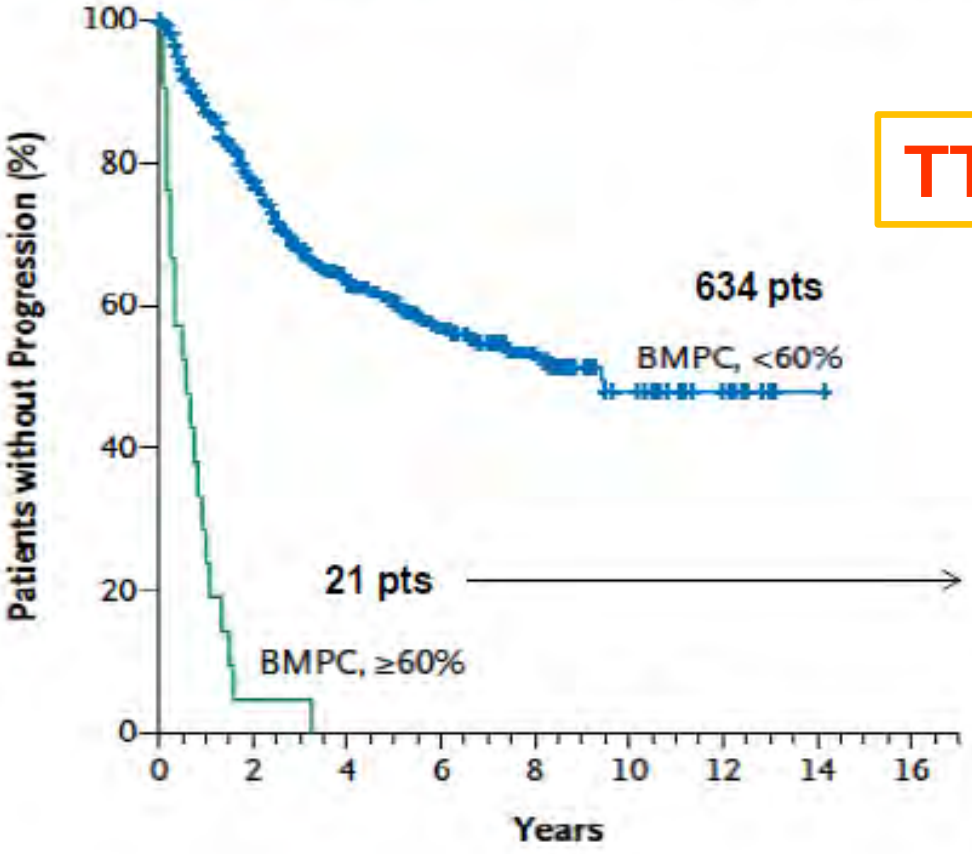
LLN, lower limit of normal; PET-CT=18F-fluorodeoxyglucose PET with CT; ULN, upper limit of normal.
*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Rajkumar, S.S. et al. Lancet Oncol 2014; 15: e538–48.

Bone Marrow Plasma Cell

Clonal bone marrow PC ≥ 60%

Biomarker validated in two independent series [1,2]



TTP within 2 years: 90%

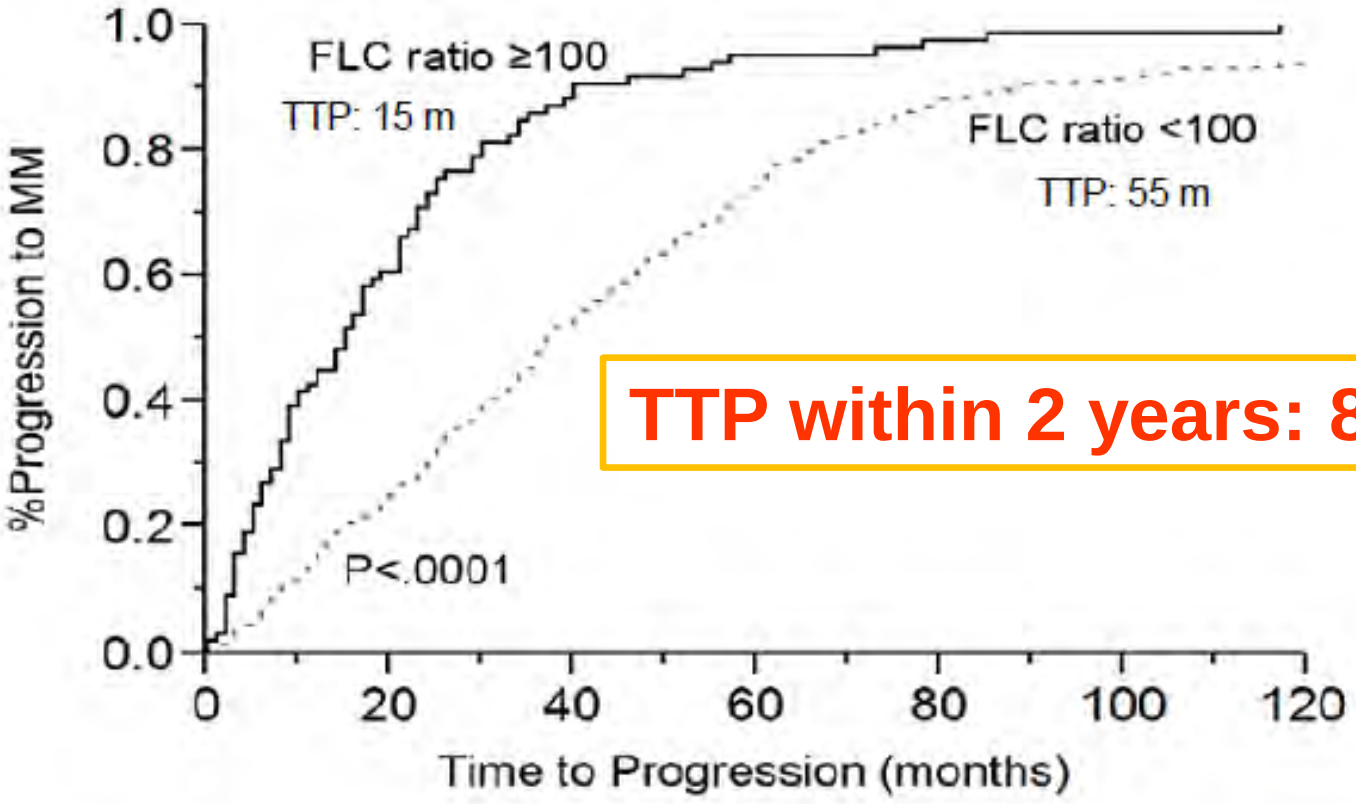
"In these patients (3.2%), median TTP was 7m and 95% of them progressed to symptomatic MM within 2y" [1]

1. Rajkumar et al. N Engl J Med 2011; 365:474-475
2. Kastritis et al. Leukemia 2013;27(4):947-53

FLC ratio and risk of progression to MM

Involved/uninvolved serum FLC ratio ≥ 100 (and involved FLC level must be ≥ 100 mg/l)

Biomarker validated in three independent series [1-3]



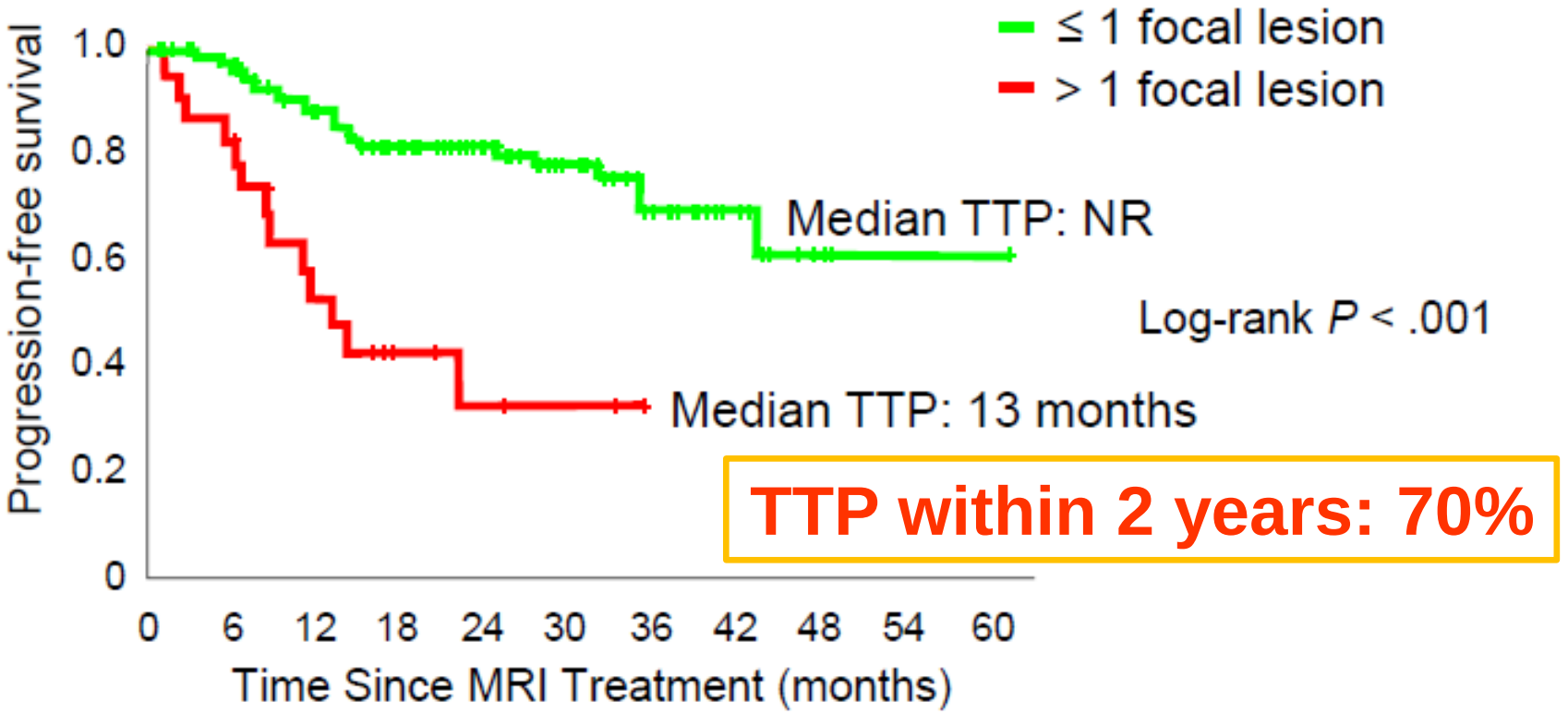
TTP within 2 years: 80%

1. Larsen et al. Leukemia 2013;27(4):941-6
2. Kastritis et al. Leukemia 2013;27(4):947-53
3. Waxman et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8607)

Focal lesion on advanced imaging

➢> 1 focal lesions on MRI studies (at least of 5 mm)

Biomarker validated in two independent series [1,2]



TTP within 2 years: 70%

1. Hillengass et al. J Clin Oncol 2010;28:1606-1610
2. Kastritis et al. Leukemia 2014;28(12):2402-3

How I treat smoldering multiple myeloma

Irene M. Ghobrial and Ola Landgren

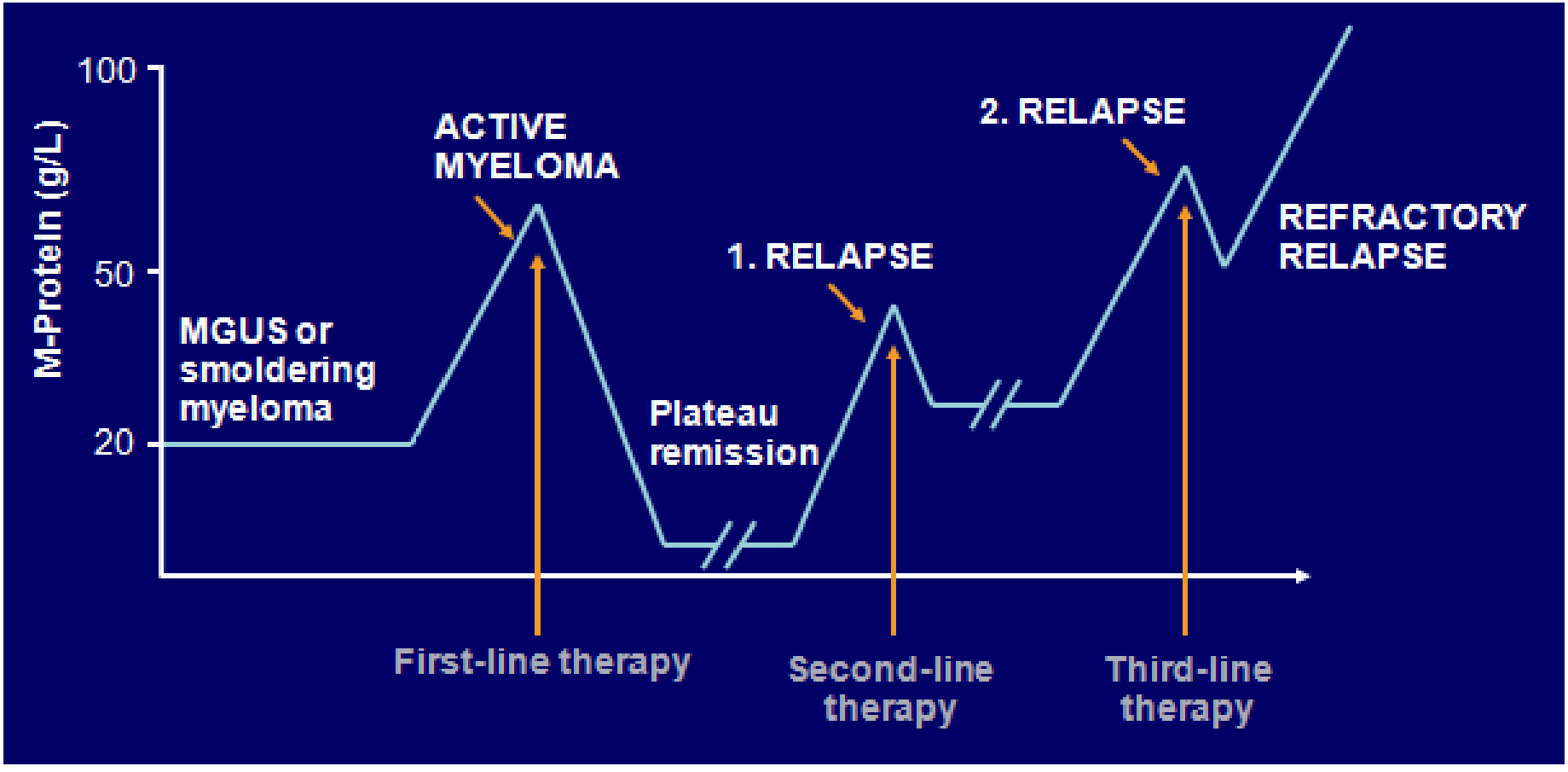
blood Prepublished online October 8, 2014;
doi:10.1182/blood-2014-08-551549

Myeloma requiring therapy

- Clonal bone marrow plasma cells ≥10% or biopsy proven plasmacytoma **and**
- Any CRAB criteria
- **Or any MYELOMA DEFINING EVENTS (MDE)** as follows:
  - Clonal bone marrow plasma cell percentage*≥ 60%
  - An abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda)
  - 2 or more focal lesions on MRI or PET-CT studies

- **TREATMENT SHOULD BE INITIATED IN THESE PATIENTS**

Natural History of Multiple Myeloma

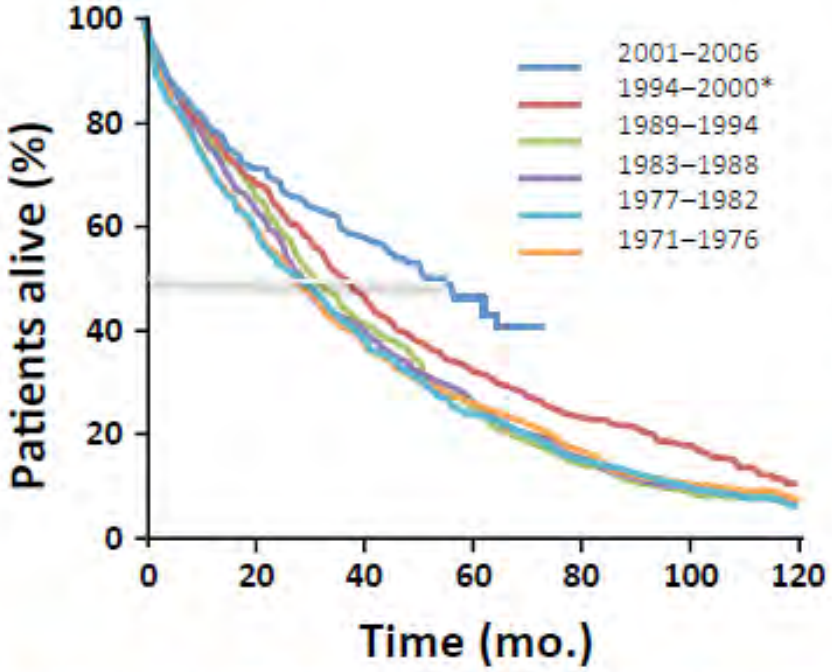


- MM is characterized by a pattern of remission and relapse
- Remission duration decreases with each line of therapy

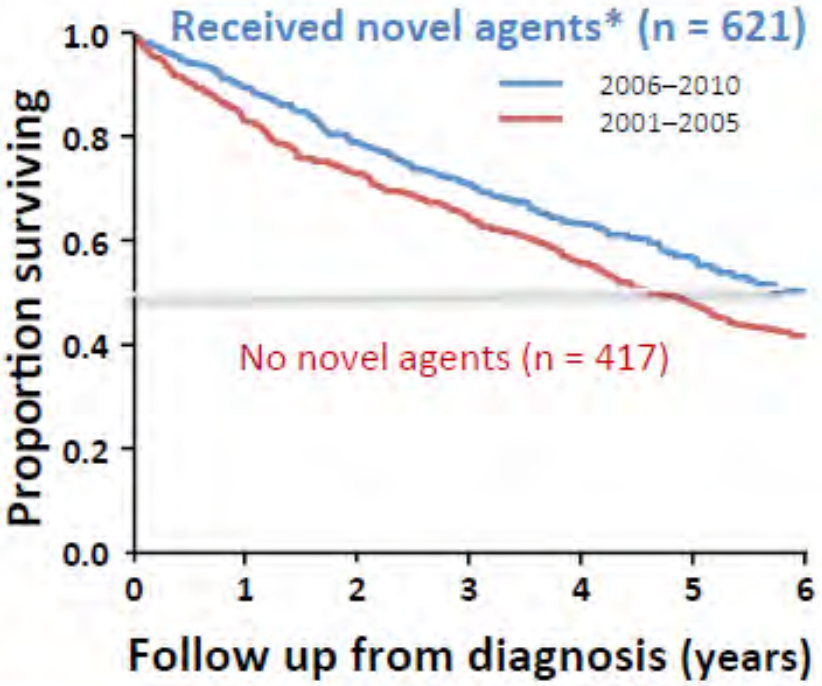
Durie. *Concise Review of the Disease and Treatment Options: Multiple Myeloma*. International Myeloma Foundation; 2011/2012 edition;
Kumar. *Mayo Clin Proc*. 2004;79:867.

OS in MM continues to improve vs historical estimates

OS from diagnosis between 1971 and 2006 (N = 2,981)[1]



OS from diagnosis between 2001 and 2010 (N = 1,038)[2]

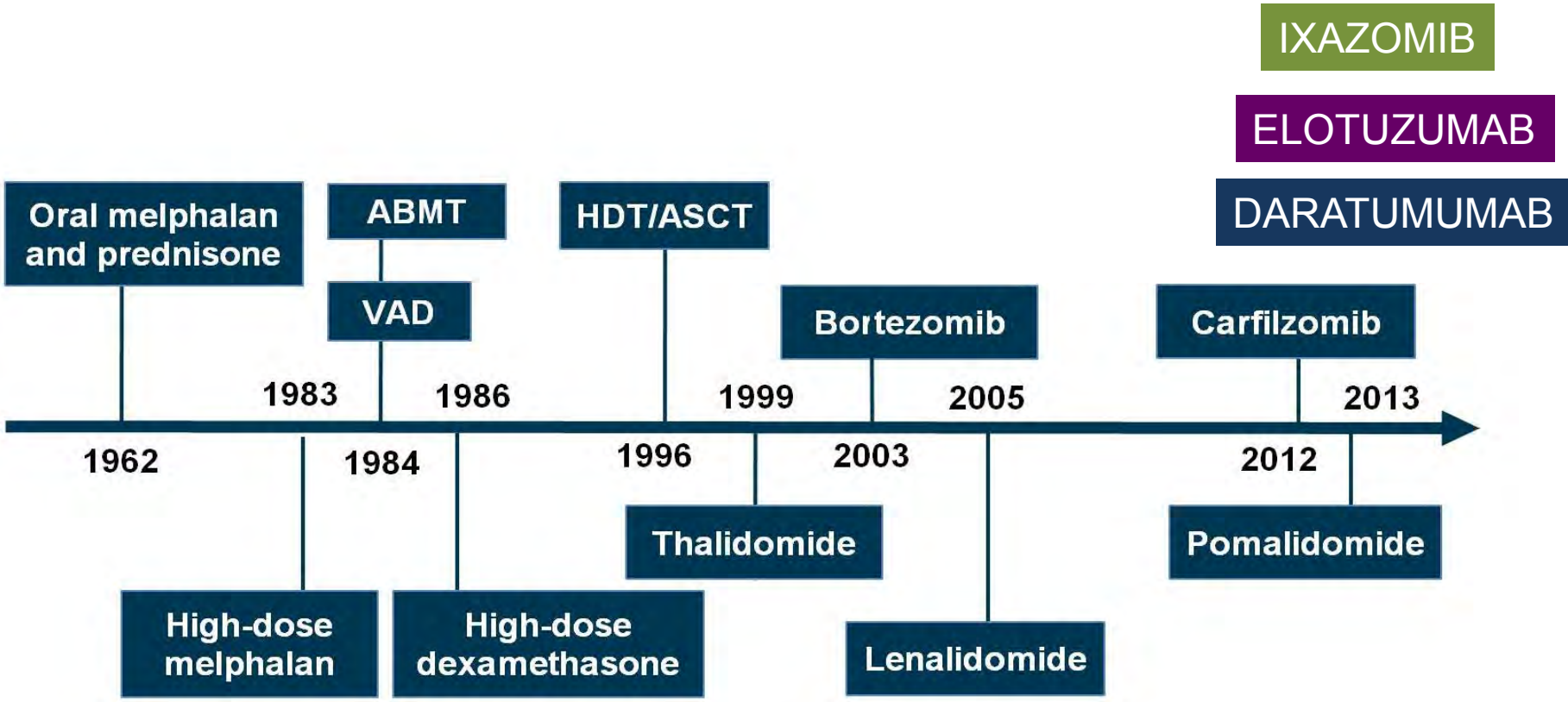


*Bortezomib (BTZ), lenalidomide (LEN) or thalidomide (THAL) as part of initial therapy

Kumar SK, et al. Blood 2008;111:2516–2520;

Kumar SK, et al. Leukemia 2014;28:1122–1128.

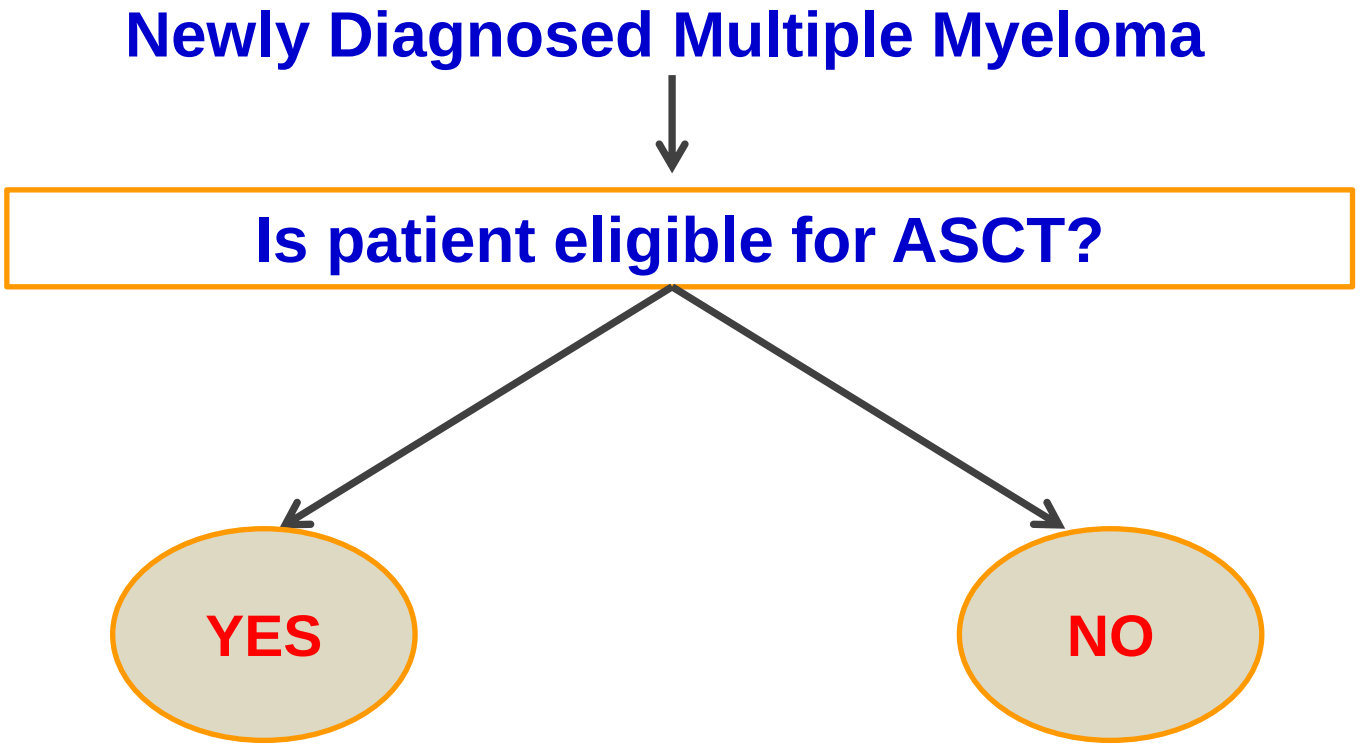
Myeloma Drug Development



Classi di farmaci	Nome del farmaco	Target del farmaco	Combinazioni approvate da FDA e/o EMA
Immunomodulanti	Talidomide	Effetto pro-apoptotico diretto e immunomodulante sul microambiente midollare	Td, MPT, CTD, VTD
	Lenalidomide		Rd, MPR, VRD, KRd, IRd, DaraRd, EloRd
	Pomalidomide		Pd, DaraPd
Inibitori del proteasoma	Bortezomib	Blocco dello smaltimento proteico cellulare mediante l'inibizione del proteasoma	VD, VMP, VCD, VTD, VRD, PAD, PanoVd
	Carfilzomib		KRd
	Ixazomib		IRd
Inibitori dell'istone deacetilasi	Panobinostat	Controllo epigenetico di diversi processi cellulari	PanoVd
Anticorpi monoclonali	Elotuzumab	Anti-CS1	EloRd
	Daratumumab	Anti-CD38	DaraRd, DaraVd

T: talidomide; R: lenalidomide; P: pomalidomide; V: bortezomib; P: bortezomib; K: carfilzomib; I: ixazomib; Pano: panobinostat; Elo: elotuzumab; Dara: daratumumab

First-line Therapy



Age *per se* is not a contraindication for auto-SCT in an elderly but fit myeloma patient

The Transplant Eligibility Discussion

- ASCT remains a standard of care for patients ≤65 years of age in most countries - IFM 2009 and EMN studies[1,2]
- No large phase 3 randomized study has established the role of ASCT in elderly fit patients in the era of novel agents
- ASCT routinely performed in some countries/centers for elderly fit patients between 65 and 75 years of age
- TIME TO HAVE A STUDY FOCUSED ON FIT ELDERLY

1. Attal M et al. *Blood*. 2015;126: Abstract 391.
2. Gay F et al. *Blood*. 2015;126: Abstract 392.

TRANSPLANT ELIGIBLE: induction phase

PHASE	Cycles	Drug-based treatment	TERAPIA APPROVATE	TERAPIA STANDARD
Induction	4-6	Three-drug combination: VTD/VCD/VRD/KRD	**VTD VD**	**VTD x4→x2**

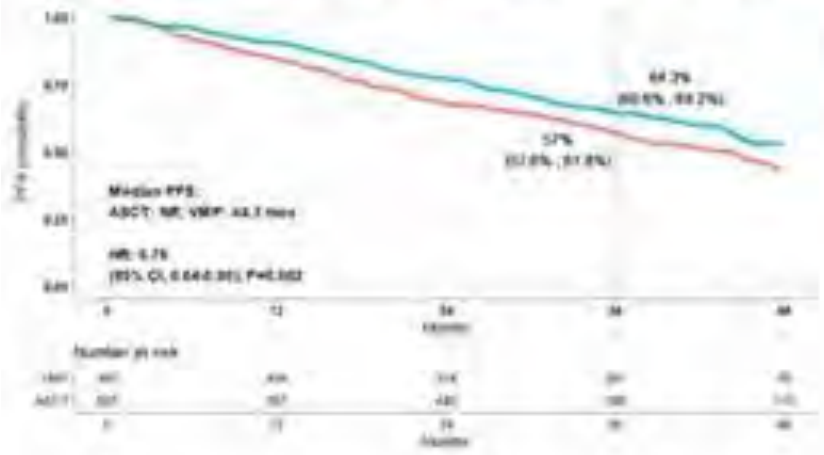
AIFA	Modalità di somministrazione:	Raccomandazioni:
VTD	Velcade 1,3 mg/mq gg+1+4+8+11/28gg Dex 40mg gg1, 2, 3, 4, 8, 9, 10 e 11/28gg Talidomide 50mg/100mg/200mg	4 CICLI Se PR→+2 cicli
VD	Velcade 1,3 mg/mq gg+1+4+8+11/21gg Dex 40mg gg1, 2, 3, 4, 8, 9, 10 e 11/21gg	4 CICLI Se PR→+2 cicli

Upfront ASCT: state of the art

Autograft 1 or 2

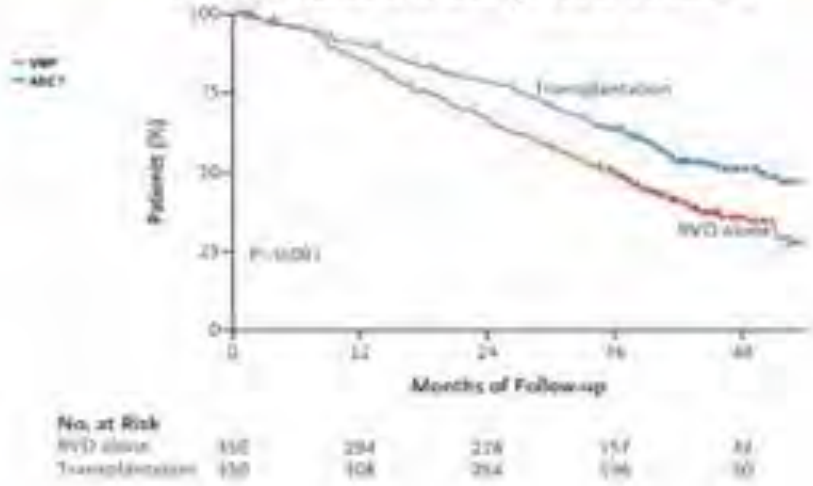
ESMO Guidelines 2017
High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment in fit patients.

EMN02/HO95 phase 3 study: VMP vs ASCT



- Median follow-up: 37.8 months

IFM 2009 phase 3 study: RVD vs ASCT



- Median follow-up: 43.5 months

Attal M, et al. NEJM 2017; 376: 1311-1320.
Cavo M, et al. ASH 2017 (Abstract 397), oral presentation.

TRANSPLANT ELIGIBLE: post transplant phase

PHASE	Cycles	Drug-based treatment	TERAPIA APPROVATE	TERAPIA STANDARD
Post-transplant consolidation	2-4	**Combining different PIs and IMIDs.** *VTD/VRD... not well established*	Nessuna	?
Maintenance	Untill PD/ toxicity	**Individualization of treatment:** *Lenalidomide,Bortezomib novel PI*	Lenalidomide*	Lenalidomide*

AIFA*	Modalità di somministrazione:	Raccomandazioni:
Lenalidomide	10mg gg1-28, dopo 3 cicli 15mg	Terapia di mantenimento fino a PD o intolleranza

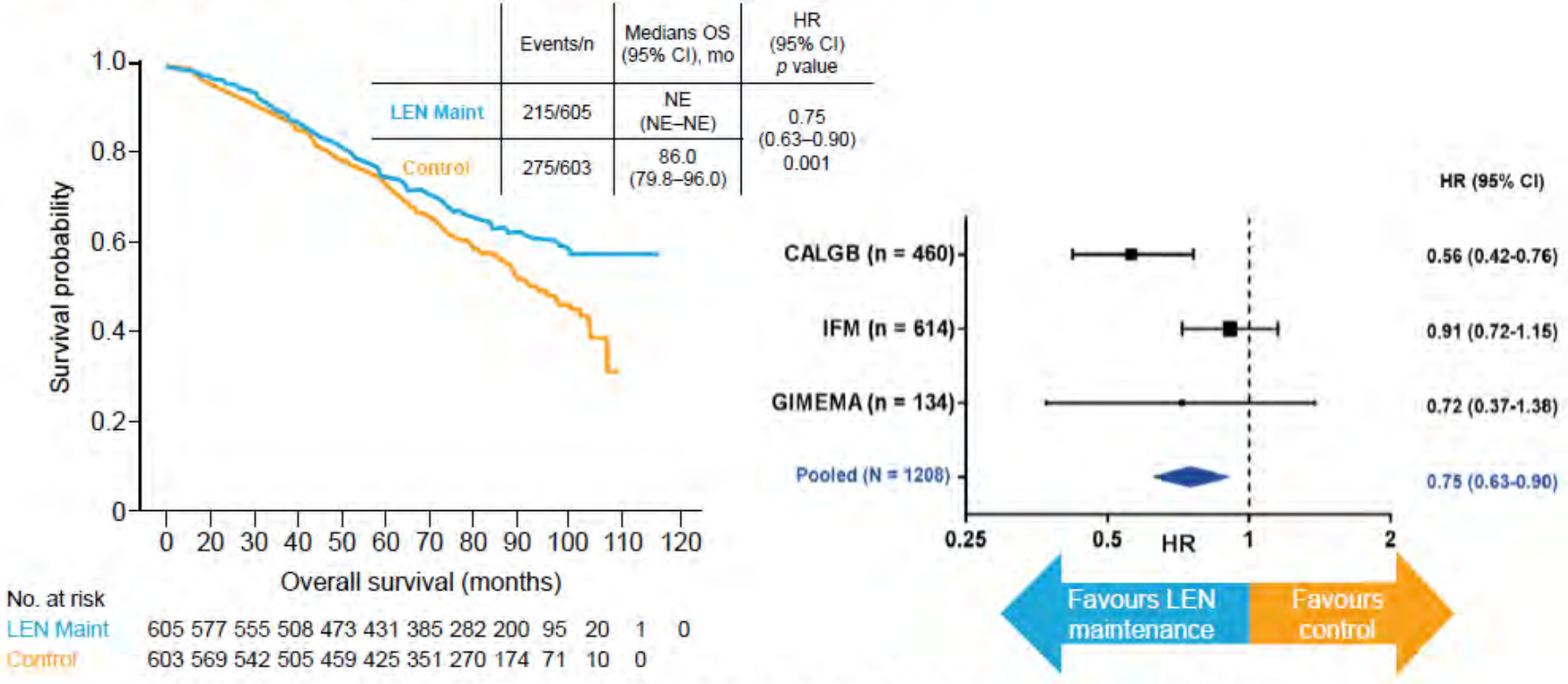
Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

Philip L. McCarthy, Sarah A. Holstein, Maria Teresa Petrucci, Paul G. Richardson, Cyrille Hulin, Patrizia Tosi, Sara Bringhen, Pellegrino Musto, Kenneth C. Anderson, Denis Caillot, Francesca Gay, Philippe Moreau, Gerald Marit, Sin-Ho Jung, Zhinuan Yu, Benjamin Winograd, Robert D. Knight, Antonio Palumbo, and Michel Attal

J Clin Oncol 35. © 2017

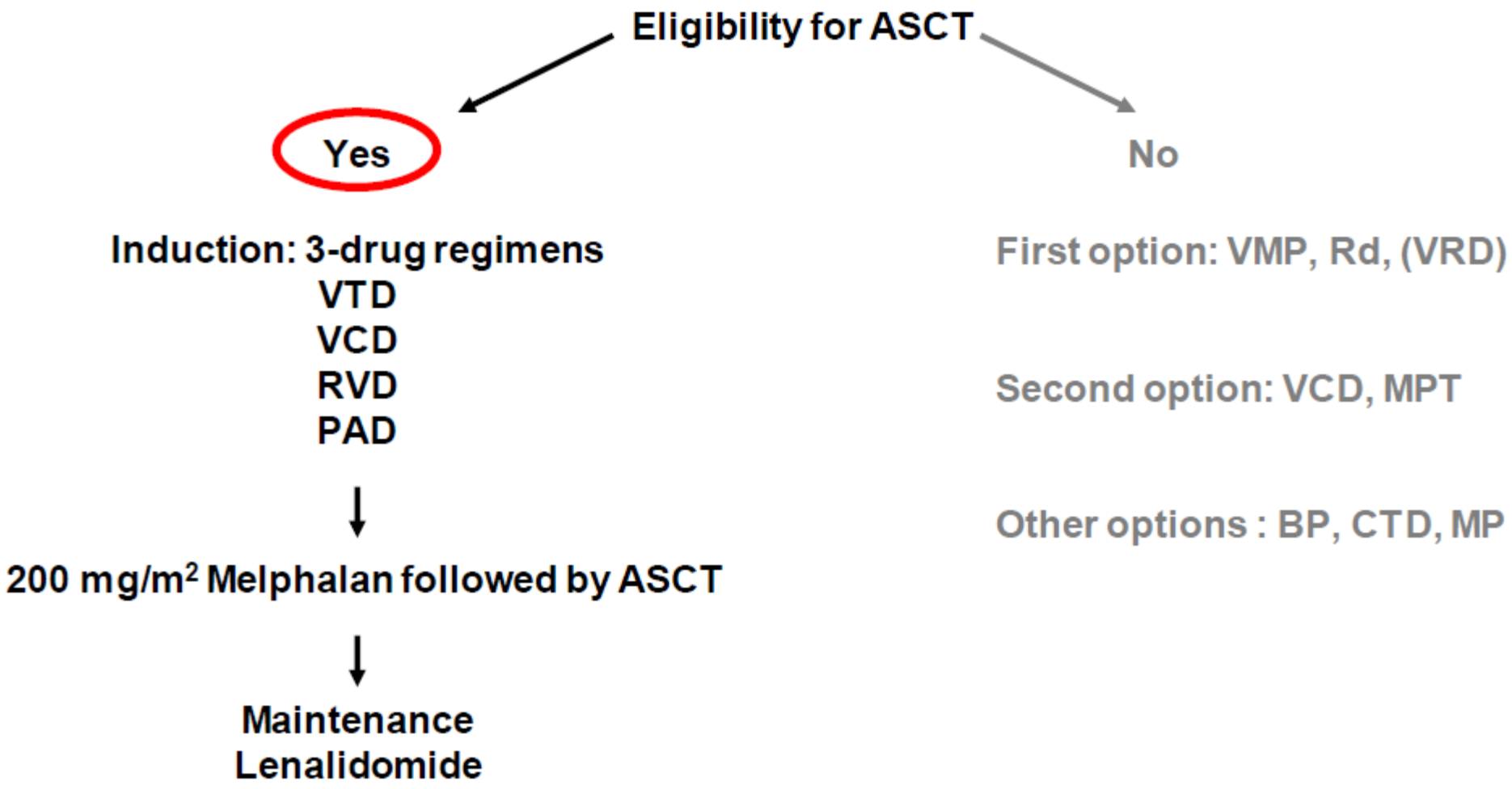
Meta-analysis: OS

Data cut-off: March 2015; Median follow up: 80 months



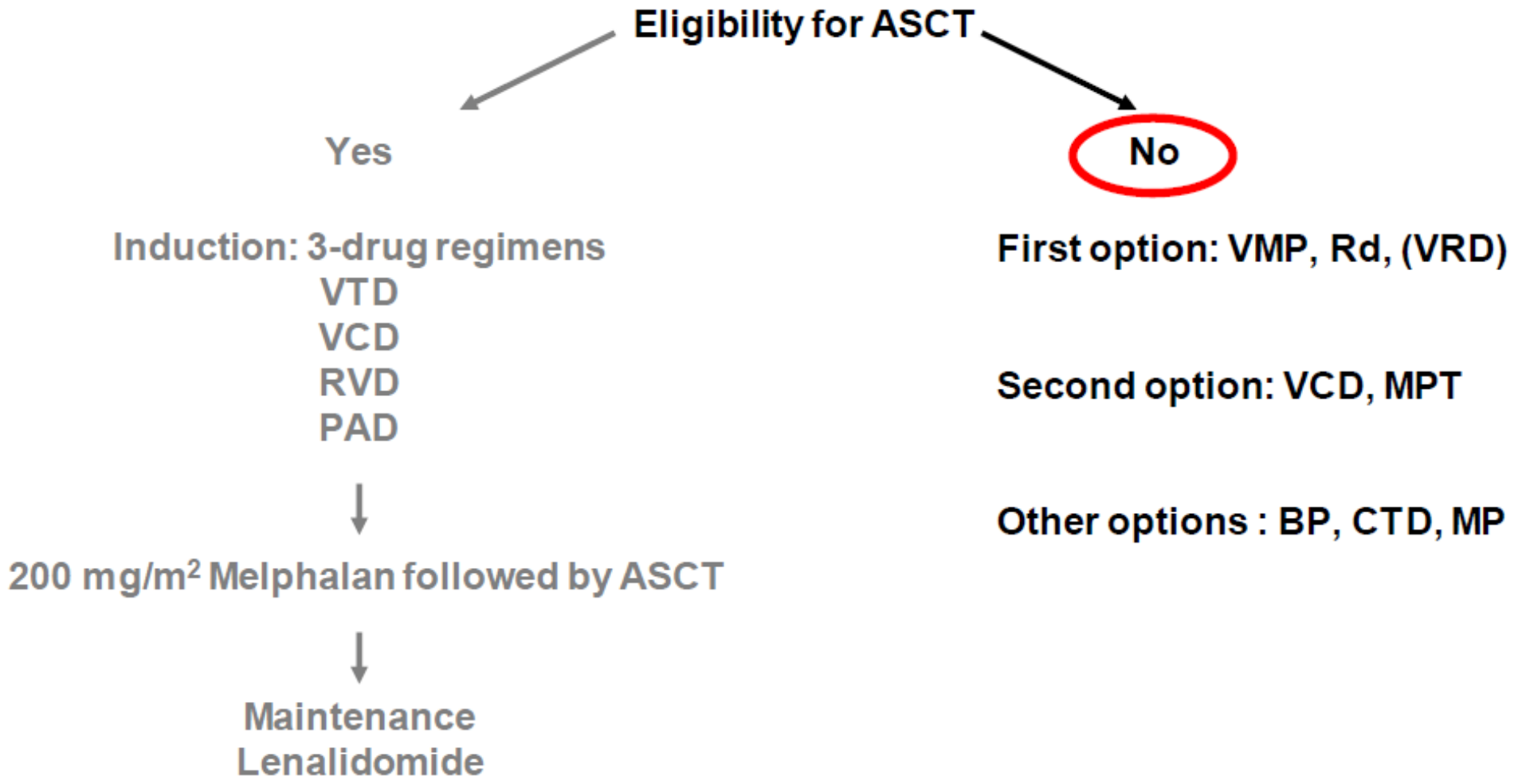
Improvement in median survival of approximately 2.5 years

Frontline Therapy: ESMO guidelines 2017
Young patients



Moreau P, et al. Ann Oncol 2017;28(suppl_4):iv52-iv61.

Frontline Therapy: ESMO guidelines 2017
Elderly patients



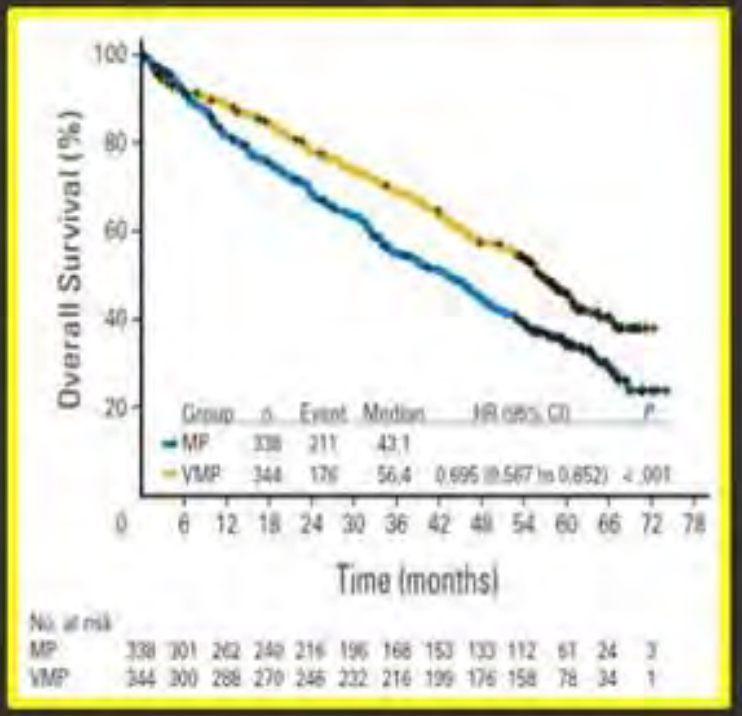
Moreau P, et al. Ann Oncol 2017;28(suppl_4):iv52-iv61.

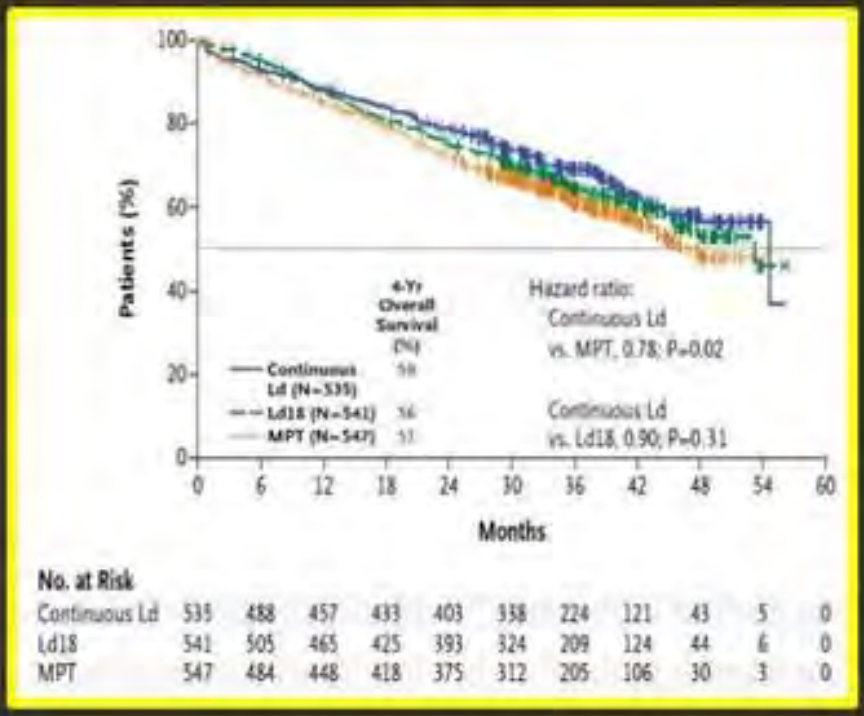
Frontline Therapy in Elderly patients

2 STANDARDS OF CARE IN EUROPE FOR TX-INELIGIBLE

VMP – bortezomib-melphalan-prednisone

Rd – Lenalidomide-dexamethasone





San Miguel JF et al. J Clin Oncol 2013; 31:448-455

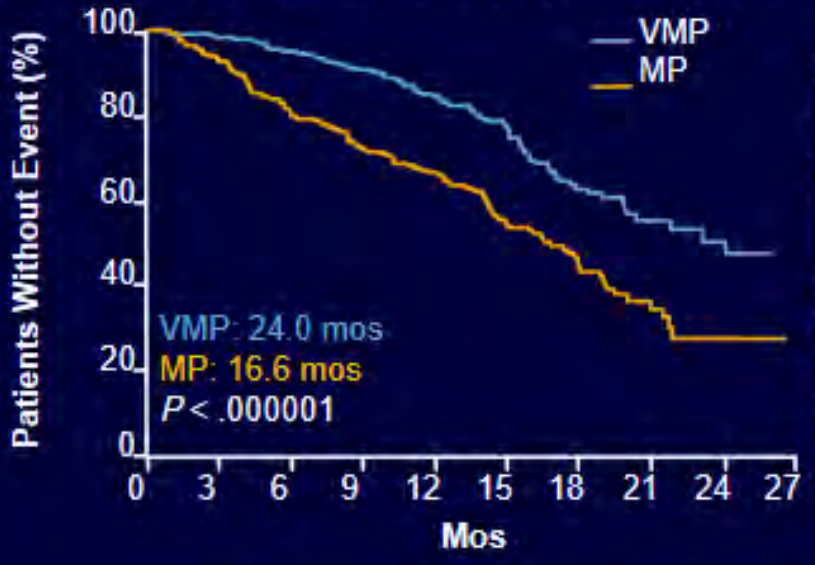
Benboubker L et al. N Engl J Med 2014;371:906-917

VMP vs MP in Untreated Myeloma: Efficacy Data

ORR: VMP 71%, MP 35%

TTP

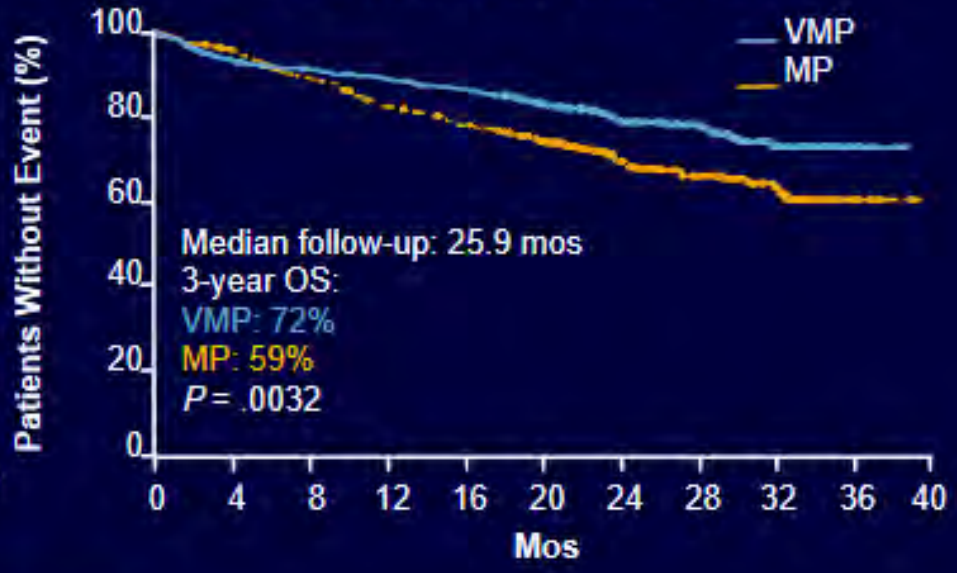
~ 52% reduced risk of progression on VMP



CR: VMP 30%, MP 4%

OS

~ 36% reduced risk of death on VMP



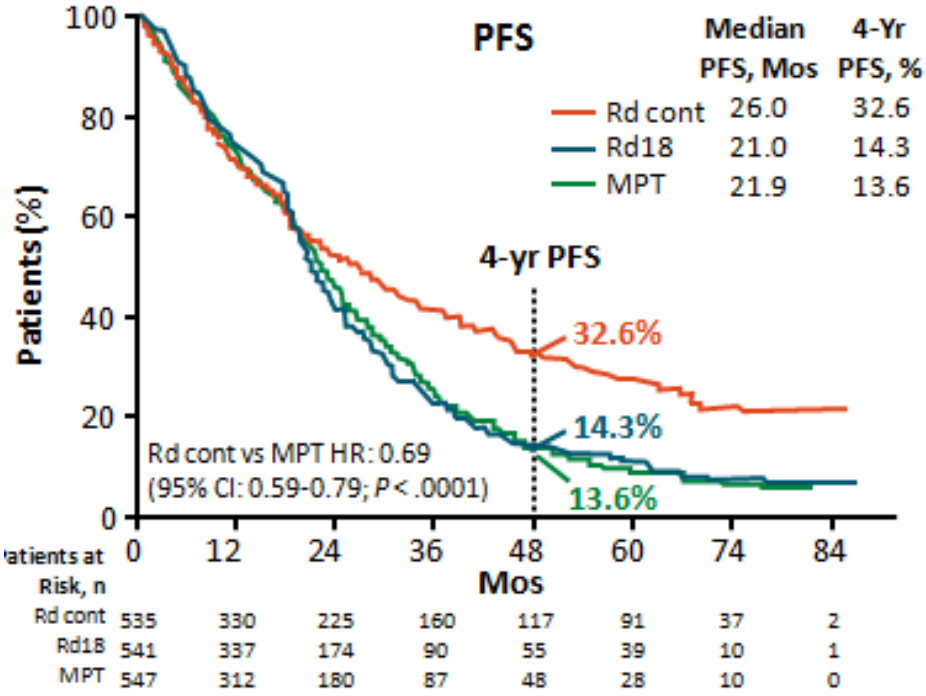
- *43% of MP patients received bortezomib upon progression*
- OS with > 4 cycles bortezomib: 98.5% at 1 yr, 89% at 2 yrs
- Treatment-related death: 2% in both arms

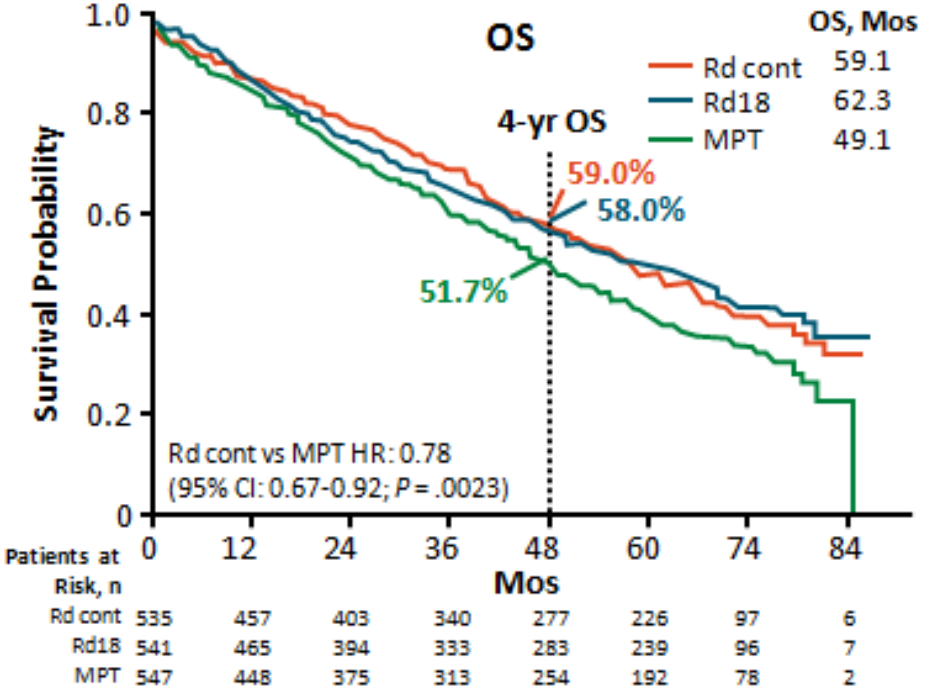
San Miguel JF, et al. N Engl J Med. 2008;359:906-917.

San Miguel JF, et al. ASH 2008. Abstract 650.

Phase III FIRST Trial: Survival With Rd Continuous vs Rd for 18 Mos vs MPT in Older or ASCT-Ineligible Patients

- ORR: 81% with Rd cont; 79% with Rd 18-mo; 67% MPT

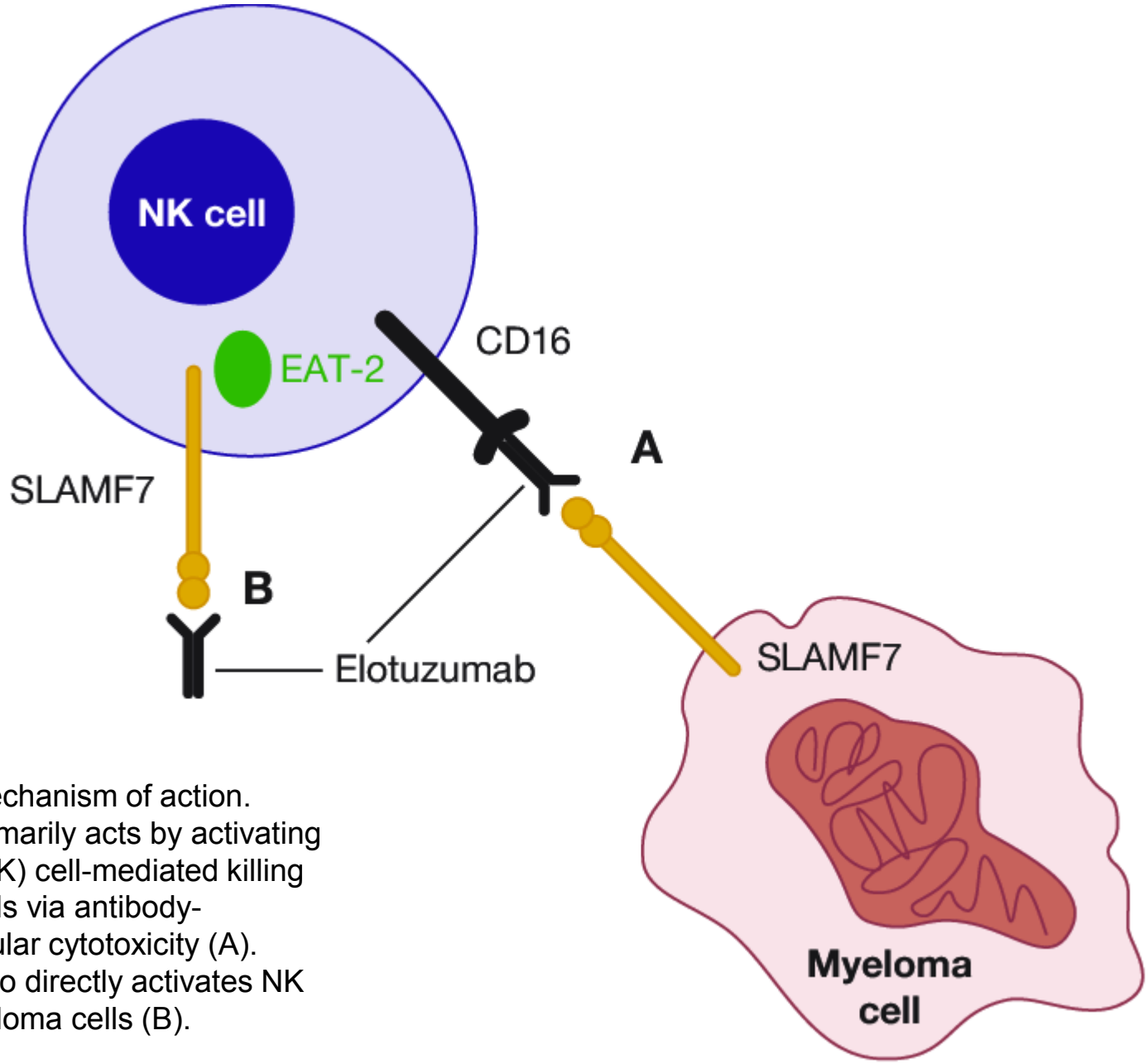




Facon. 2018;131:301.

NUOVI FARMACI

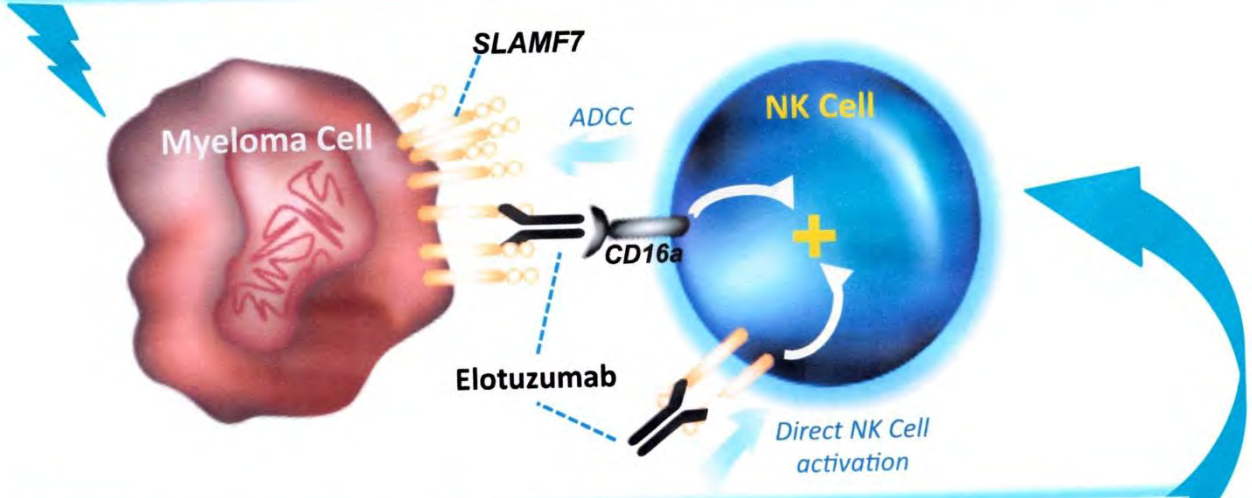
Ac monoclonali:	**elotuzumab** **daratumumab**
Inibitore proteasoma:	**carfilzomib** **ixazomib**



Elotuzumab mechanism of action. Elotuzumab primarily acts by activating natural killer (NK) cell-mediated killing of myeloma cells via antibody-dependent cellular cytotoxicity (A). Elotuzumab also directly activates NK cells to kill myeloma cells (B).

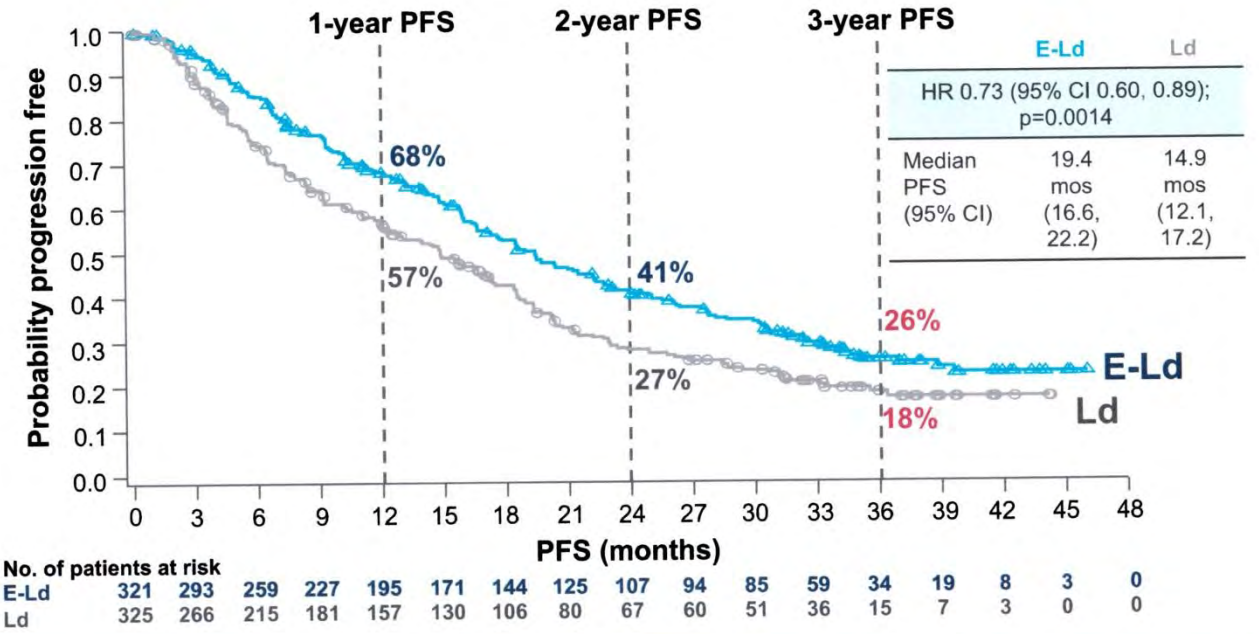
Elotuzumab Synergizes with Lenalidomide to Enhance Myeloma Cell Death

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



Lenalidomide[1]
Enhances adaptive and innate immune system including production of IL2 to increase NK cell activity

Co-Primary Endpoint: Extended Progression-Free Survival



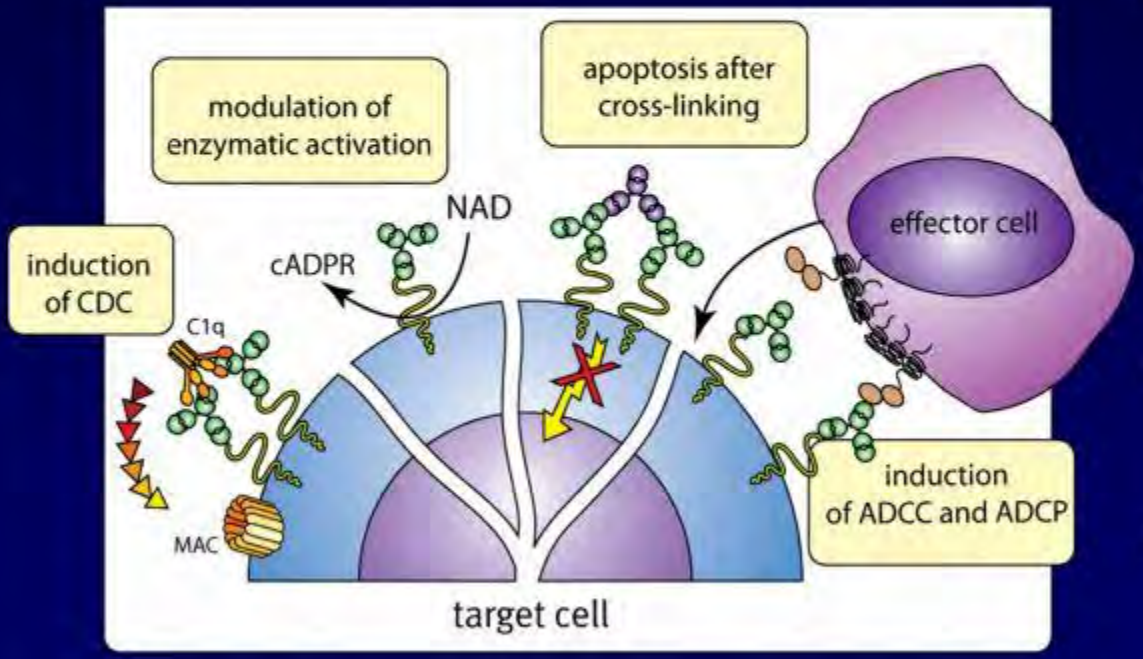
	E-Ld	Ld
HR 0.73 (95% CI 0.60, 0.89); p=0.0014		
Median PFS (95% CI)	19.4 mos (16.6, 22.2)	14.9 mos (12.1, 17.2)

PFS benefit with E-Ld was maintained over time (vs Ld):
- **Overall 27% reduction in the risk of disease progression or death**
- **Relative improvement in PFS of 44% at 3 years**

DARA: Background

DARATUMUMAB

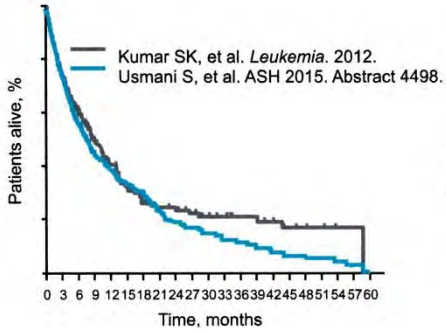
- A human CD38 mAb with broad-spectrum killing activity of CD38-expressing tumor cells
- DARA+LEN enhanced killing of MM cells *in vitro* and is hypothesized to lead to synergistically higher efficacy in clinical setting, as well as other agents (eg, bortezomib)



- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Antibody-dependent cellular phagocytosis (ADCP)
- Complement-dependent cytotoxicity (CDC)
- Apoptosis

Lokhorst H, et al. *J Clin Oncol.* 2014;21(5S): Abstract 8513. Plesner T, et al. *J Clin Oncol.* 2014;32(5S): Abstract 8533.

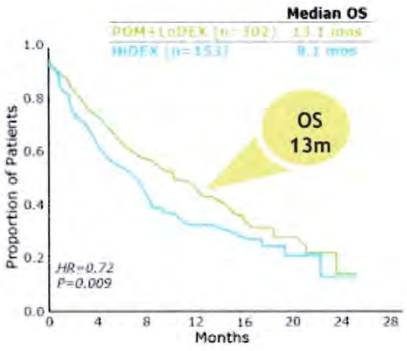
The Breakthrough (BT) population outcome



RRMM:

Median OS 5-9 months in patients relapsed or refractory MM after ≥3 prior lines of therapy, including IMID and PI

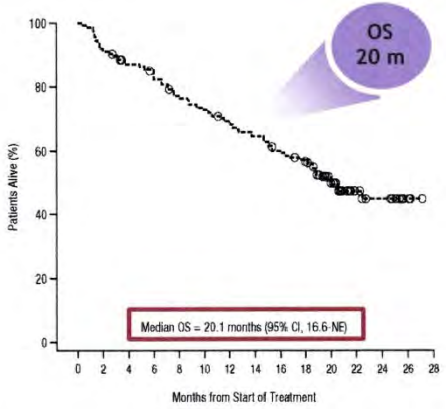
1. Kumar SK, et al. Leukemia. 2012;26(1):149-157.
2. Usmani S, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 4498.



Pomalidomide:

Median OS 13,1months in patients relapsed or refractory MM after ≥2 prior lines of therapy, including IMID and PI

San Miguel J et al. Lancet Oncol 2013; 14: 1055–66



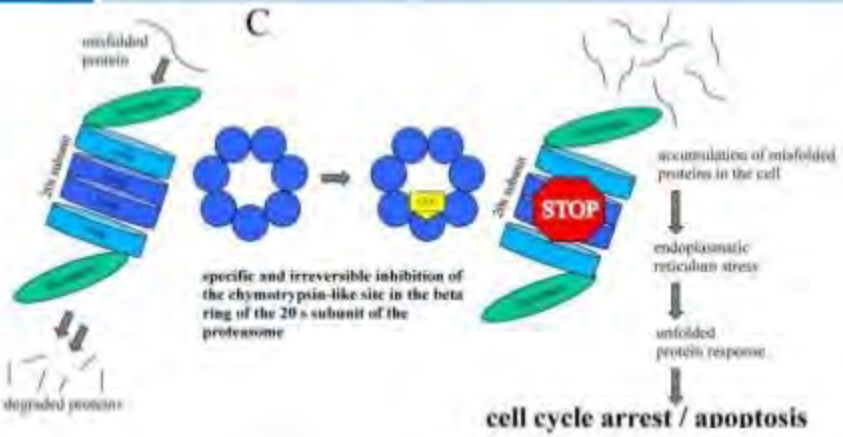
Daratumumab – Single Agent:

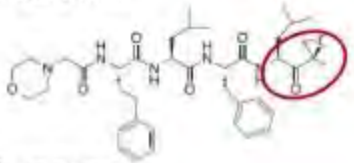
Median OS of 20 months in patients with relapsed or refractory, double refractory or relapsed after ≥3 lines of therapy, including pomalidomide and carfilzomib

Usmani S et al. Blood. 2016;128(1):37-44

WATTANOSOTH HOSPITAL
BANGKOK CANCER HOSPITAL

Carfilzomib



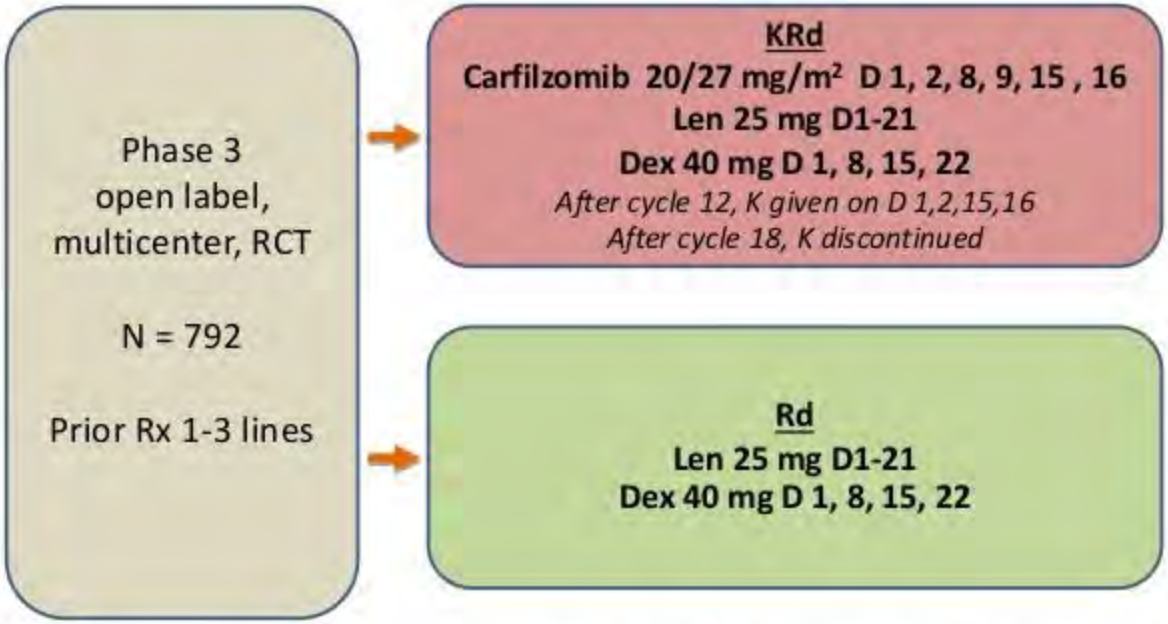


- Second-generation proteasome inhibitor
- Tetrapeptide Epoxyketone
- Highly selective and irreversible proteasome binding
- Minimal off-target effect → less neurotoxicity

Kortuem KM et al. Blood 2013.7;121(6):893-7.

WATTANOSOTH HOSPITAL
BANGKOK CANCER HOSPITAL

ASPIRE : KRd vs Rd in Relapsed MM



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

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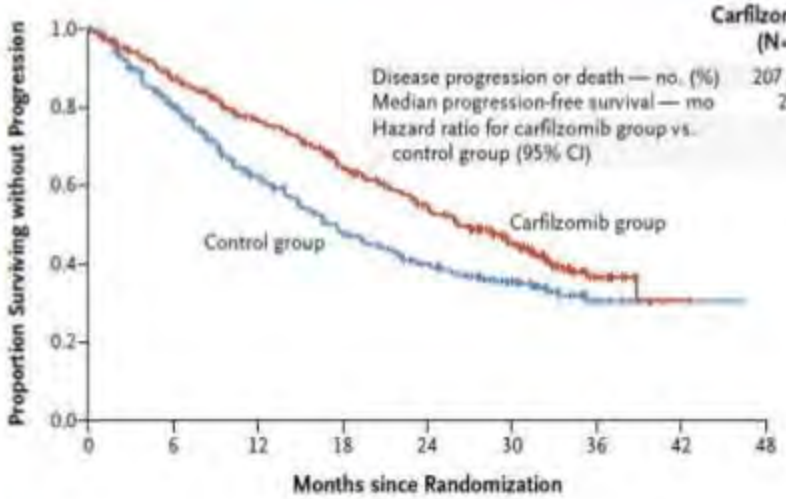
ASPIRE : Progression Free Survival



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	
	P=0.0001	

No. at Risk

Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

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

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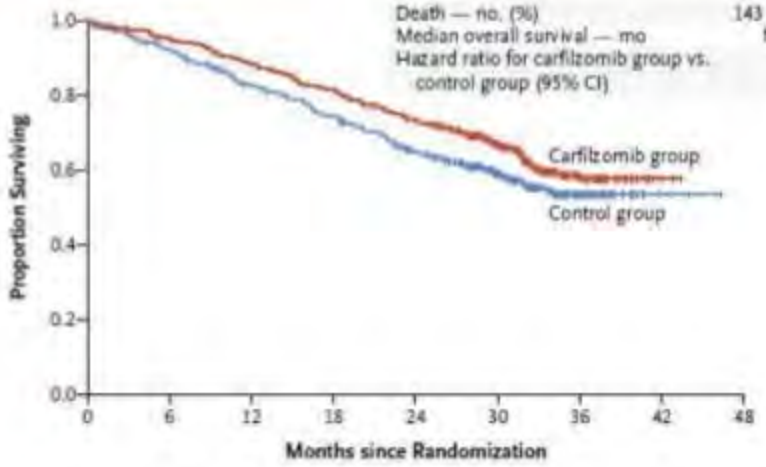
ASPIRE : Overall Survival



	Carfilzomib Group (N=396)	Control Group (N=396)
Death — no. (%)	143 (36.1)	162 (40.9)
Median overall survival — mo	NE	NE
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.79 (0.63–0.99)	
	P=0.04	

No. at Risk								
Carfilzomib group	396	369	343	315	280	191	52	2
Control group	396	356	313	281	237	144	39	3

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

First Oral PI: IXAZOMIB
TOURMALINE-MM1 Study Design

28-day cycles

Randomization
N=722

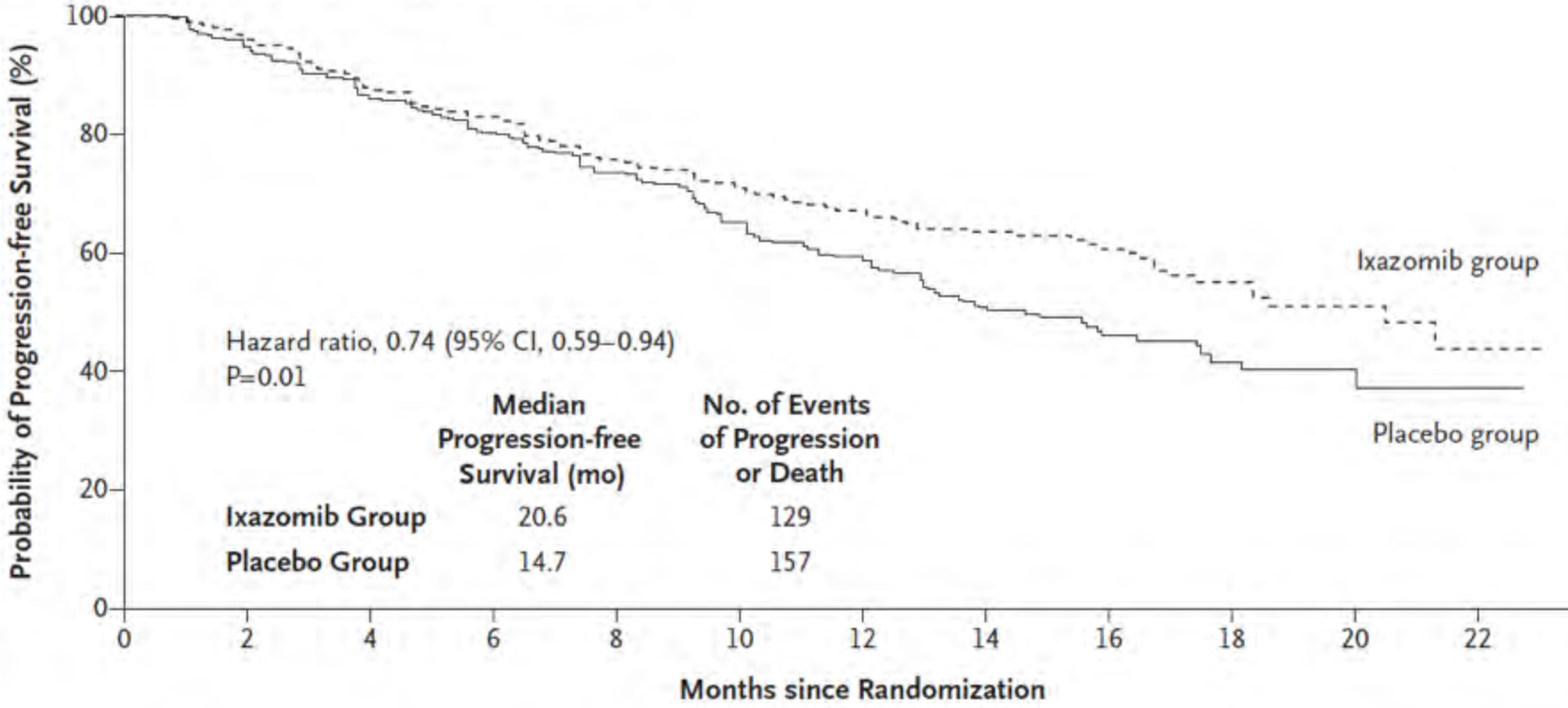
Stratification:
- Number of prior therapies
- PI exposure
- ISS stage

IRd
Ixazomib 4 mg *Days 1, 8, 15*
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

Rd
Lenalidomide 25 mg *Days 1–21*
Dexamethasone 40 mg *Days 1, 8, 15, 22*

LEN NAÏVE OR LEN SENSITIVE

A **Progression-free Survival in the Intention-to-Treat Population**



	Median Progression-free Survival (mo)	No. of Events of Progression or Death
Ixazomib Group	20.6	129
Placebo Group	14.7	157

No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0

IXAZOMIB

- **INDICATION:**
- Indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

.

- **MODE OF ADMINISTRATION :**
- Recommended starting dose of 4 mg taken orally on Days 1, 8, and 15 of a 28-day cycle.
- Dose should be taken at least one hour before or at least two hours after food

- **ADVERSE EVENTS :**
- In ≥ 20%, Diarrhoea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral oedema, vomiting, and back pain.

- **WARNINGS :**
- Thrombocytopenia , Hepatotoxicity , Peripheral Neuropathy

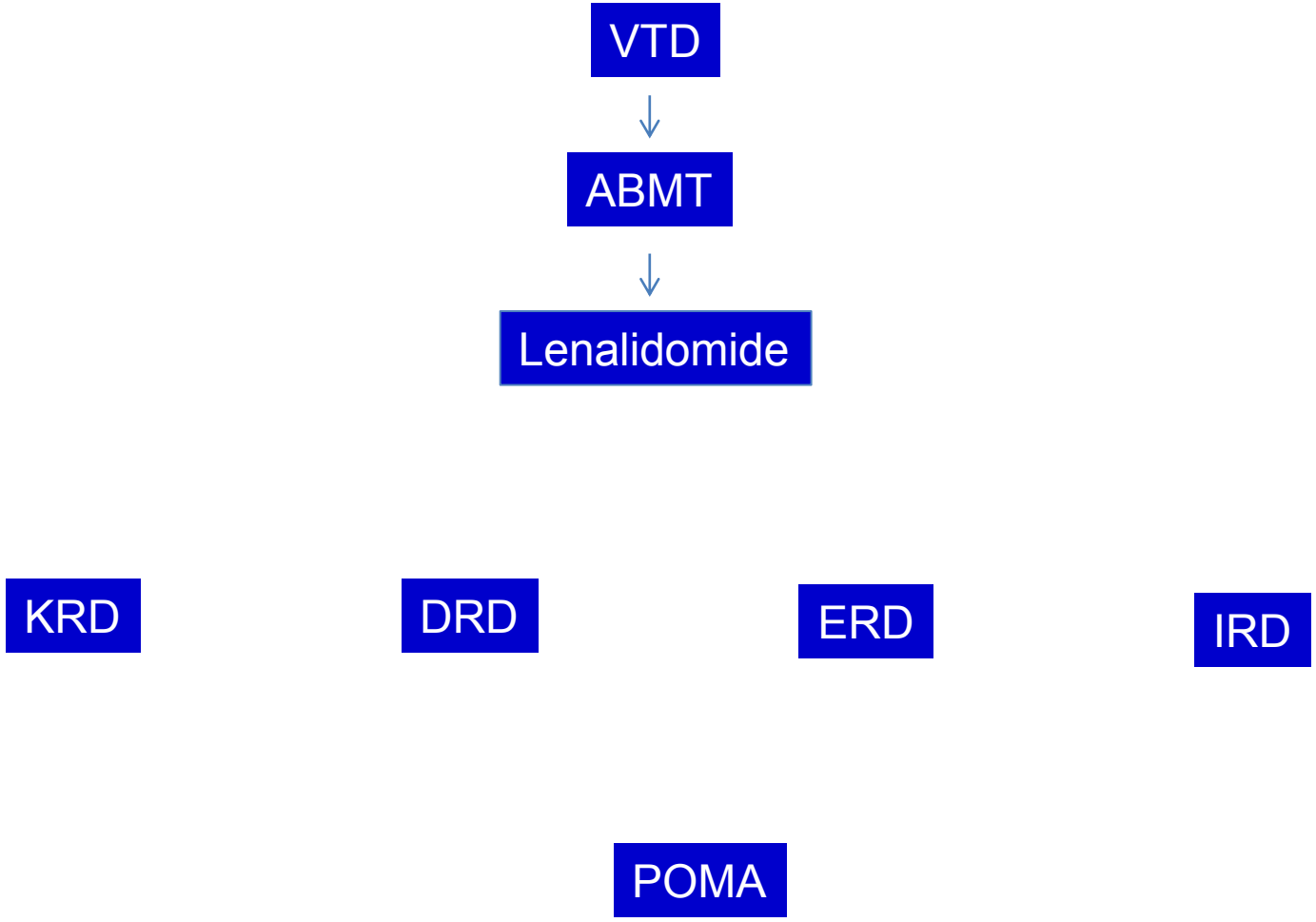
POMALIDOMIDE

- **INDICATION:**
- a thalidomide analogue indicated for patients, who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

- **MODE OF ADMINISTRATION :**
- 4 mg per day taken orally on days 1-21 of repeated 28-day cycles until disease progression.

- **ADVERSE EVENTS :**
- In ≥ 30% patients :: Fatigue and asthenia, Neutropenia, anemia, constipation, nausea, upperrespiratory tract infections, back pain and pyrexia .

- **WARNINGS :**
- Hematologic Toxicity: Neutropenia was the most frequently reported Grade 3/4 adverse event.


VTD
ABMT
Lenalidomide
KRD
DRD
ERD
IRD
POMA