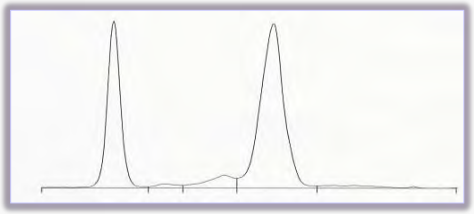
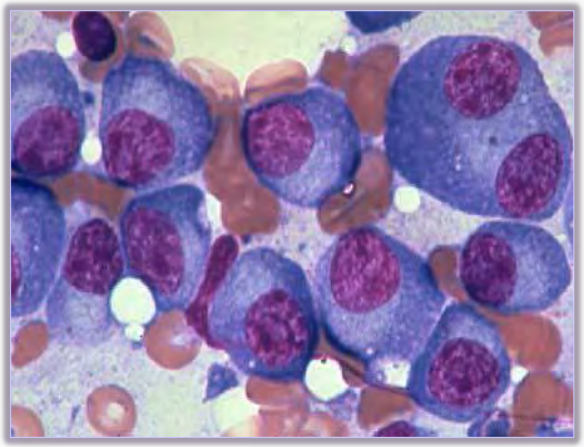
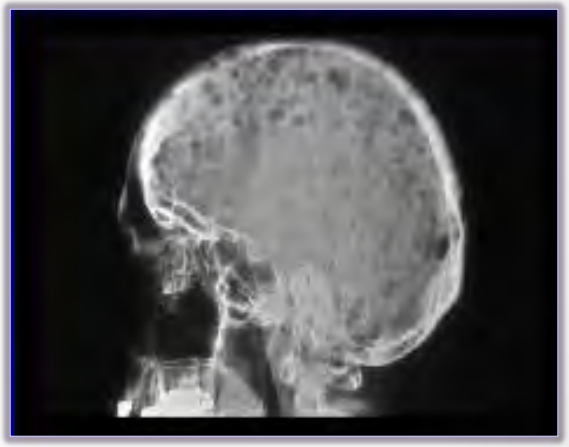
I risultati della sperimentazione clinica nella terapia del mieloma multiplo







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MIELOMA MULTIPLO: Epidemiologia

E' la seconda neoplasia ematologica dopo il Linfoma non Hodgkin

Rappresenta circa l' 1% di tutte le neoplasie e il 2% delle morti per neoplasia

L'incidenza varia da paese a paese con la percentuale più bassa in Cina (1/100.000) e la più alta nei paesi occidentali (4/100.000)

MIELOMA MULTIPLO: Epidemiologia in Italia

- 1,2% di tutti i tumori diagnosticati tra gli uomini
- 1,3% tra le donne

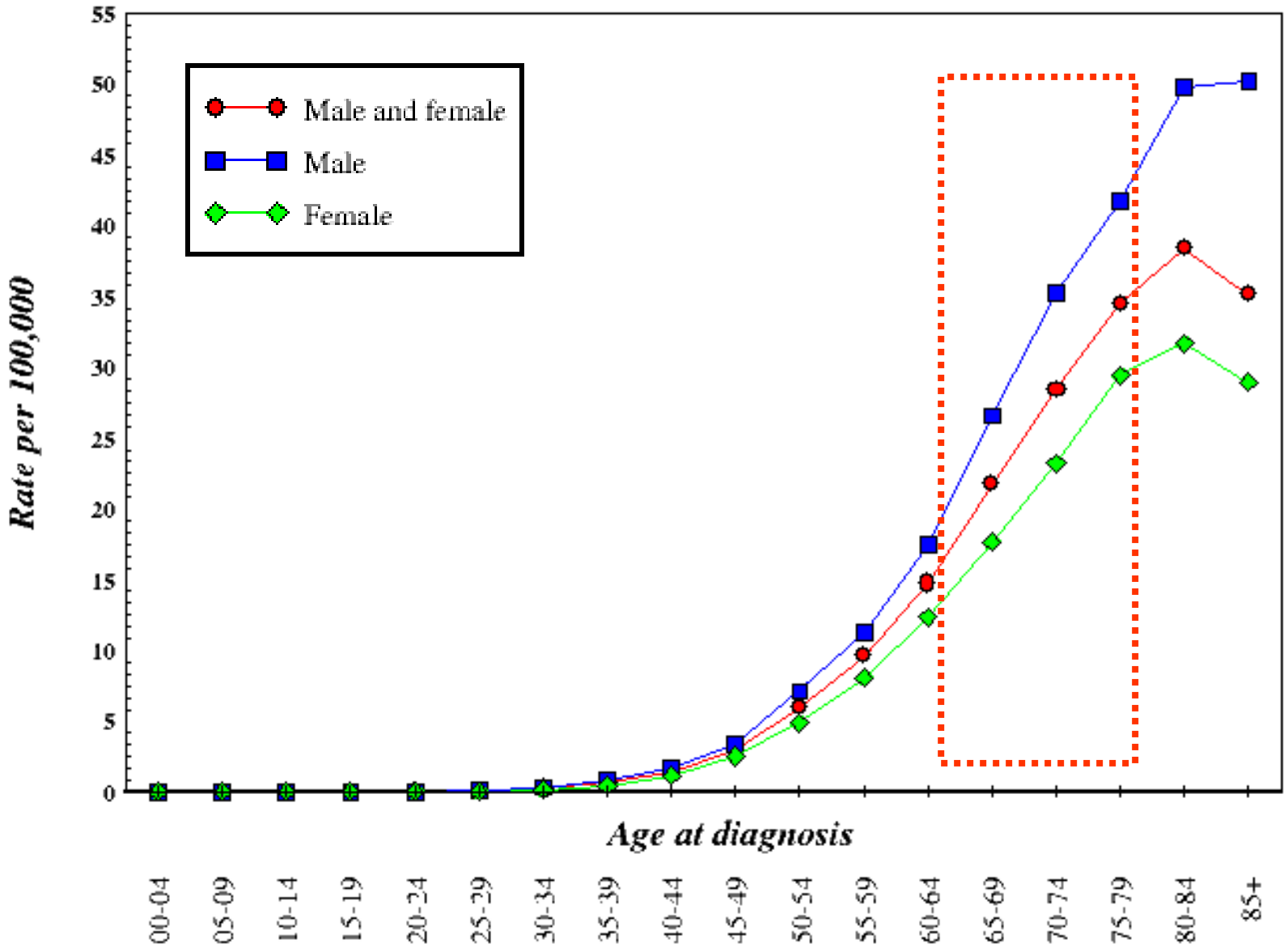
Incidenza media annua:

- 9,5 casi ogni 100.000 uomini
- 8,1 ogni 100.000 donne.

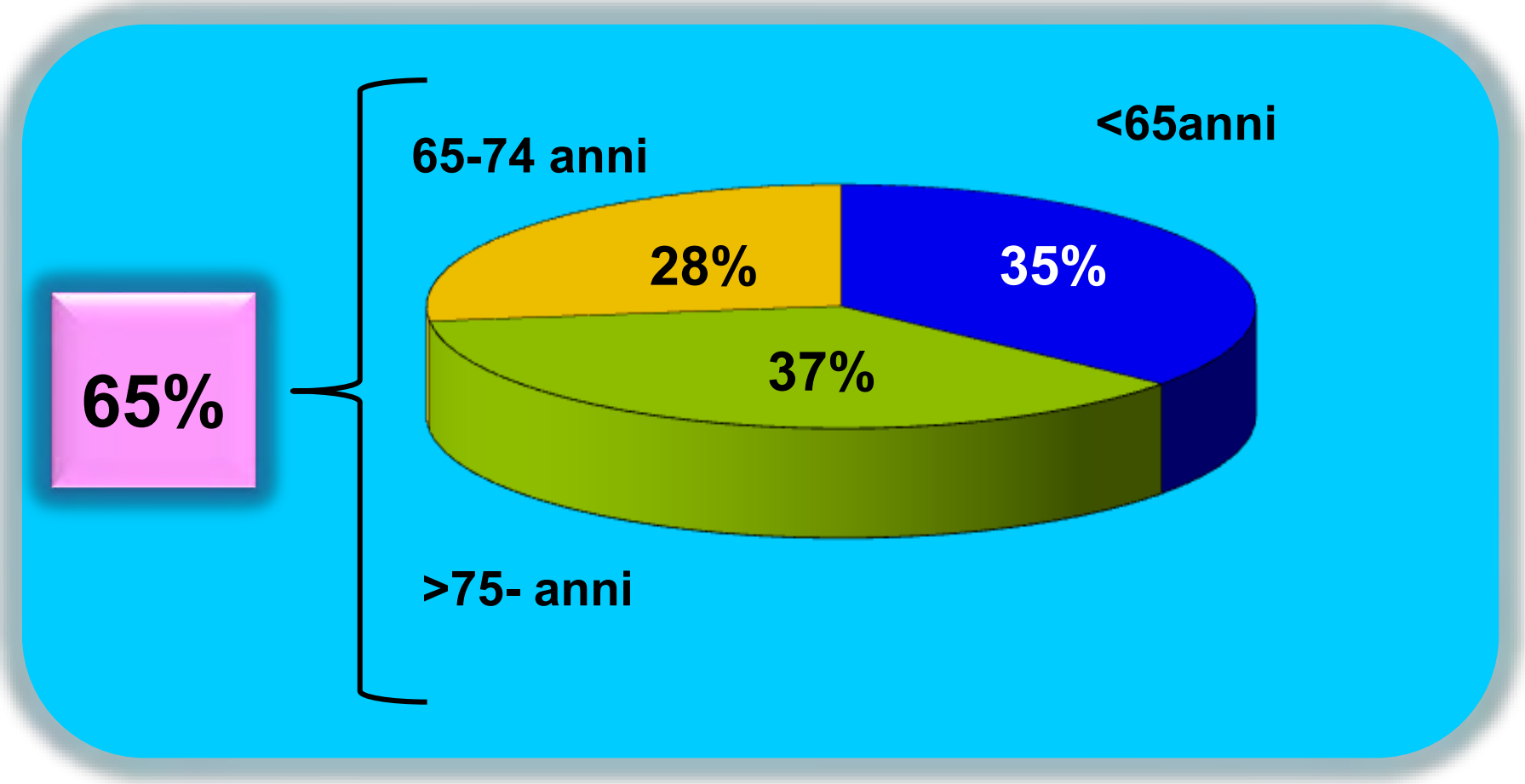
Diagnosi di nuovi casi ogni anno:

- 2.315 fra i maschi
- 2.098 fra le femmine

MM: Distrubuzione per età e sesso

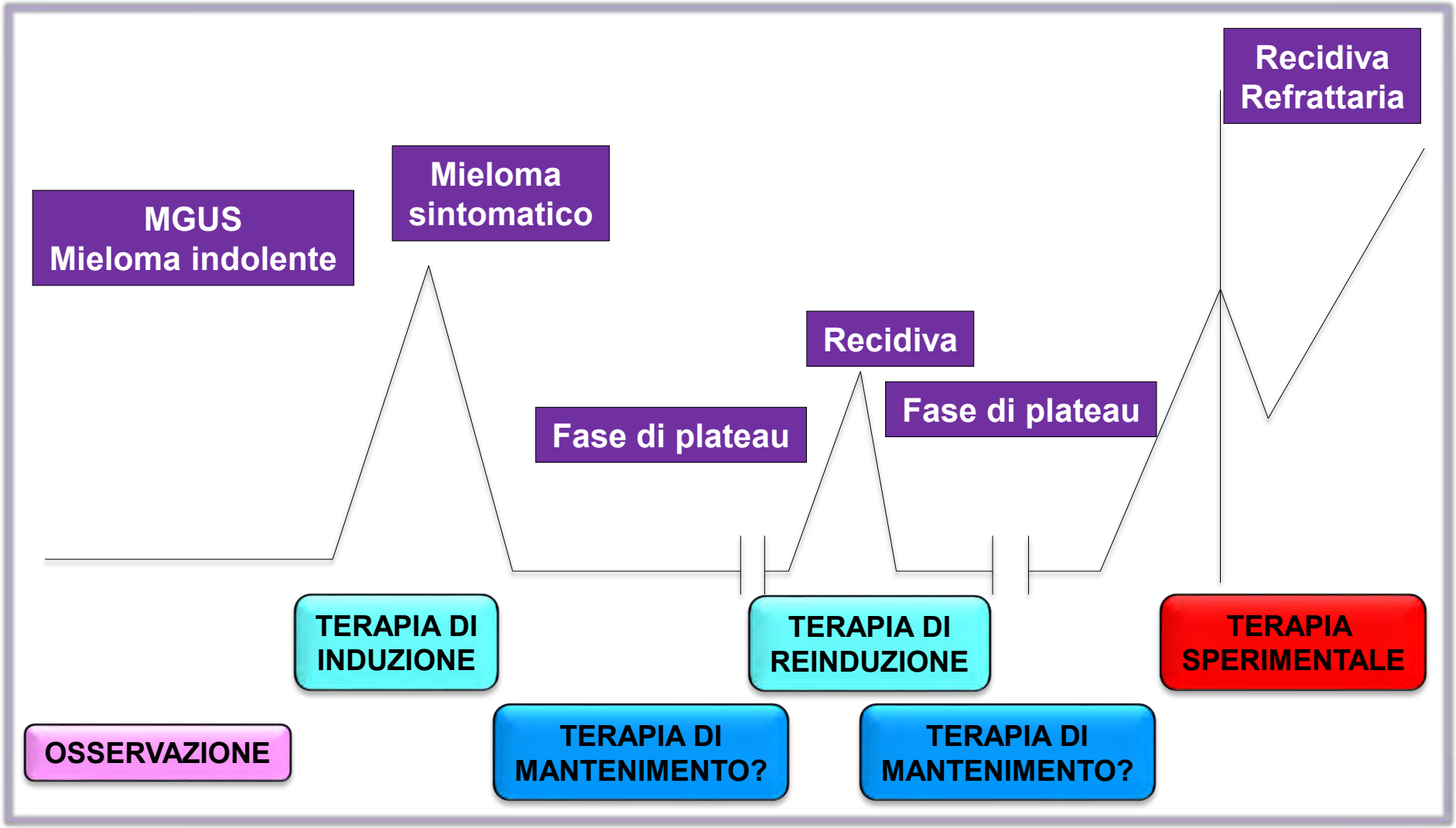


Epidemiologia

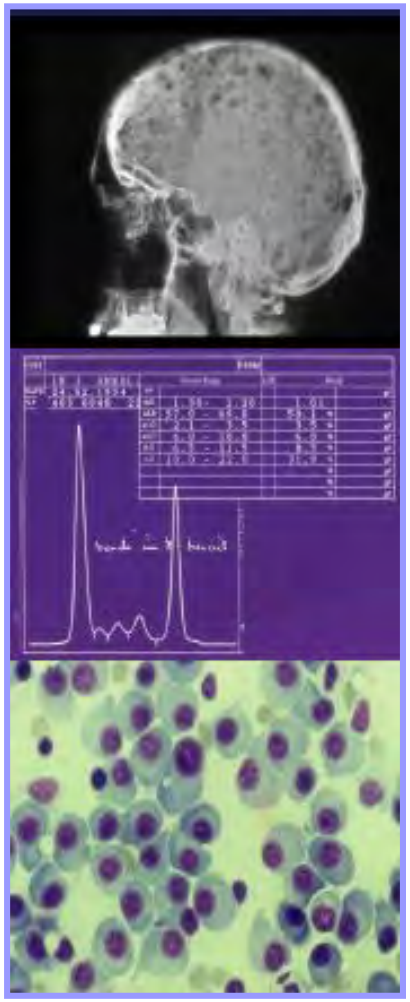


Età mediana alla diagnosi: 70 anni

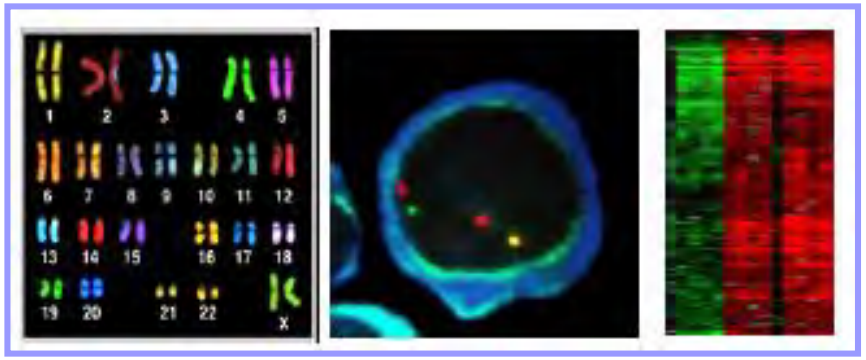
Decorso generale e comportamento terapeutico



Mieloma Multiplo: Un'unica malattia?



Ultimi 30 anni



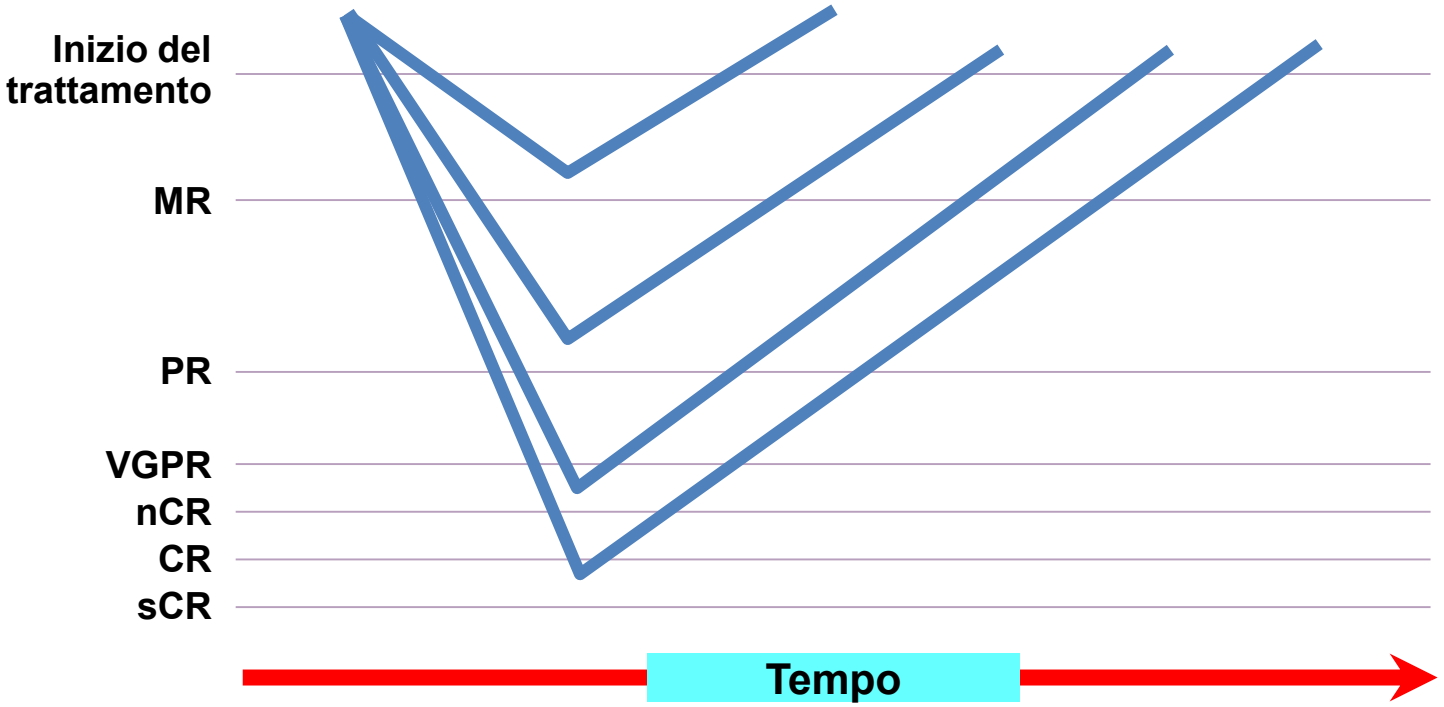
- **Stratificazione del rischio**
- **Individualizzazione del trattamento**

Alcune considerazioni nel paradigma terapeutico del MM

- Importanza di ottenere la massima risposta sia in induzione che in recidiva

Profondità di risposta

Tempo alla Progressione



La profondità delle risposte è correlata al TTP

Importanza della risposta completa indipendentemente dalla terapia eseguita: chemioterapia convenzionale o HD+ASCT

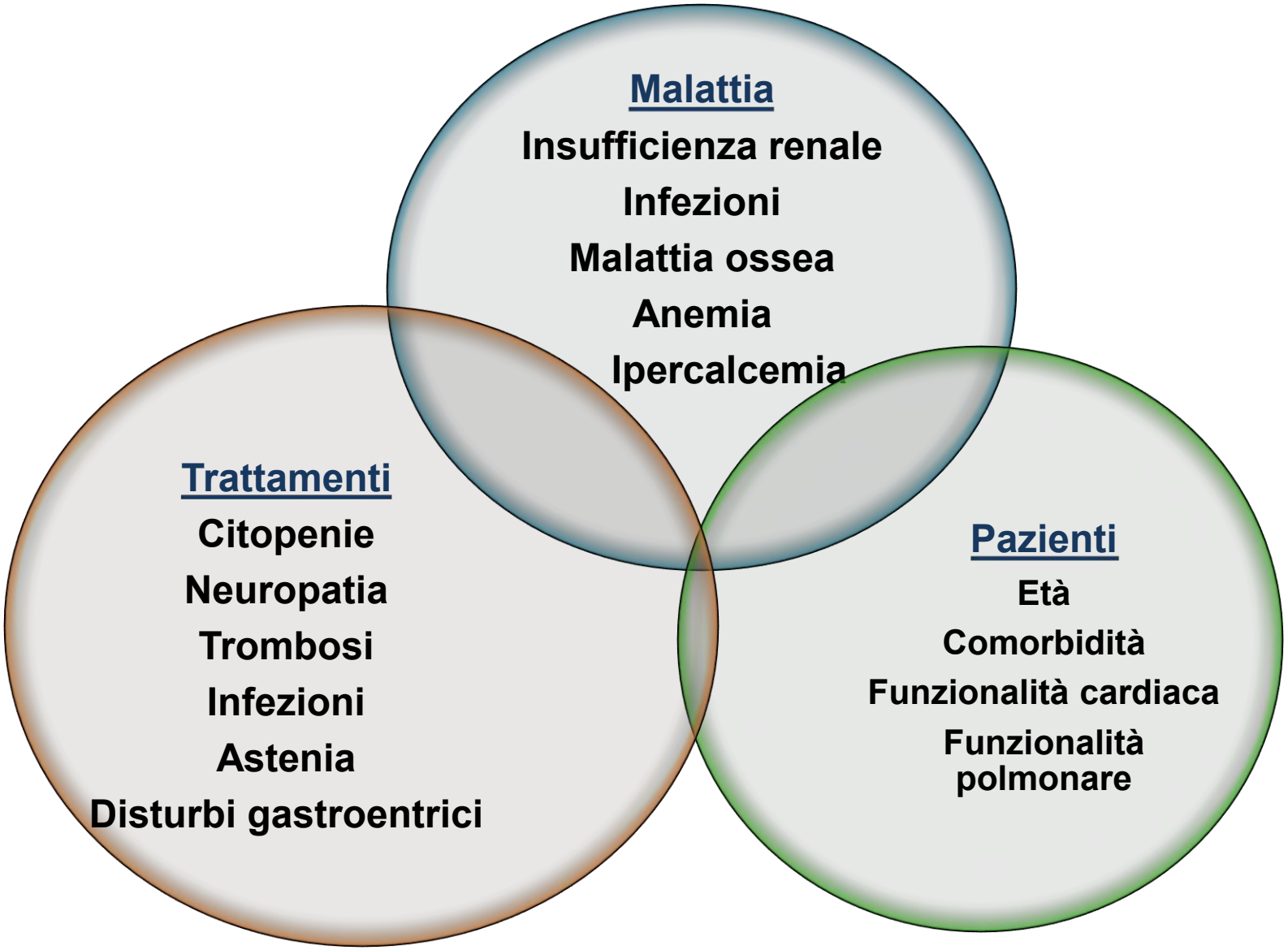
Gruppo di pazienti	Sopravvivenza mediana
CR raggiunta dopo terapia iniziale	10-15 anni
CR raggiunta dopo ulteriori terapie in pz con PR o NR	10-15 anni
Risposta Parziale	4 anni
Malattia Resistente	2.2 anni

Wang et al. ASCO 2008

Alcune considerazioni nel paradigma terapeutico del MM

- Importanza di ottenere la massima risposta sia in induzione che in recidiva
- Il Mieloma è caratterizzato da successive recidive con una riduzione della durata di risposta:
  - La prima remissione è quella più duratura con un più lungo tempo libero da terapia (TFI)
  - Importante prolungare la durata di questa remissione utilizzando la più attiva terapia a disposizione
- Sfida: Come scegliere la migliore sequenza terapeutica per il singolo paziente bilanciando l'efficacia con la tossicità?

Fattori che condizionano le scelte terapeutiche

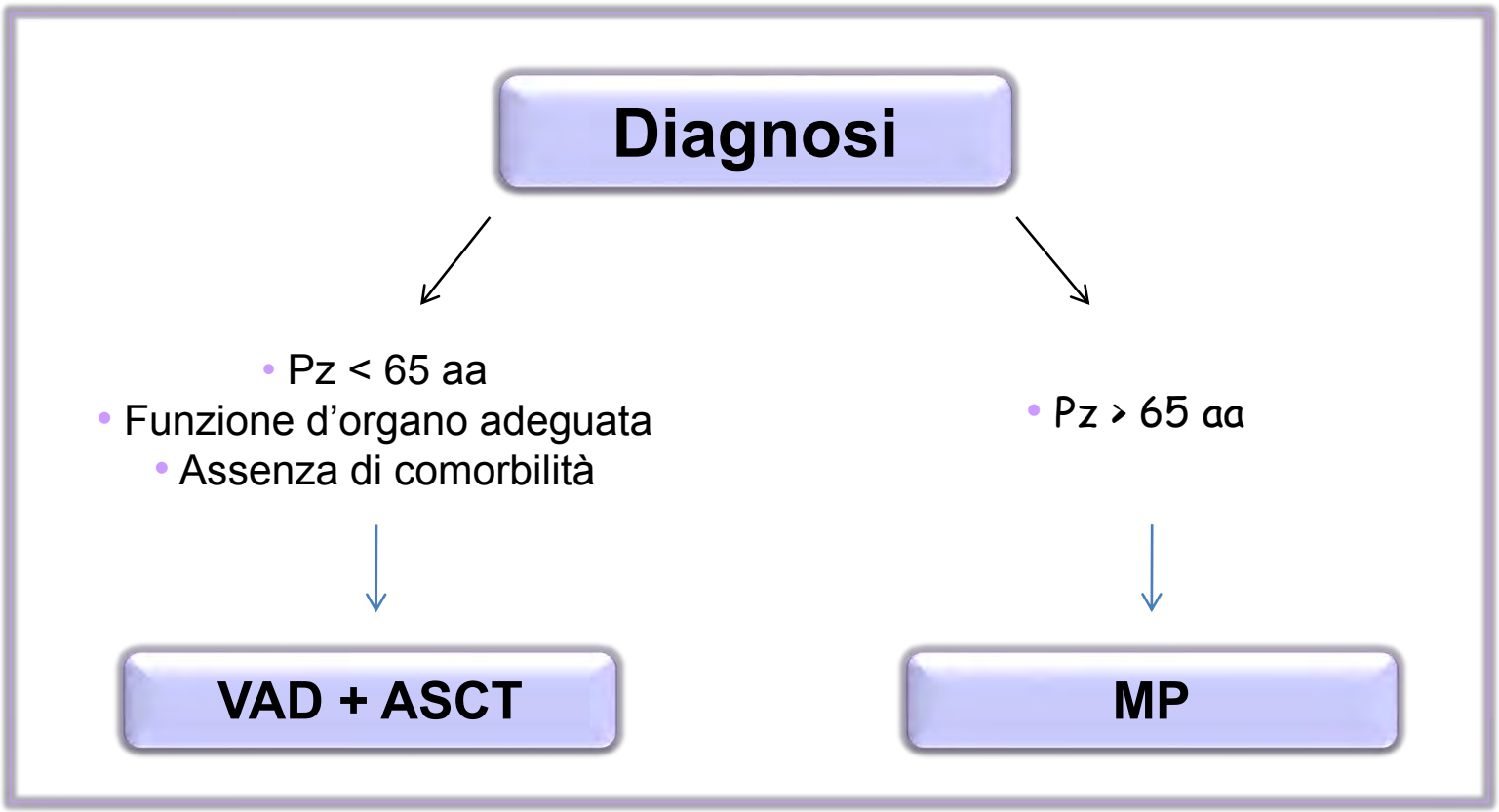


Il nuovo paradigma terapeutico nell'era dei nuovi farmaci

- ✓ **Talidomide**
- ✓ **Velcade**
- ✓ **Lenalidomide**

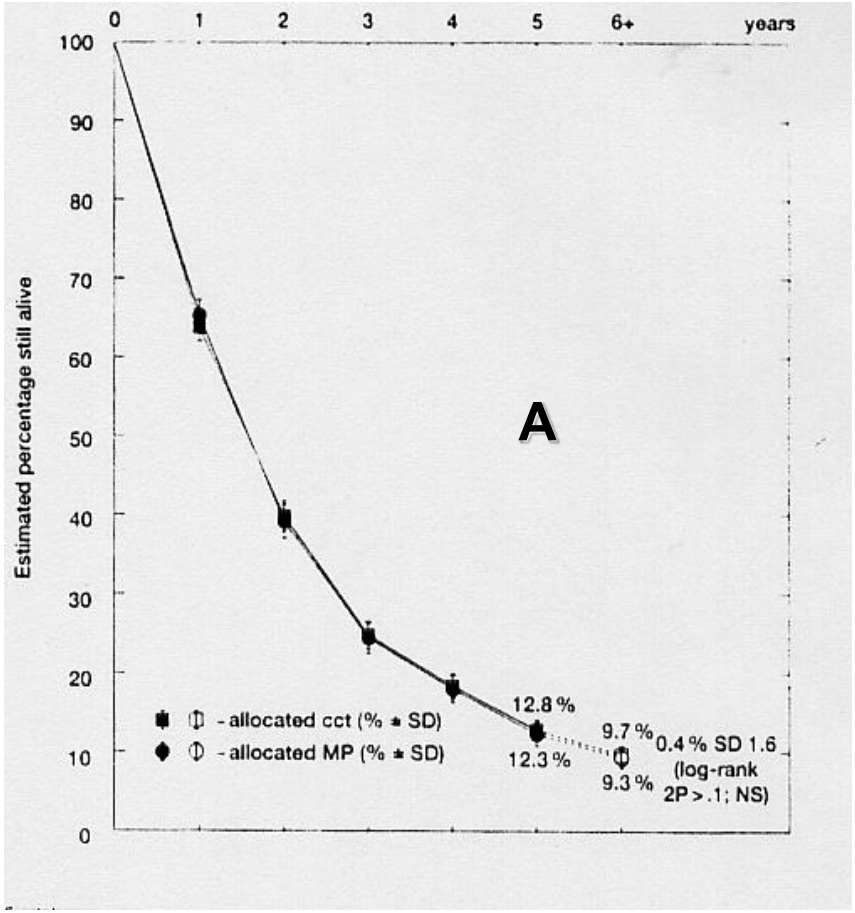
Sono stati incorporati nei regimi di induzione nell'ottica di aumentare la percentuale di CR **per migliorare la PFS, OS**

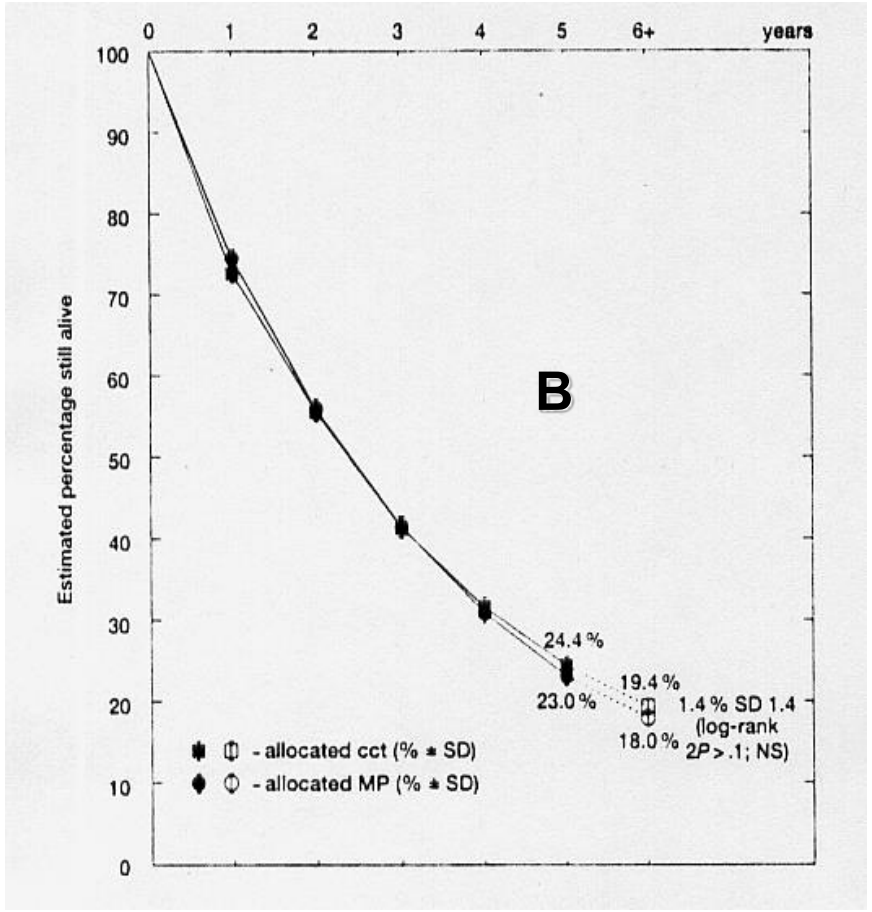
MM all'esordio



Combination chemotherapy vs MP

Overview of 6,663 pts from 27 randomized trials

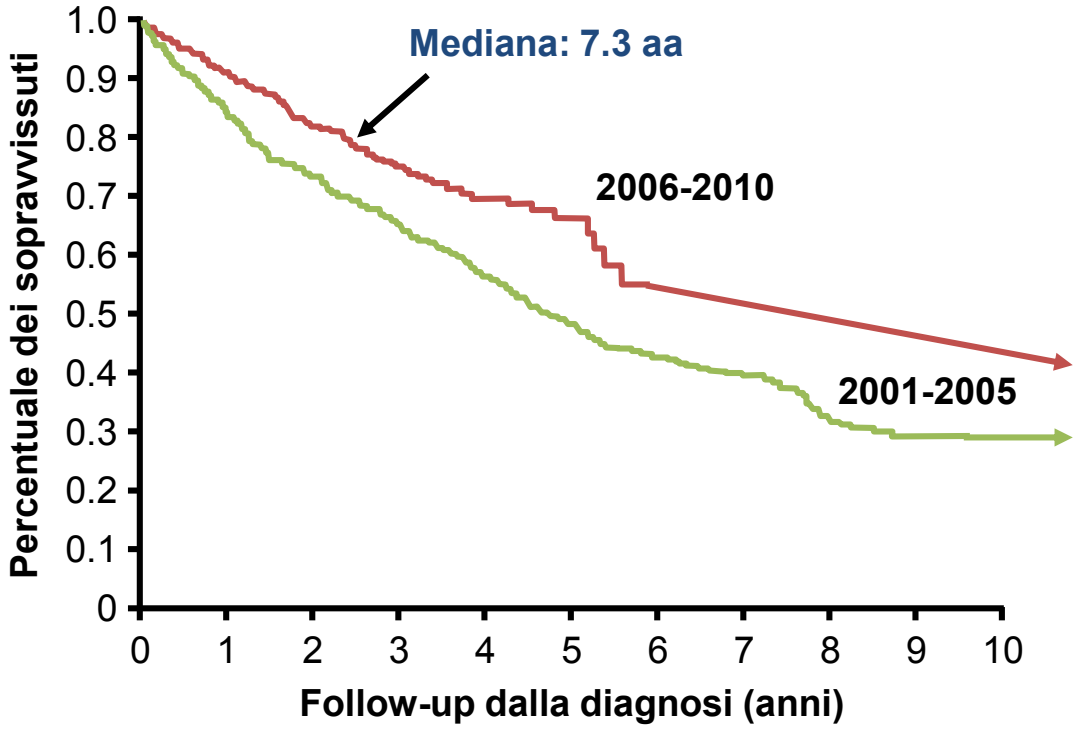




Response duration (A) and mortality (B) in trials of CCT vs MP

The Myeloma Trialists' Collaborative Group, JCO, 1998, 12,3832

MM: Sopravvivenza più lunga utilizzando i nuovi farmaci

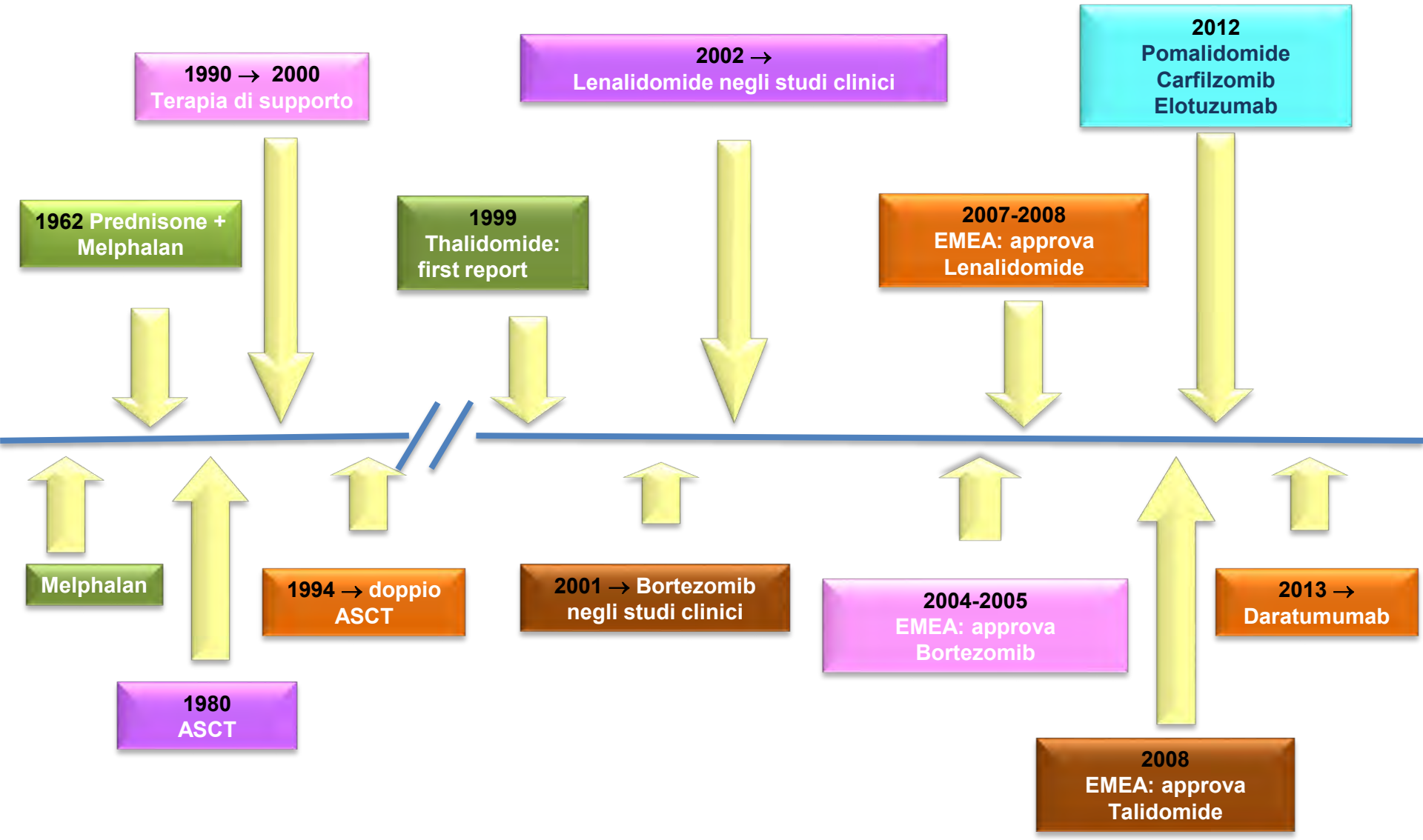


Sopravvivenza mediana a 5 anni

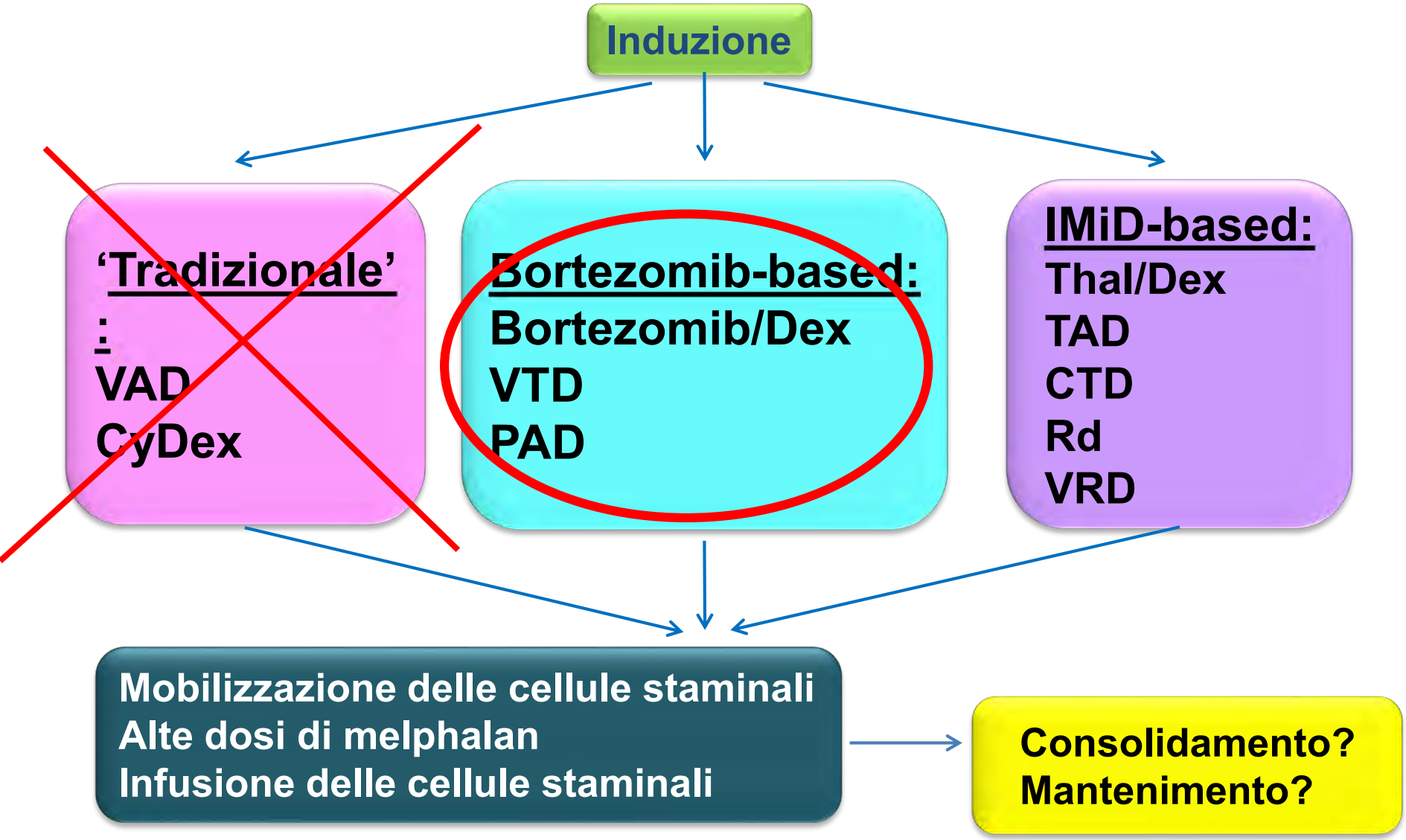
	≤ 65 aa	> 65 aa
2006-2010	73 %	56 %
2001-2005	63 %	31 %

Kumar SK, et al. ASH 2012. Abstract 3972.

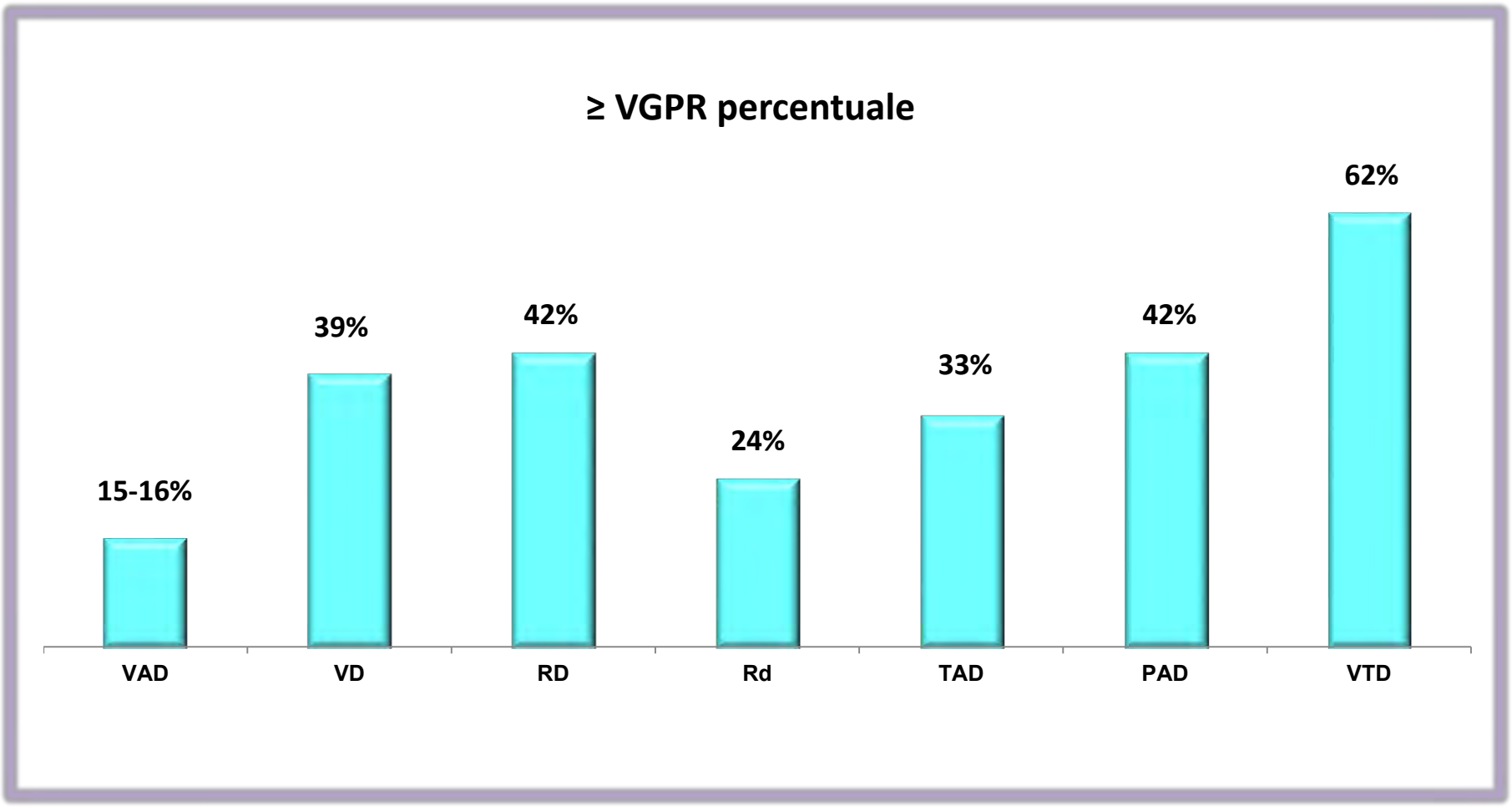
Storia della terapia delMM



Opzioni di trattamento per i pazienti elegibili a trapianto



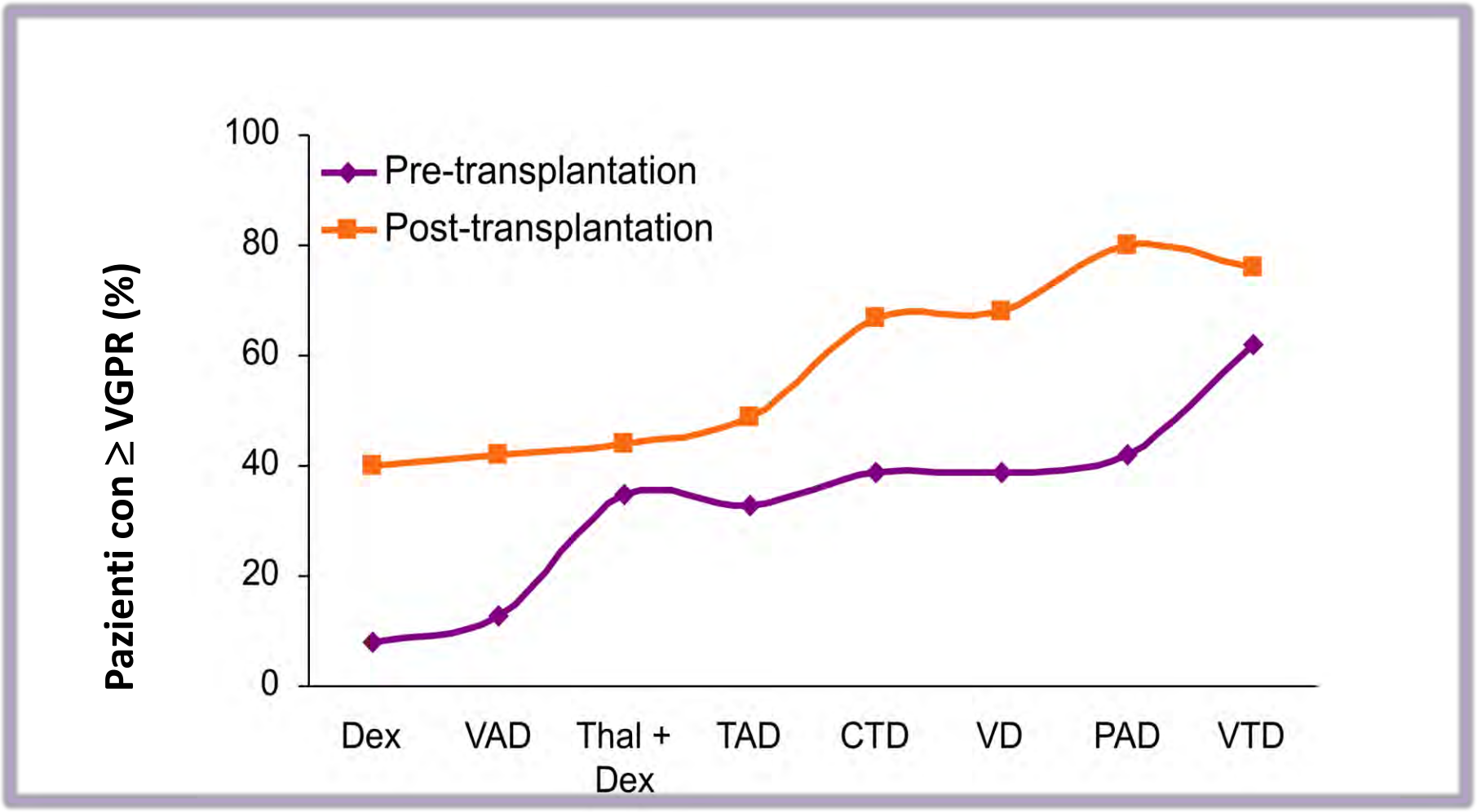
Nuovi farmaci nelle terapie di induzione (studi randomizzati)



Harousseau *et al*. ASH/ASCO symposium during ASH 2008
Rajkumar *et al*. ASCO 2008 (Abstract 8504);
ASH/ASCO symposium during ASH 2008

Lokhorst et al. Haematologica 2008;93:124–7
Sonneveld et al. ASH 2008 (abstract 653); IMW (abstract 152)
Cavo et al. ASH 2008 (abstract 158); IMW 2009 (abstract 451)

Aumento delle risposte con il trapianto dopo la terapia di induzione



Kumar SK et al. *Mayo Clinic proceedings*. 2009 Dec;84(12):1095-110.

Risultati dell'autotrapianto nel MM induzione con i nuovi farmaci

• Risposte complessive	**70 - 100 %**
• **Risposte complete**	**31 - 57 %**
• Sopravvivenza mediana **3 anni**	**>85%**
• **PFS 3 anni**	**>65%**
• Mortalità correlata a trapianto	**< 2 %**
• Buona qualità di vita post auto	

Indicazione assoluta nei pazienti < 65 aa

Nuovi standard per i pazienti non elegibili a trapianto

MPT

(Melfalan, Prednisone,Talidomide)

approvato per pazienti di nuova diagnosi non elegibili per le alte dosi di chemioterapia

età ≥ 65 anni

Italia: Marzo 2009

MPV

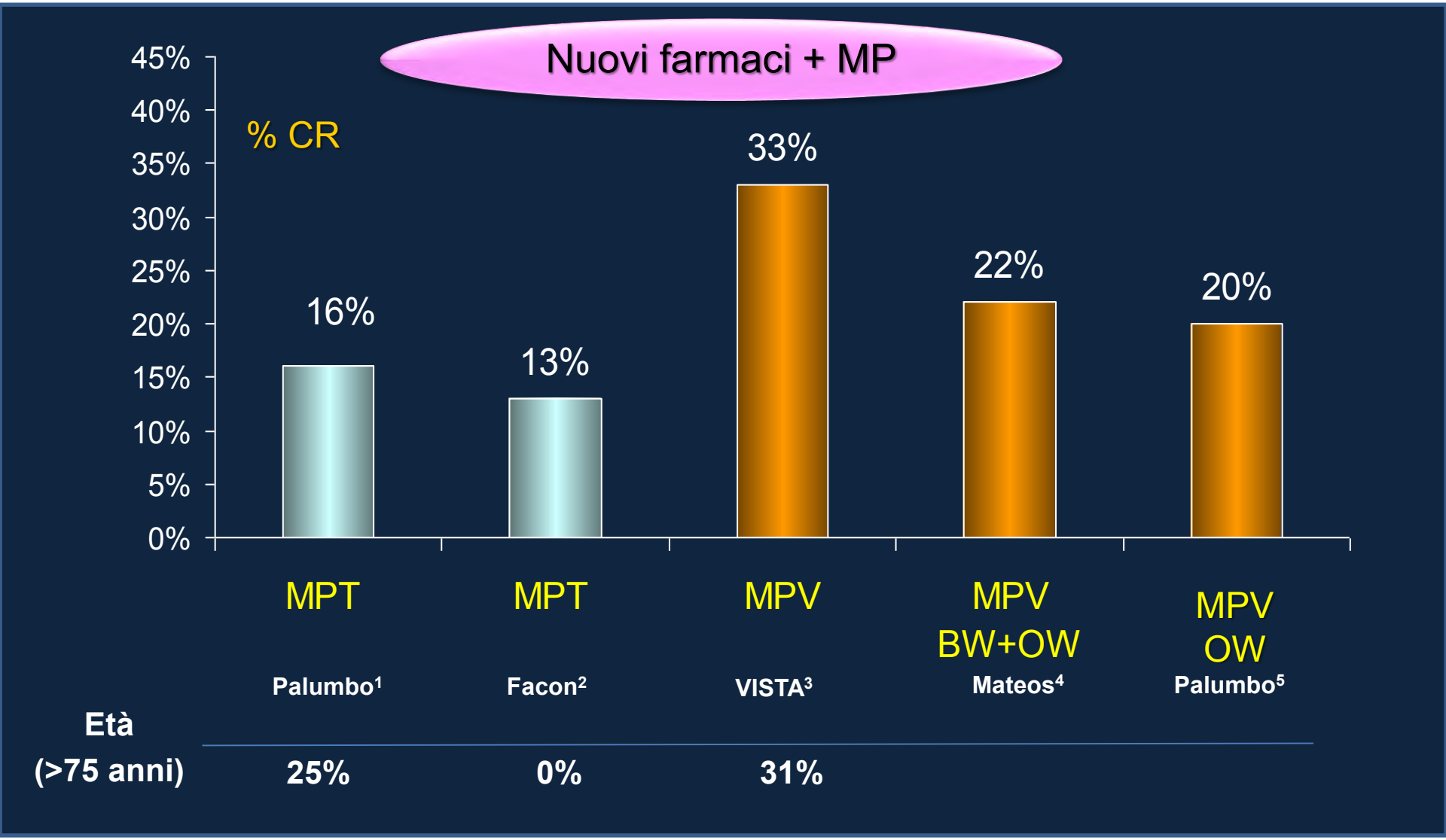
(Melfalan, Prednisone, Velcade)

approvato per pazienti di nuova diagnosi non elegibili per le alte dosi di chemioterapia

età ≥ 65 anni

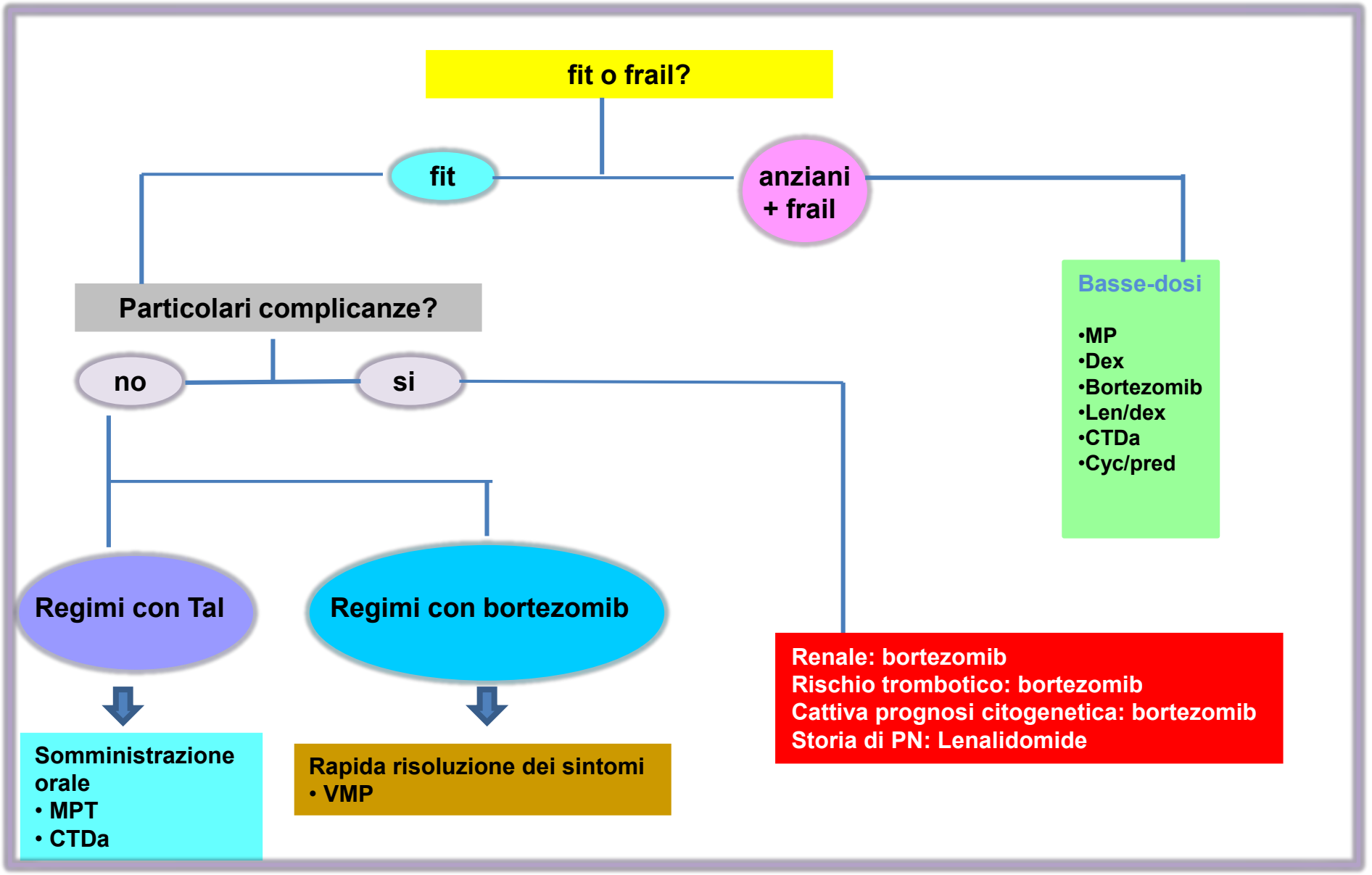
Italia: Luglio 2009

Pazienti non elegibili a trapianto



1. Palumbo et al. Lancet 2006
2 .Facon et al. Lancet 2007
3. San Miguel NEJM 2008
4. Mateos JCO 2010
5. Palumbo JCO 2010

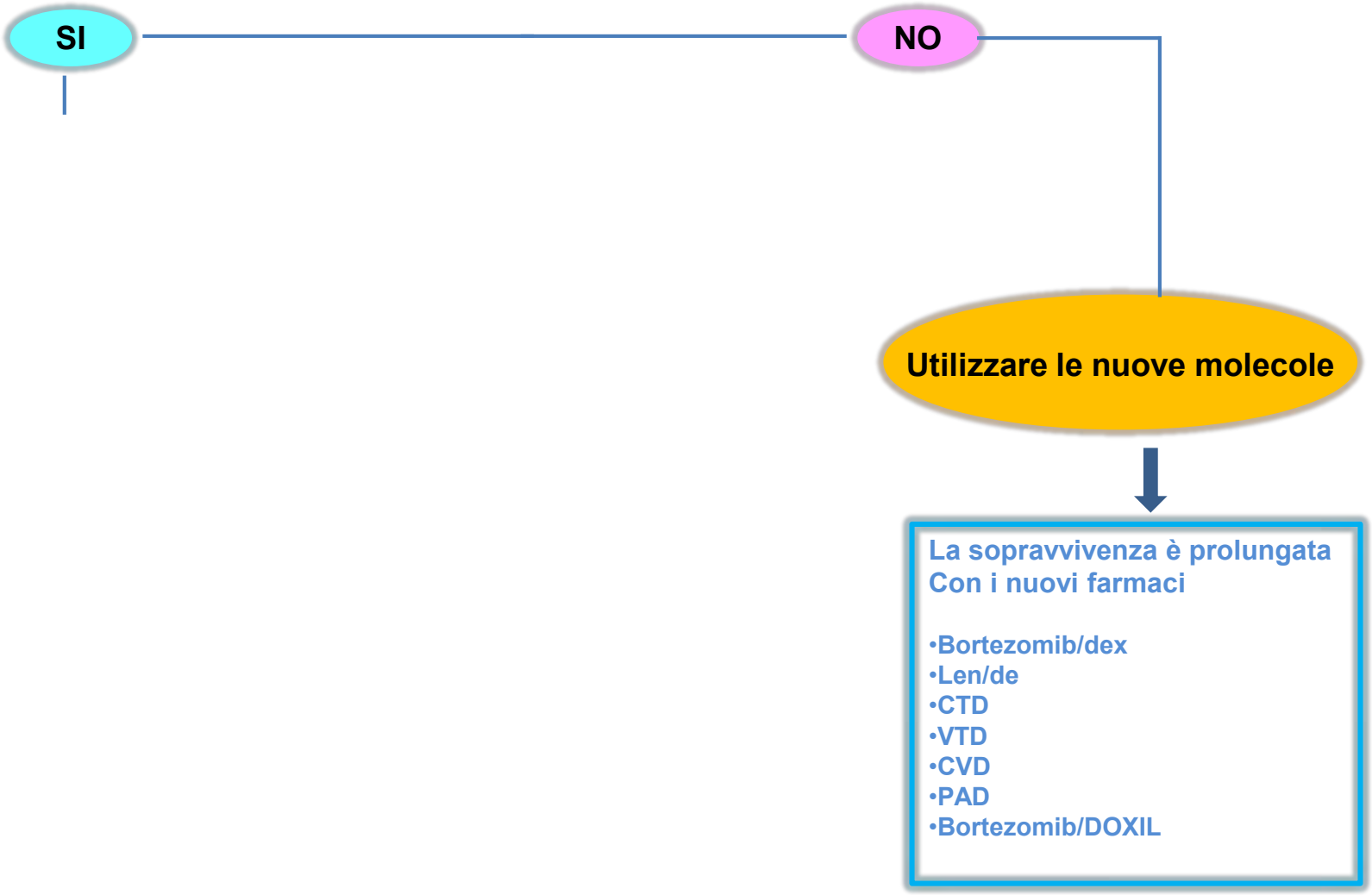
Opzioni terapeutiche per i pazienti non eleggibili per trapianto



Ludwig et al The Oncologist 2012

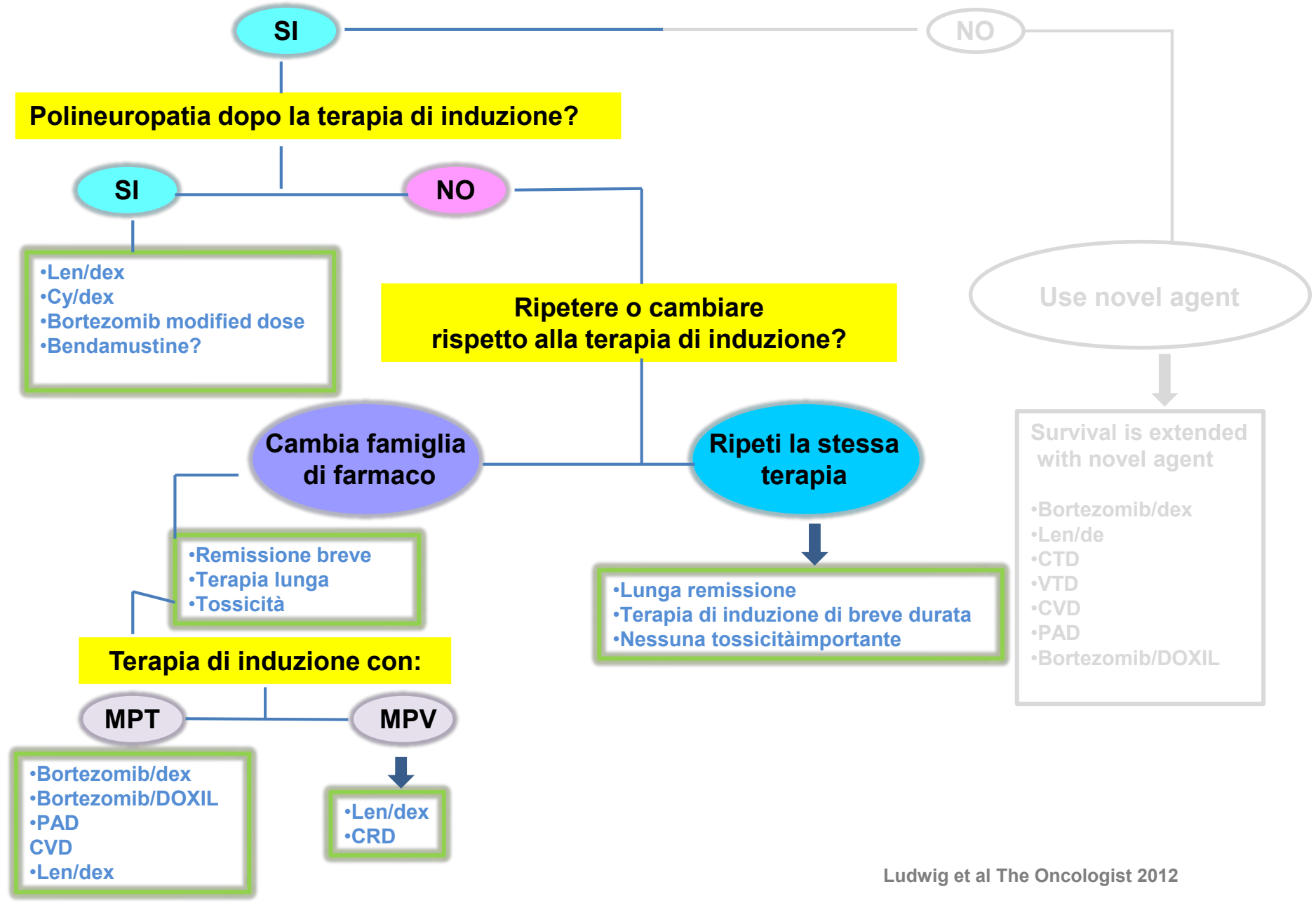
RECIDIVA

Il paziente ha già ricevuto nuovi farmaci?



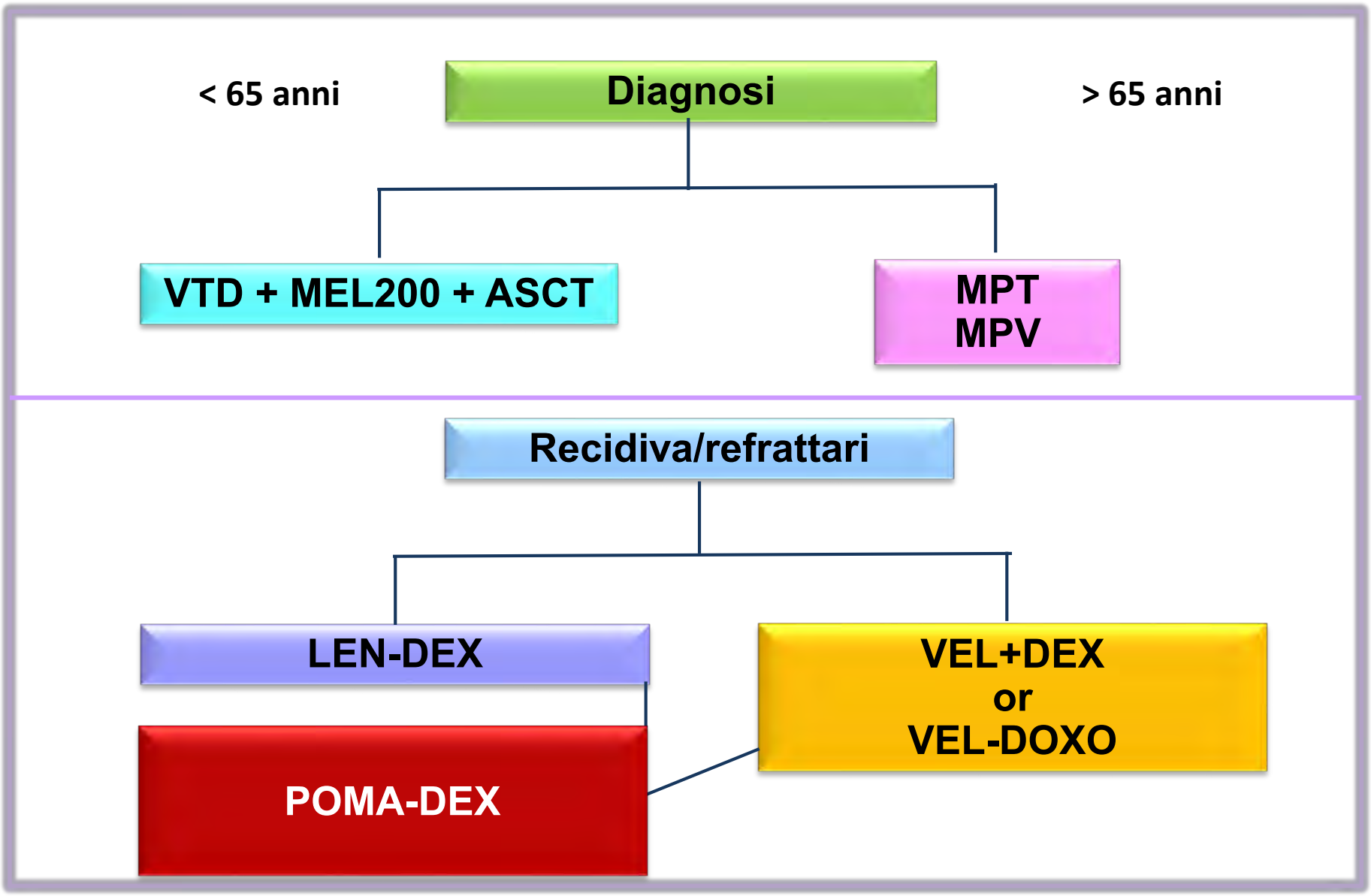
Ludwig et al The Oncologist 2012

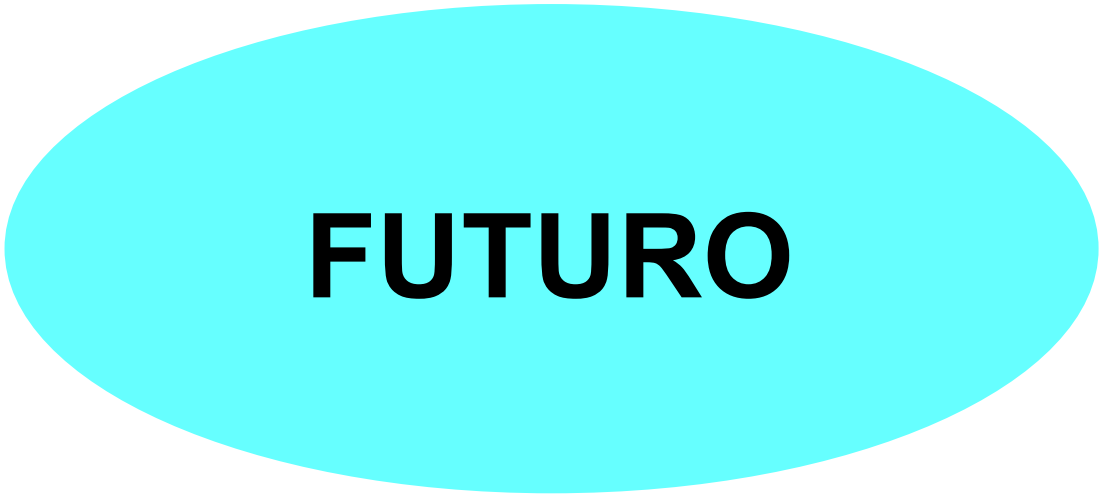
Il paziente ha già ricevuto nuovi farmaci?



Ludwig et al The Oncologist 2012

Opzioni terapeutiche in Italia




FUTURO

NUOVI FARMACI

- **Proteasome Inhibitors**
  - Carfilzomib
  - Ixazomib
  - Oprozomib
  - Marizomib
- **HDAC Inhibitors**
  - Vorinostat
  - Panobinostat
- **AKT Inhibitors**
  - Perifosine
- **mTOR Inhibitors**
  - Temsirolimus
- **Monoclonal antibodies**
  - Elotuzumab
  - Daratumumab
  - CNTO 328

NUOVI FARMACI

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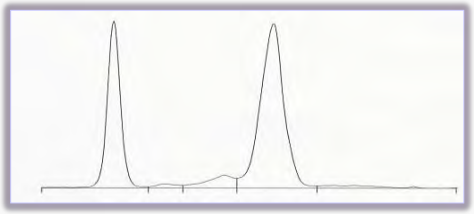
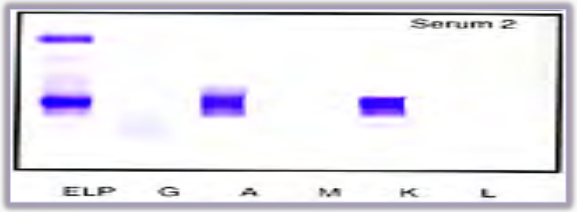
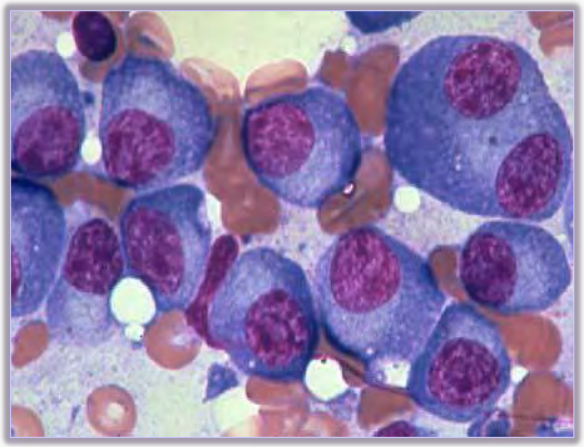
- AKT Inhibitors
  - Perifosine
- mTOR Inhibitors
  - Temsirolimus
- **Monoclonal antibodies**
  - **Elotuzumab**
  - **Daratumumab**
  - CNTO 328

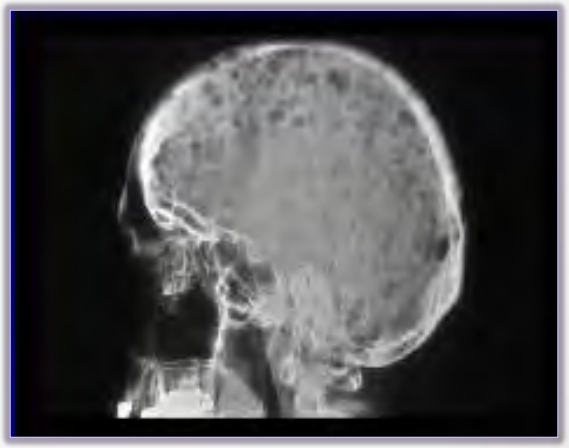

Grazie!!

Quali terapie immunoncologiche sono disponibili?









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Algoritmo terapeutico

Diagnosi

< 65 y

> 65 y

Velcade +**T**halidomide
Dexamethasone
MEL200 + SCT
(Stell Cell Transplant)

Melphalan +**P**rednisone+ **T**halidomide
Melphalan +**P**rednisone +**V**elcade
(Lenalidomide+Desametasone)

Qualunque recidiva

oggi

Lenalidomide
Desametasone

Velcade
or
Velcade-Caely**x**

Bendamustina
(+/- **V**elcade)

Pomalidomide

domani

Carfilzomib

Elotuzumab

Panobinostat

Ixazomib

Daratumumab

Problematiche ancora aperte per il MM

Goal della terapia

- Nonostante gli IMiDs e PIs abbiano migliorato la durata di sopravvivenza dei pazienti affetti da MM, non tutti i pazienti raggiungono risposte ottimali, soprattutto i pazienti che non possono essere trattati con ASCT

Malattia complessa

- L'eterogeneità della malattia complica la scelta terapeutica. Non esiste una terapia standard per i pazienti in recidiva o refrattari.

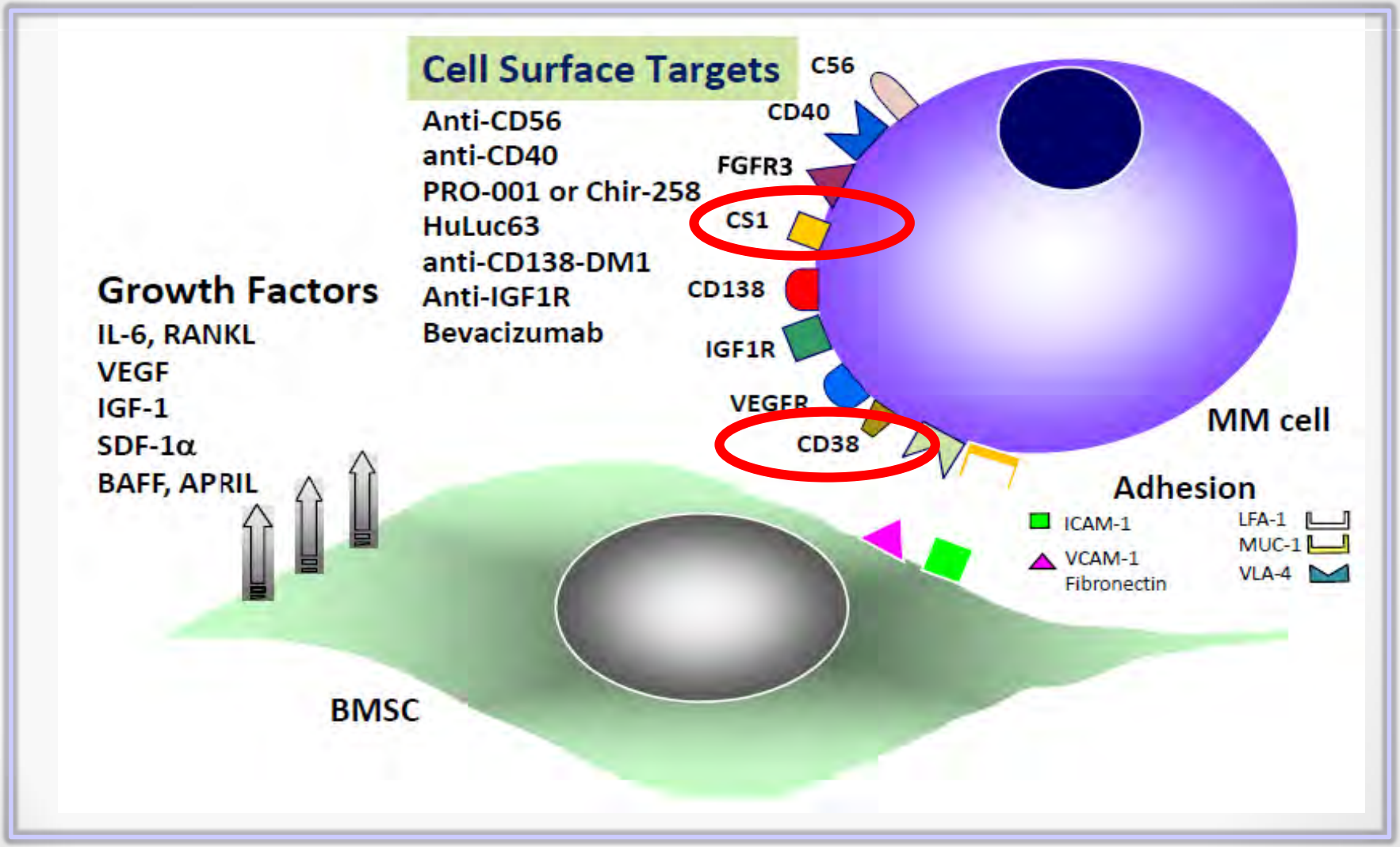
Target Specifici

- Le attuali terapie non colpiscono in modo specifico le cellule di MM, per cui agiscono anche contro le cellule normali

Eventi avversi

- Il profilo degli eventi avversi di ogni molecola deve essere sempre considerato quando si sceglie una combinazione di farmaci
- Gli eventi avversi possono limitare l'uso di trattamenti più aggressivi e ridurre la possibilità di ottenere i migliori risultati

“Targets” degli anticorpi monoclonali



Evoluzione della Ricerca della attività delle Cellule Natural Killer nella Risposta Immune del Mieloma Multiplo

1980s
Natural Killer Cells demonstrate antitumor activity in models of leukemia[1]

1990s
The Natural Killer Cell pool is initially expanded but can decrease during progression from MGUS to multiple myeloma[2,3]

2000s
Natural Killer Cells can recognize and kill patient-derived myeloma cells while sparing normal immune cells[4,5]

2010s
A larger Natural Killer Cell pool observed in patients with disease control[6]

MGUS, monoclonal gammopathy of undetermined significance.

1. Lotzová E et al. *Leuk Res*. 1987;11:1059-1066. 2. Österborg A et al. *Eur J Haematol*. 1990;45:153-157. 3. Sawanobori M et al. *Acta Haematol*. 1997;98:150-154. 4. Frohn C et al. *Br J Haematol*. 2002;199:660-664. 5. Carbone E et al. *Blood*. 2005;105:251-258. 6. Pessoa de Magalhães RJ et al. *Haematologica*. 2013;98:79-86.

Overall Survival with Immuno-Oncology Agents

- Immuno-oncology agents have been shown to improve long-term outcomes, including overall survival in melanoma (Figure)
- Immuno-oncology therapies have potential long-term survival benefits[1] in patients with multiple myeloma and may overcome treatment resistance problems when administered in combination with other agents

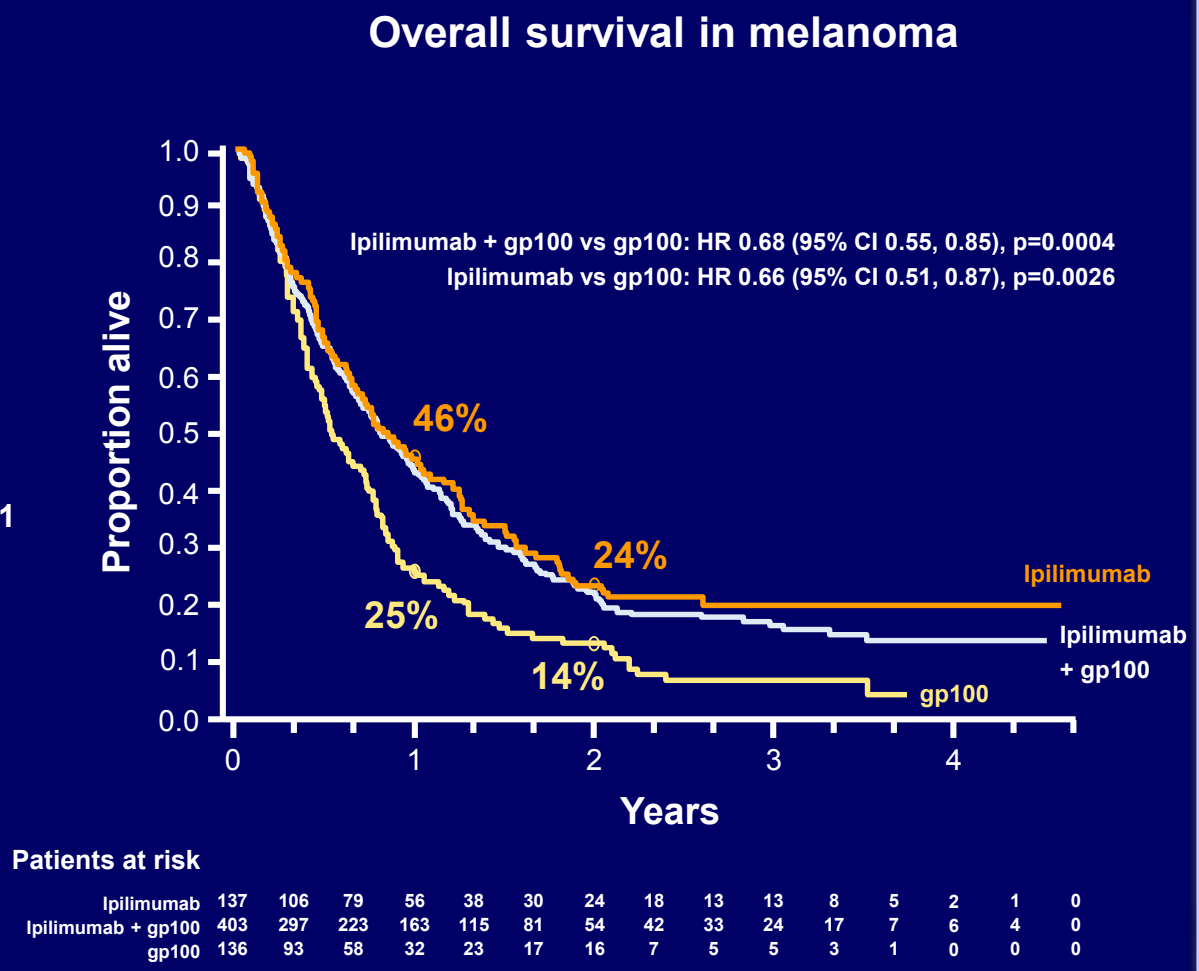
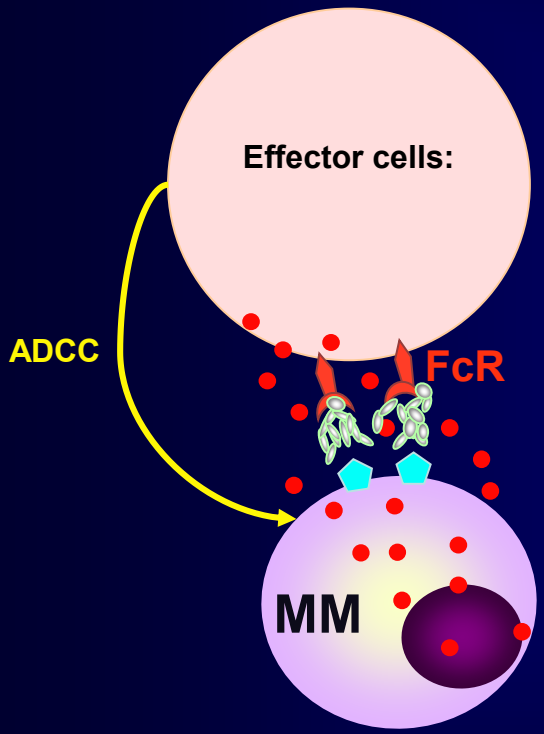


Figure reproduced with permission from Hodi FS et al. *N Engl J Med* 2010;363(8):711-723. © 2010 Massachusetts Medical Society

1. Ascierto PA et al. *J Transl Med* 2014;12:141

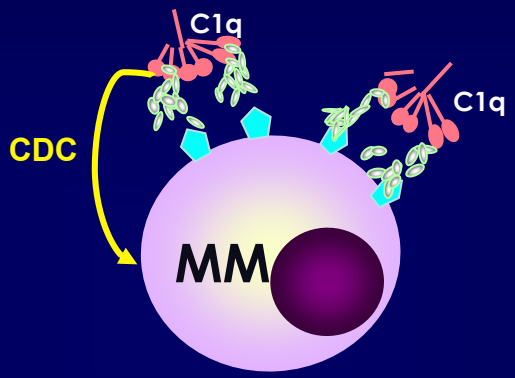
Monoclonal antibody-based therapeutic targeting of myeloma

Antibody-dependent cellular cytotoxicity (ADCC)



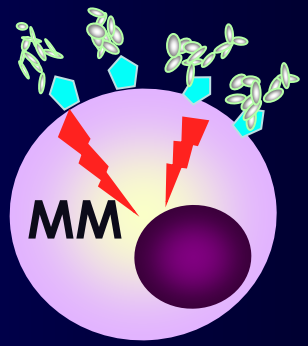
- Daratumumab (CD38)
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- XmAb®5592 (HM1.24)

Complement-dependent cytotoxicity (CDC)



- Daratumumab (CD38)

Apoptosis/growth arrest via targeting signaling pathways



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

Tai & Anderson Bone Marrow Research, Volume 2011, Article ID 924058, 14 pages

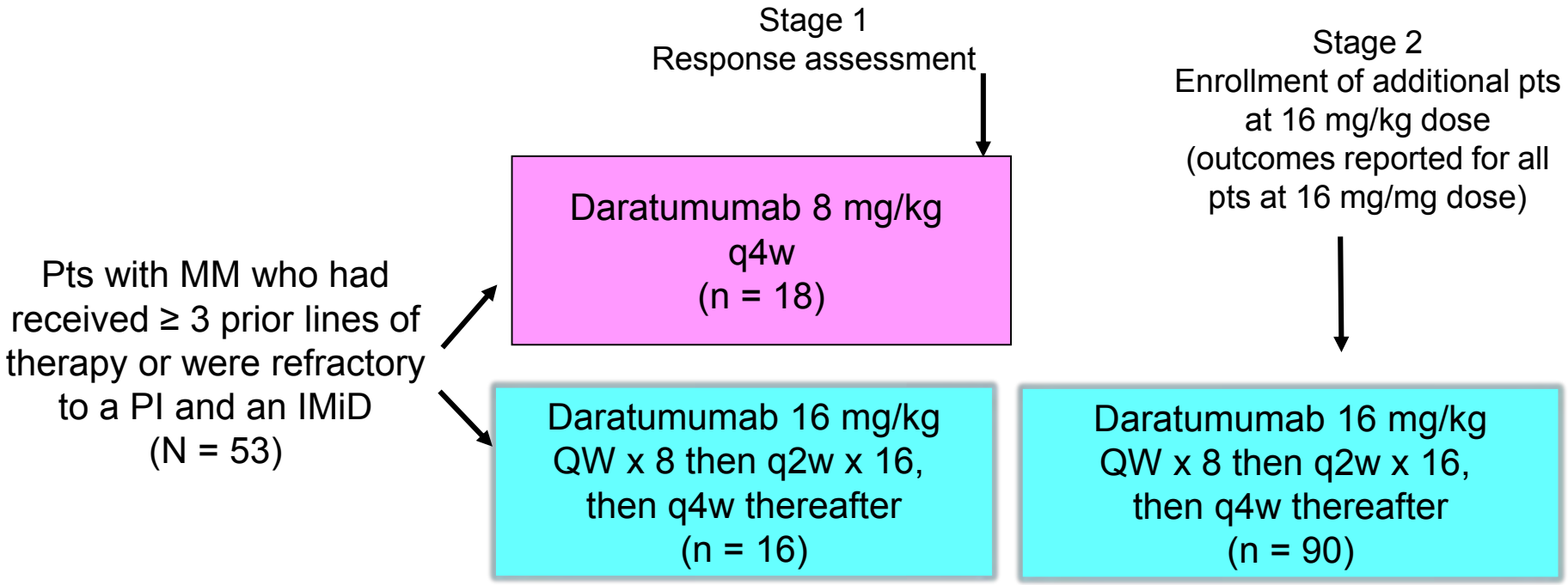
Phase II SIRIUS: Daratumumab in Myeloma

- CD38 highly expressed on myeloma cells, lower levels on normal lymphoma, myeloid cells[1]
- Daratumumab a CD38-targeted human monoclonal antibody that induces cell death through ADCC, ADCP, and CDC[2]
- Phase I/II GEN501 study showed promising safety, activity of single-agent daratumumab in relapsed/refractory MM[3]
- Current MMY2002 (SIRIUS) study further assessed safety and efficacy of single-agent daratumumab in pts with heavily pretreated MM[4]

1. Lin P, et al. Am J Clin Pathol. 2004;121:482-488. 2. Laubach JP, et al. Expert Opin Investig Drugs. 2014;23:445-452. 3. Lokhorst HM, et al. ASCO 2014. Abstract 8513. 4. Lonial S, et al. ASCO 2015. Abstract LBA8512.

SIRIUS: Study Design

- Open-label, international, multicenter, 2-stage study



- Primary objective: overall response rate
- Secondary objectives: PFS, OS, duration of response, time to response, clinical benefit rate

Lonial S, et al. ASCO 2015. Abstract LBA8512.

SIRIUS: Pt Characteristics

Characteristic	All Pts at 16 mg/kg (N = 106)
Median age, yrs (range)	63.5 (31-84)
Creatinine clearance < 60 mL/min, %	43
High-risk cytogenetics, %	19
Median time since diagnosis, yrs (range)	4.8 (1-24)
Median number prior therapies, n (range) ▪ > 3 prior lines, %	5 (2-14) 82
Prior ASCT, %	80
Prior IMiD, % ▪ Lenalidomide ▪ Pomalidomide ▪ Thalidomide	100 99 63 44
Prior PI, % ▪ Bortezomib ▪ Carfilzomib	100 99 50

Lonial S, et al. ASCO 2015. Abstract LBA8512.

SIRIUS: Efficacy

- Reductions in paraprotein occurred in majority of pts
- ORR with 16 mg/kg: 29%
  - 3% sCR; 9% VGPR; 17% PR; 34% CBR (ORR + MR)
- Responses observed across subgroups
- Deepening of responses with continued treatment
  - Median time to response: 1 mo
  - Median DoR: 7.4 mos (95% CI: 5.5-NE)
- Median PFS: 3.7 mos (95% CI: 2.8-4.6)
- 1-yr OS: 65% (95% CI: 51.2% to 75.5%)

Lonial S, et al. ASCO 2015. Abstract LBA8512.

SIRIUS: Safety

- Most common grade 3/4 AEs: thrombocytopenia (25%), anemia (24%), neutropenia (14%)
  - Grade 3/4 anemia, thrombocytopenia more frequent in nonresponders
  - Note that trial allowed pts with hemoglobin > 7.5 g/dL, platelet count ≥ 50 x 10^9/L at baseline
- Infusion-related reactions: 43%
  - Primarily grade 1/2, > 90% occurred during first infusion
  - 7% of pts had another infusion reaction beyond first dose
- No discontinuations due to treatment-related AEs, including infusion reactions

Lonial S, et al. ASCO 2015. Abstract LBA8512.

SIRIUS: Conclusion

- Daratumumab associated with single-agent activity in heavily pretreated MM; ORR 29%[1]
- Responses were rapid, appeared durable, and improved over time (appearance of sCRs, VGPR)
- Daratumumab was well tolerated, with no discontinuations due to Aes
  - Infusion reactions mild to moderate, manageable
- Investigators concluded daratumumab is a potential new standard of care in this population
- Study is currently ongoing[2]

1. Lonial S, et al. ASCO 2015. Abstract LBA8512. 2. ClinicalTrials.gov. NCT01985126.

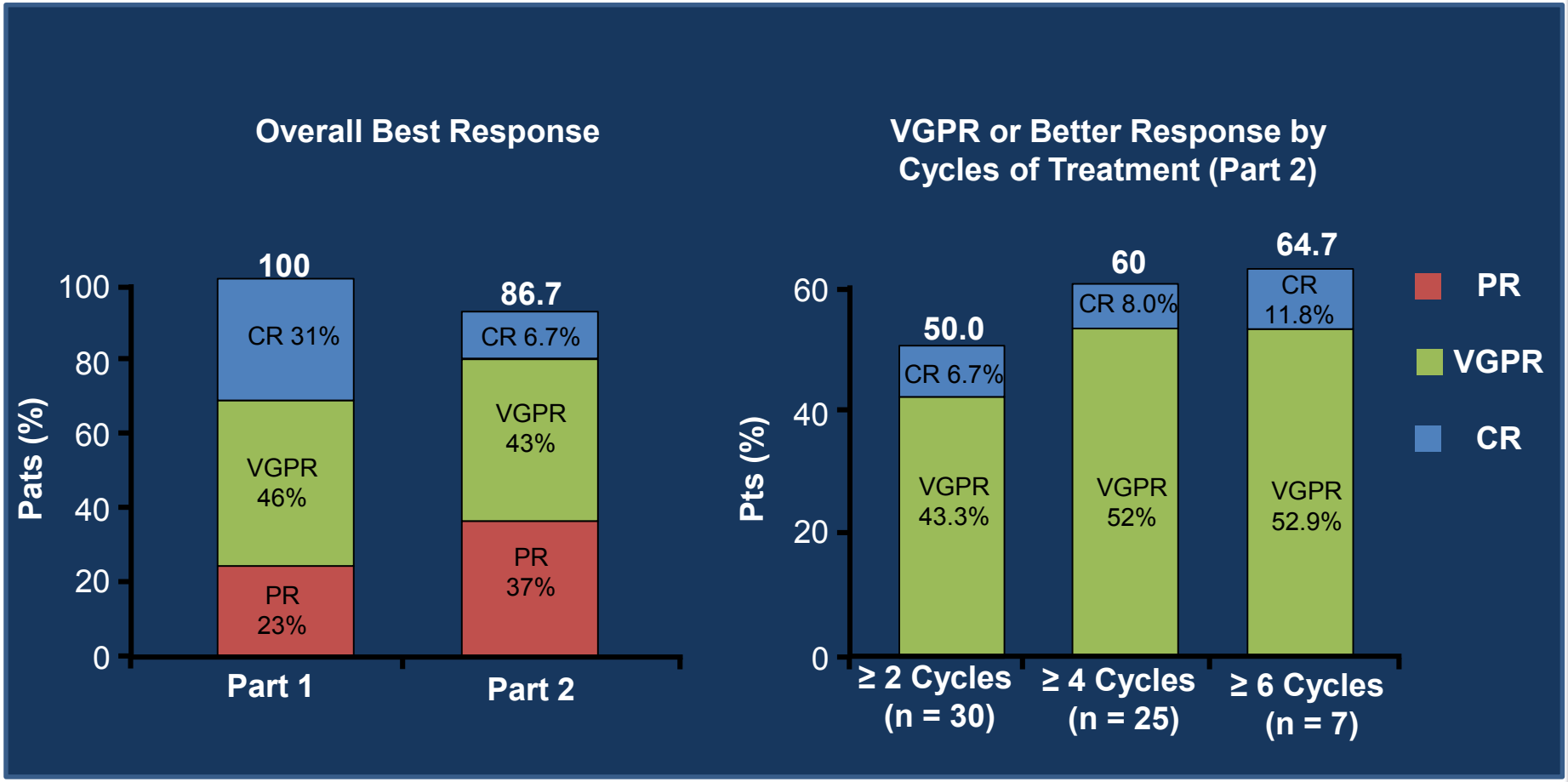
Phase I/II Trial: Daratumumab in Combination With Len/Dex in Rel/Ref MM

- Phase I/II dose-escalation trial of daratumumab in combination with len/dex in rel/ref MM (safety cohort: n =45; efficacy cohort: n = 43)
  - Daratumumab is a human mAb targeting CD38-expressing cells
  - Dose escalation: daratumumab 2-16 mg/kg/wk for 8 wks, twice monthly for 16 wks, then once monthly for 24 mos in total or until PD, unmanageable AE
  - Lenalidomide 25 mg on Days 1-21 of each 28-day cycle
  - Dexamethasone 40 mg/wk for of each 28-day cycle
- Median prior lines of therapy: 2 (range: 1-4); most with prior exposure to IMiDs and/or a proteasome inhibitor; 3 pts refractory to len
- MTD: daratumumab 16 mg/kg + len 25 mg and dex 40 mg/wk

Plesner T, et al. ASH 2014. Abstract 84.

Daratumumab in Combination With Len/Dex: Overall Best Response

45 pts, 1-4 prior lines, not refractory to lenalidomide



- Mean follow-up: 12.9 mos (Part 1); 5.6 mos (Part 2)
- Median time to response: 1 mo for 16 mg/kg in Part 2; median time to CR: 4.9 mos in Part 2

Plesner T, et al. ASH 2014. Abstract 84. Reproduced with permission.

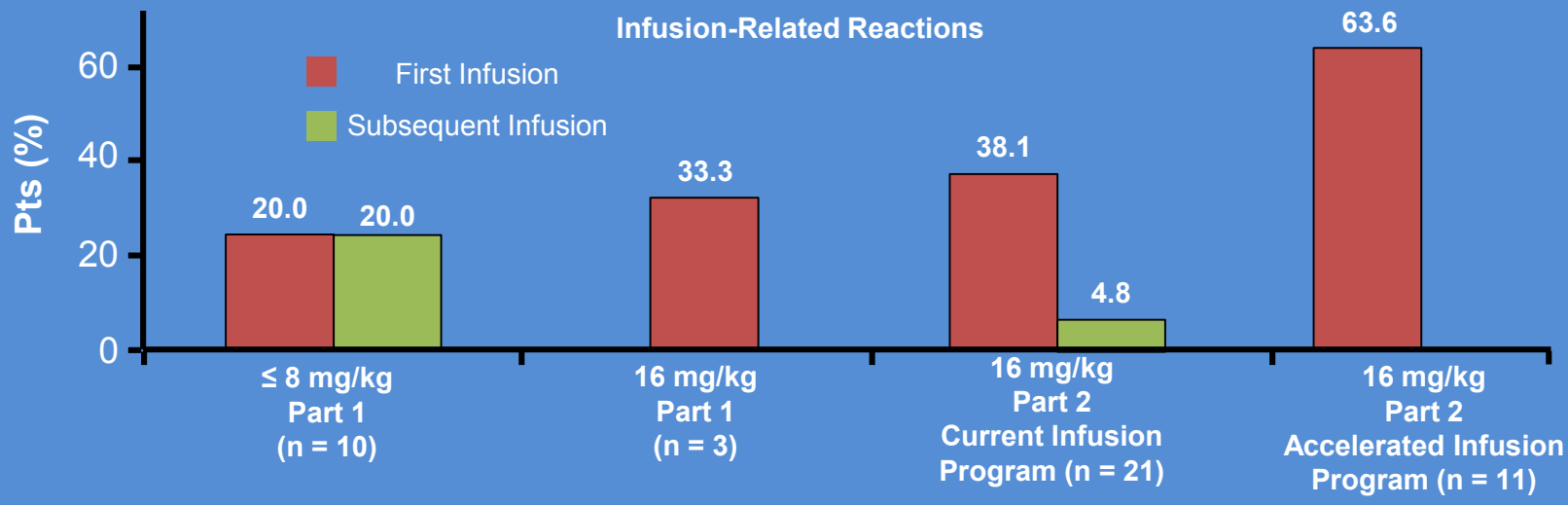
Daratumumab in Combination With Len/Dex: Adverse Events

Most Common (Incidence in > 10% Pts) AEs, %	Part 1 (n = 13)	Part 2 (n = 32)	Total (N = 45)
Total number of pts with AEs	100	100	100
Neutropenia	62	65	64
Muscle spasms	62	38	44
Diarrhea	54	18	31
Fatigue	62	16	29
Cough	31	28	29
Constipation	54	13	27
Nausea	38	19	24
Nasopharyngitis	62	3	20
Bone pain	31	13	18
Upper respiratory tract infection	46	3	16
Insomnia	31	6	16
Dyspnea	23	6	11
Anemia	31	19	11

Plesner T, et al. ASH 2014. Abstract 84.

Daratumumab in Combination With Len/Dex: Safety

- Daratumumab related serious AEs
  - Pneumonia, neutropenia, diarrhea (1 pt each receiving 16 mg/kg, early infusion program)
  - Laryngeal edema (1 pt receiving 16 mg/kg, accelerated infusion program)



- 19/45 pts reported infusion-related reactions; mostly grade 1/2
  - 18/19 pts with infusion-related reactions recovered and were able to continue the subsequent infusion

Plesner T, et al. ASH 2014. Abstract 84.

Daratumumab in Combination With Len/Dex: Conclusions

Combination daratumumab with len/dex appears safe and effective in heavily pretreated pts with relapsed/refractory MM

- ORR: 100% in Part 1 (31% CR, 46% VGPR); 87% in Part 2 (7% CR, 43% VGPR)
- Favorable safety profile with manageable toxicities in relapsed and relapsed/refractory MM pts
- Accelerated infusion tolerable but associated with higher incidence of grade 1/2 Aes

Plesner T, et al. ASH 2014. Abstract 84.

Dara: ongoing studies

MMY-3003

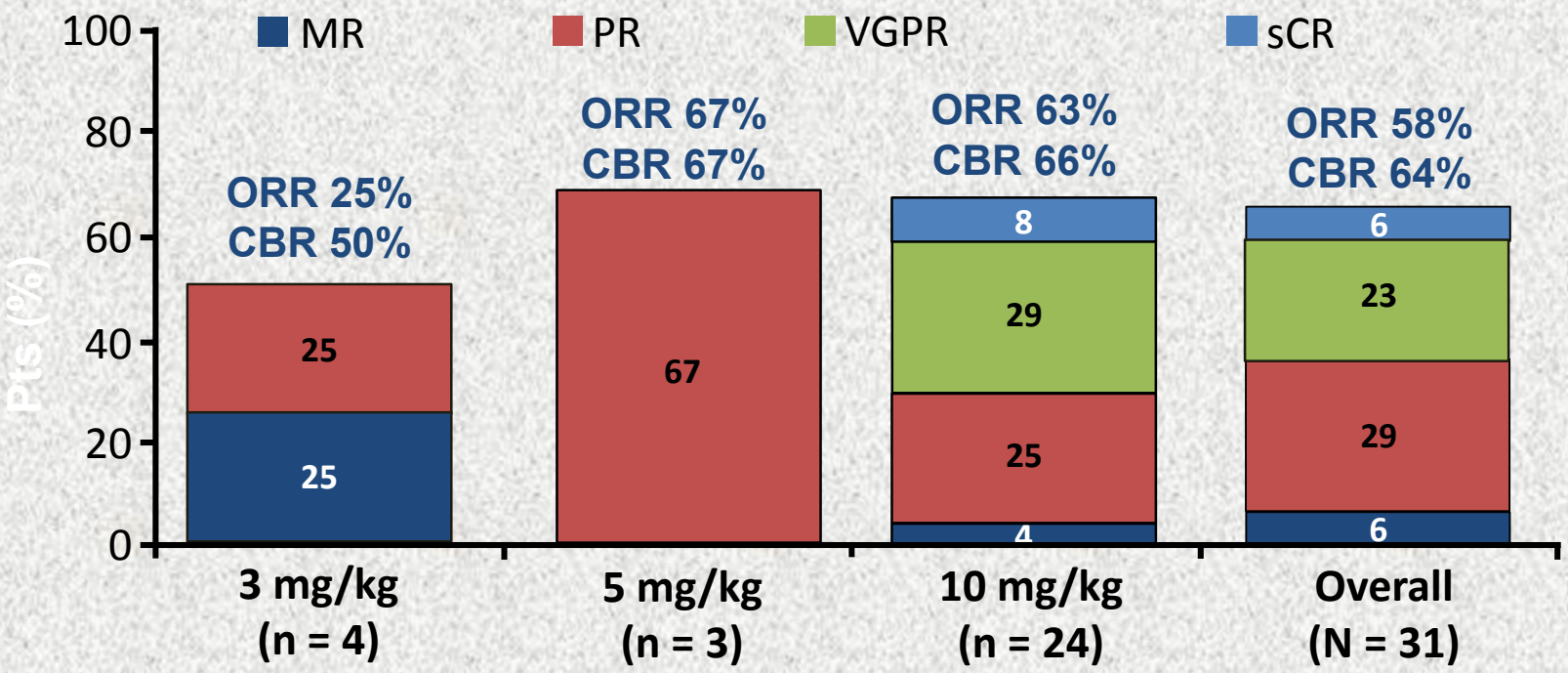
Phase III Study of Lenalidomide and Dexamethasone with or without Daratumumab to Treat Relapsed or Refractory Multiple Myeloma (POLLUX)

MMY-3004

Phase III Study of Bortezomib and Dexamethasone with or without Daratumumab to Treat Relapsed or Refractory Multiple Myeloma (CASTOR)

SAR650984 in Combination With Len/Dex in RR MM (Phase Ib): Efficacy

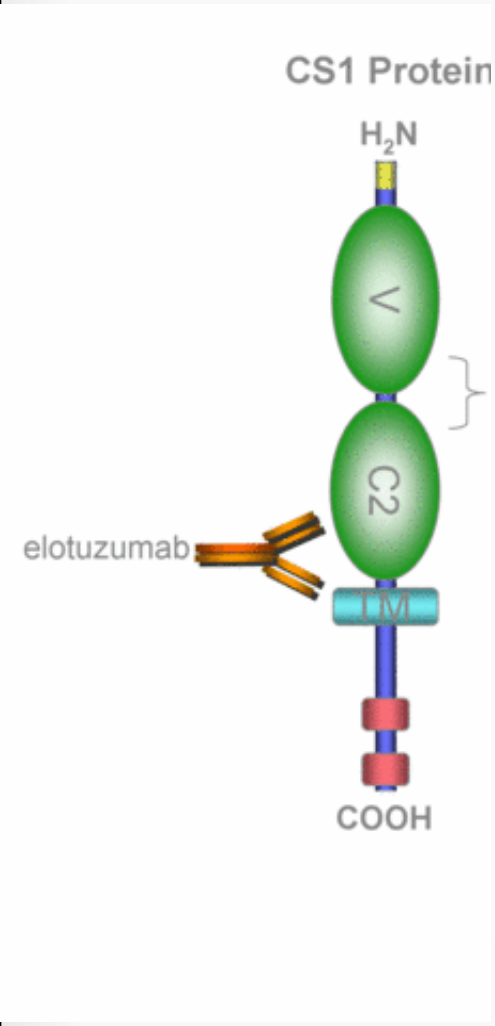
- DoR: 9.13 mos (range: 1.2-15.2)



- Most common treatment-related grade 3/4 AEs: neutropenia, anemia, thrombocytopenia, and febrile neutropenia
- 15 incidences of infusion reaction, all occurring in the first 2 cycles

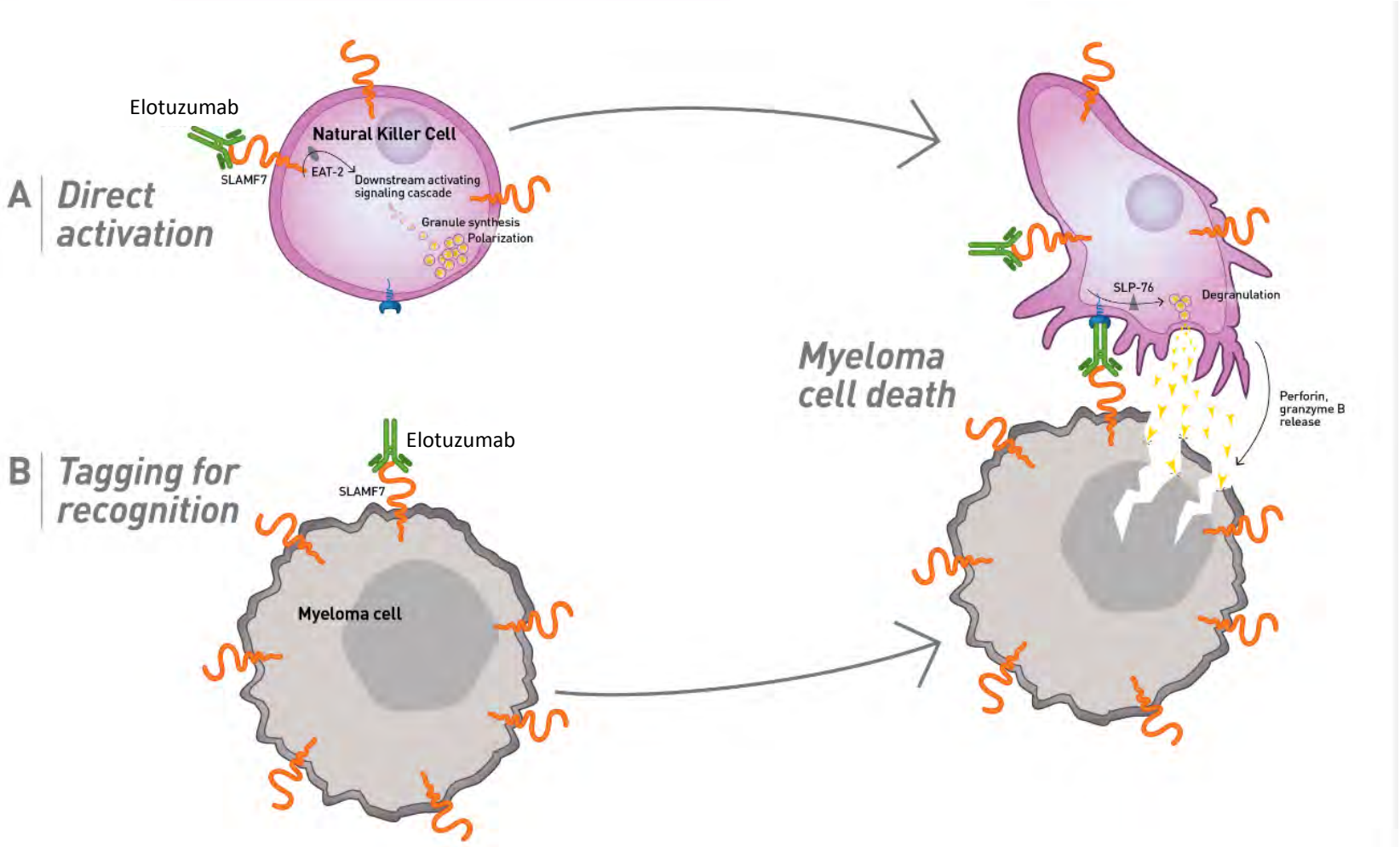
Martin TG, et al. ASH 2014. Abstract 83

Targeting CS-1/SLAM7 in myeloma:
Elotuzumab mAb

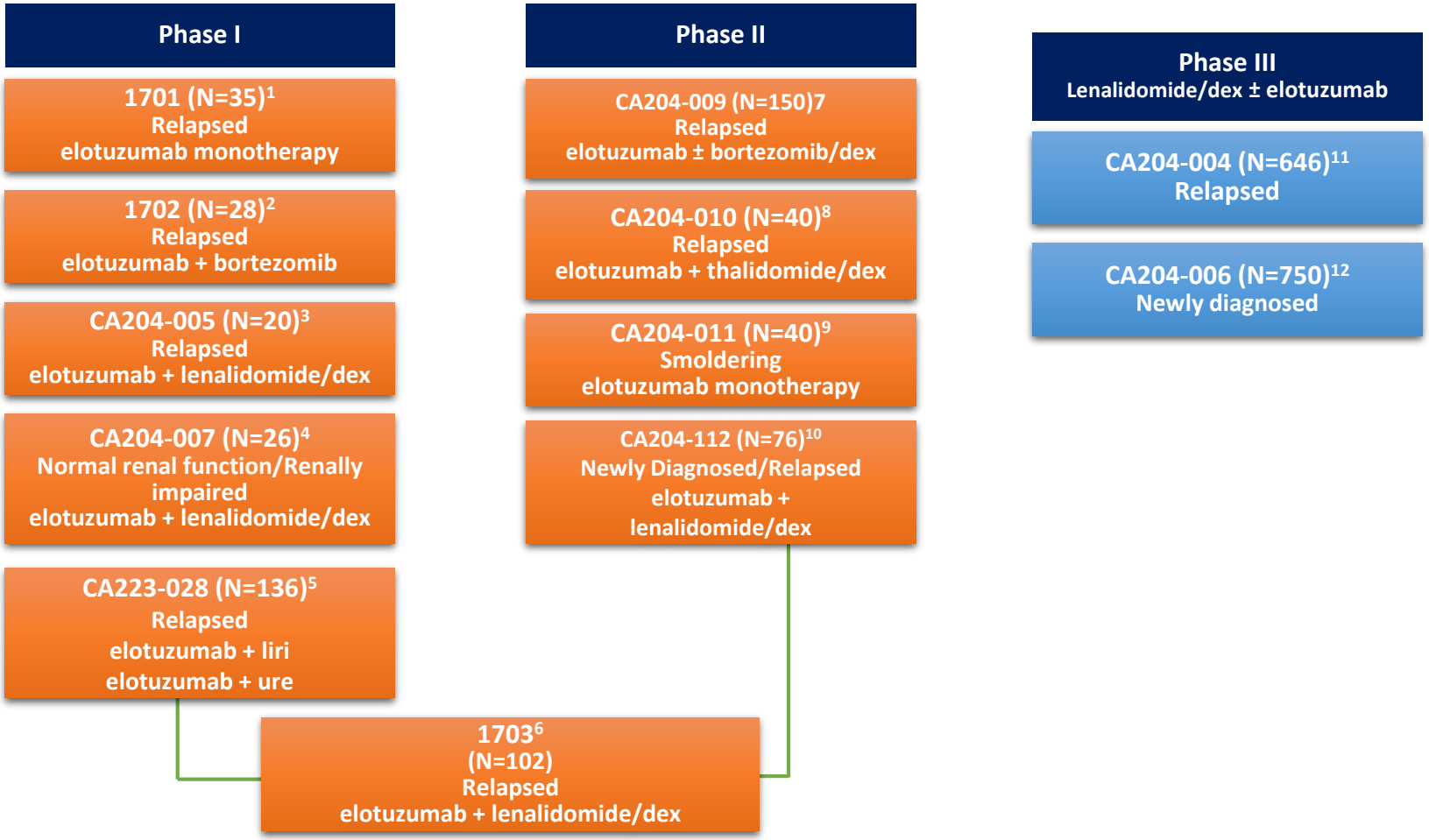


- Humanized, IgG1 mab specific for human CS-1/SLAMF7.
- Binds to a membrane-proximal motif of the receptor
- Mediates ADCC towards SLAMF7$^+$ myeloma cells
- Directly activates NK cells
- Enhances elimination of myeloma cells in combination with anti-myeloma agents
- Profound reduction of efficacy after NK depletion (human xenografts)
- No agonist activating effect of myeloma cells (lacking EAT-2)

Elotuzumab works via a dual mechanism of action by both directly activating Natural Killer Cells and through antibody-dependent cell-mediated cytotoxicity (ADCC) to cause targeted Myeloma cell death



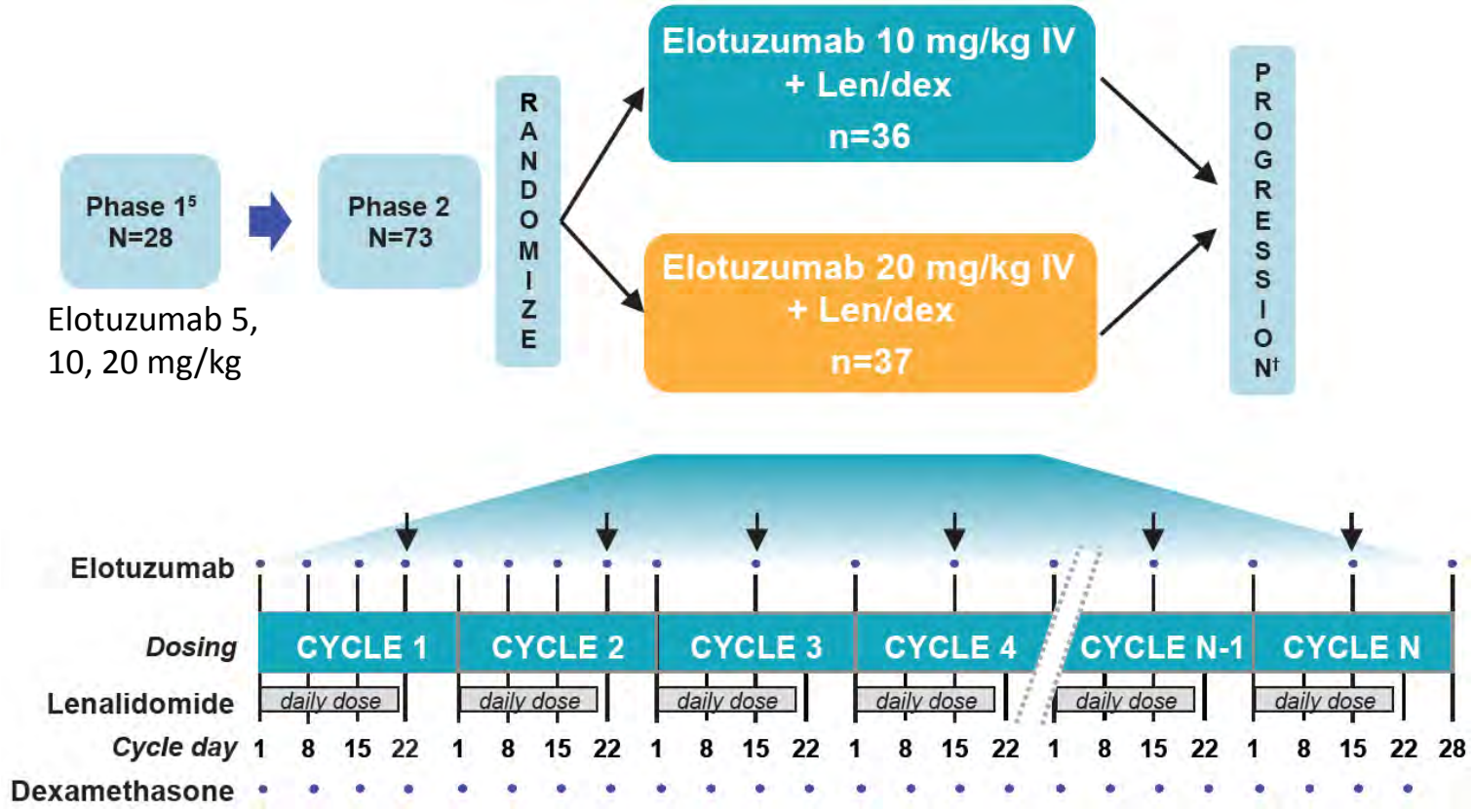
Elotuzumab: Programma sviluppo clinico



Dex, dexamethasone; liri, lirilumab; ure, urelumab.

1. Clinicaltrials.gov. NCT00425347. 2. Clinicaltrials.gov. NCT00726869. 3. Clinicaltrials.gov. NCT01241292. 4. Clinicaltrials.gov. NCT01393964. 5. Clinicaltrials.gov. NCT02252263. 6. Clinicaltrials.gov. NCT00742560. 7. Clinicaltrials.gov. NCT01478048.
8. Clinicaltrials.gov. NCT01632150. 9. Clinicaltrials.gov. NCT01441973. 10. Clinicaltrials.gov. NCT02159365.
11. Clinicaltrials.gov. NCT01239797. 12. Clinicaltrials.gov. NCT01335399.

1703 A Phase Ib/II, Multicenter, Open-Label, Dose-Escalation Study of Elotuzumab in Combination With Lenalidomide and Dexamethasone in Subjects With RRMM



5. First 5 pts limited to 6 cycles of therapy; additional 23 pts received elo until progression or unacceptable toxicity.

Stratification in phase II: prior therapies (1 vs 2 or 3 lines), prior thalidomide or thalidomide analogs

Len/dex: lenalidomide plus low dose dexamethasone

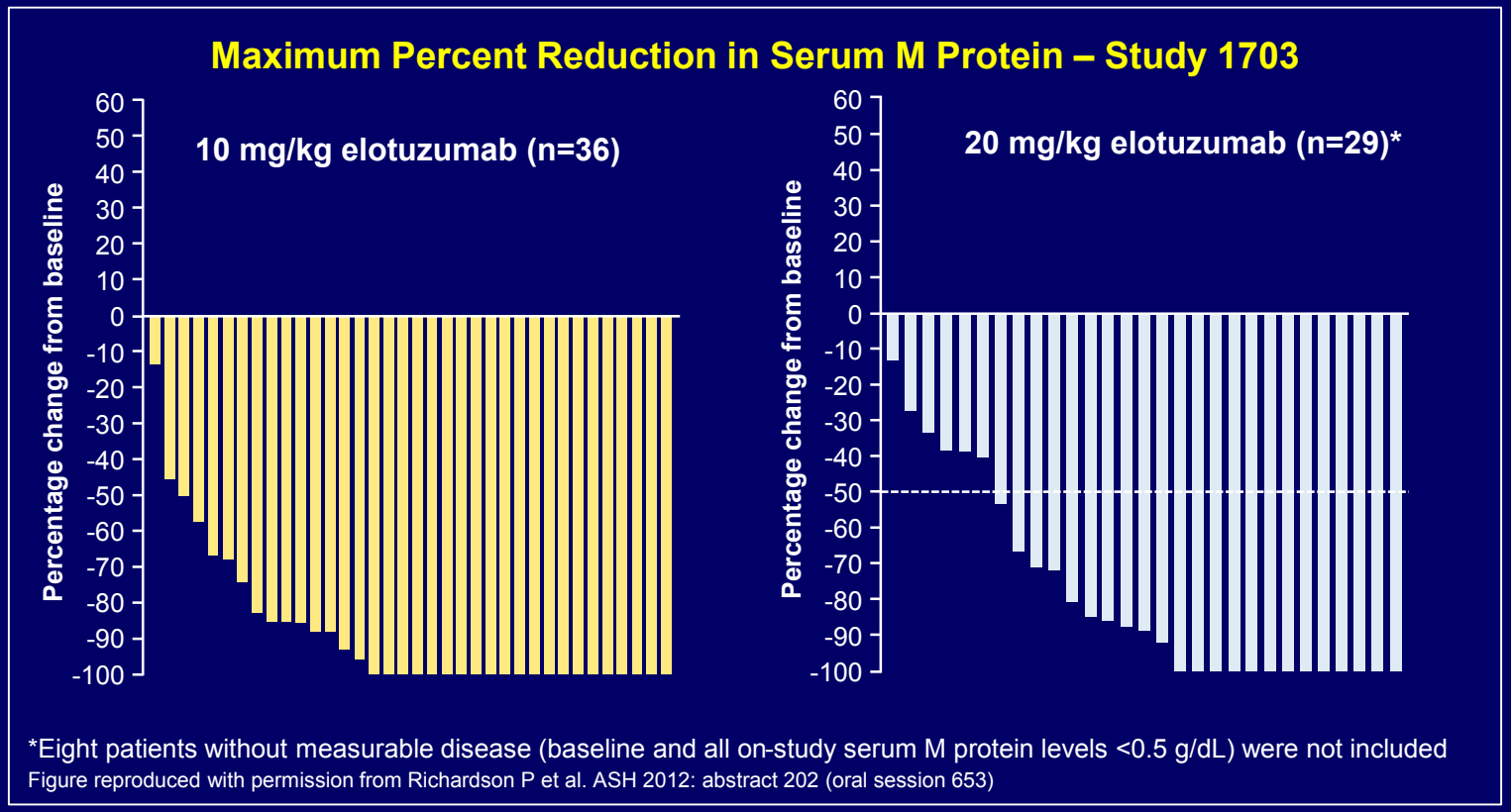
↓ Assessments were performed once per cycle

†Progression defined by IMWG Criteria

Richardson PG et al. ASH 2014 Abstract 302

Immuno-Oncology Agents in Multiple Myeloma

- **Elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) demonstrated a high response rate and PFS benefits in an open-label phase 1b/2 study[1] in patients with multiple myeloma**
- **Elotuzumab has FDA breakthrough therapy designation in multiple myeloma**



*Eight patients without measurable disease (baseline and all on-study serum M protein levels <0.5 g/dL) were not included

Figure reproduced with permission from Richardson P et al. ASH 2012: abstract 202 (oral session 653)

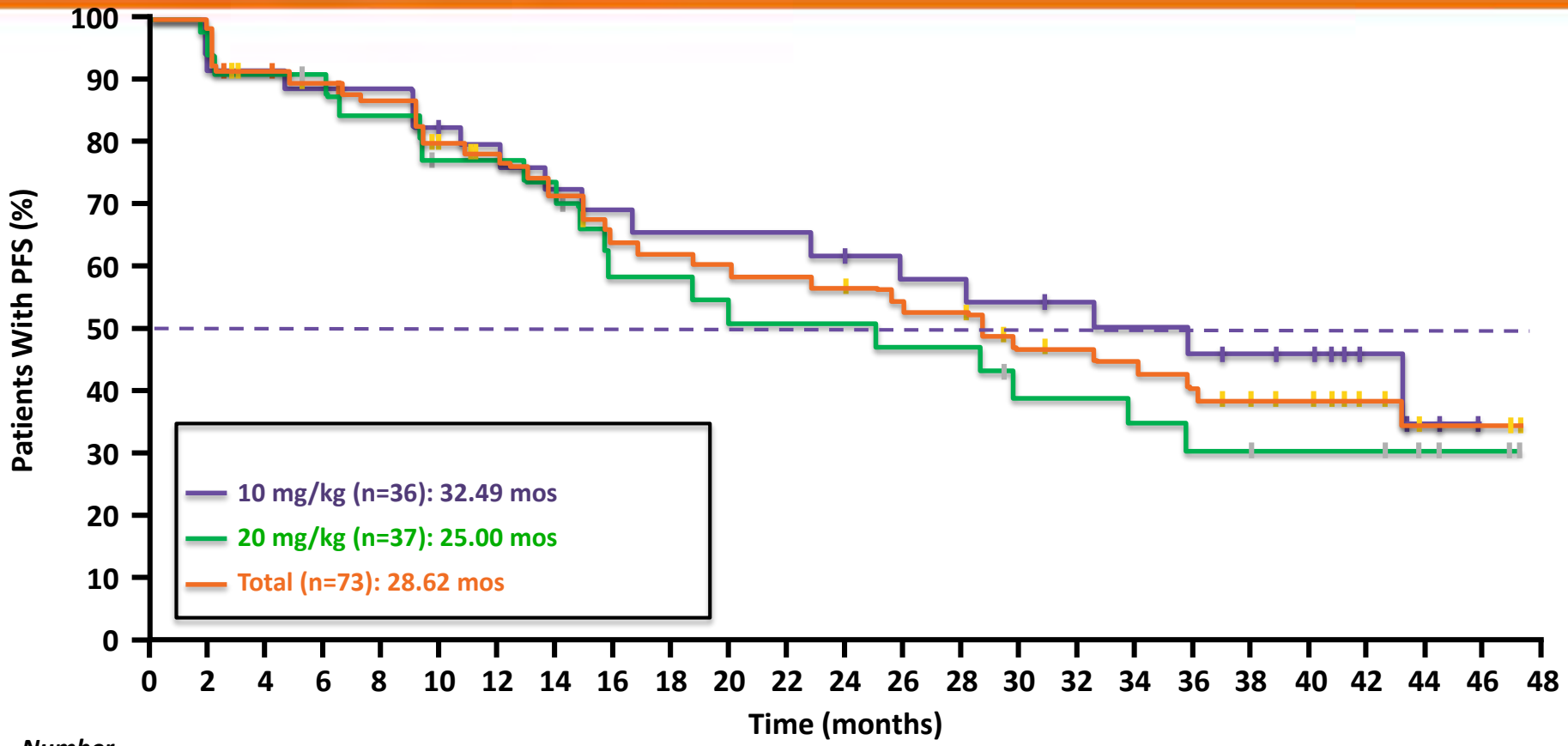
1. Richardson PG et al. *Blood* 2014;124:302

Phase 2 Efficacy: Response Rate

Assessment	Elo 10 mg/kg (n=36)	Elo 20 mg/kg (n=37)	Total (n=73)
Overall response*, n (%)	33 (92)	28 (76)	61 (84)
Best confirmed response, n (%)			
Stringent complete response (sCR)	2 (6)	1 (3)	3 (4)
Complete response (CR)	4 (11)	3 (8)	7 (10)
Very good partial response (VGPR)	17 (47)	14 (38)	31 (43)
Partial response (PR)	10 (28)	10 (27)	20 (27)
Stable disease (SD)	3 (8)	7 (19)	10 (14)
Missing	0	2 (5)	2 (3)
Median time to first response, mos	1.0	1.7	1.0
Median duration of response, mos	23.0	18.0	20.8

Richardson PG et al. ASH 2014: Abstract 2273

1703: Phase 2 Progression-Free Survival



Number at risk:																									
10 mg/kg	36	33	32	30	29	26	23	21	19	18	18	18	16	15	15	14	13	12	11	10	8	4	2	0	0
20 mg/kg	37	32	27	26	24	21	21	19	15	15	13	13	13	12	12	9	9	8	7	7	6	6	4	2	0
Total	73	65	59	56	53	47	44	40	34	33	31	31	29	27	27	23	22	20	18	17	14	10	6	2	0

Relative dose intensity was 96% for elo, 77% for len, and 75% for dex.
PFS, progression-free survival.

1. Richardson P et al. Presented at the Annual Meeting of the American Society of Hematology 2014:Abstract 302.

Summary and Conclusions

In the Phase 2 portion of this study, Elo in combination with Len/dex demonstrated encouraging efficacy

- **ORR: 92% in the 10 mg/kg treatment group (84% overall)**
- **Median PFS: 32.49 mos in the 10 mg/kg group (29 mos overall)**

Most common TEAEs included diarrhea (66%), muscle spasms (52%), fatigue (56%), and constipation (51%)

Pre-medication regimen successfully mitigated infusion reactions

Faster infusion rate (5 mL/min, infusion time <1 hour) was well tolerated

Efficacy and safety outcomes observed in the Phase 2 portion of the study concur with Phase 1b results[1]

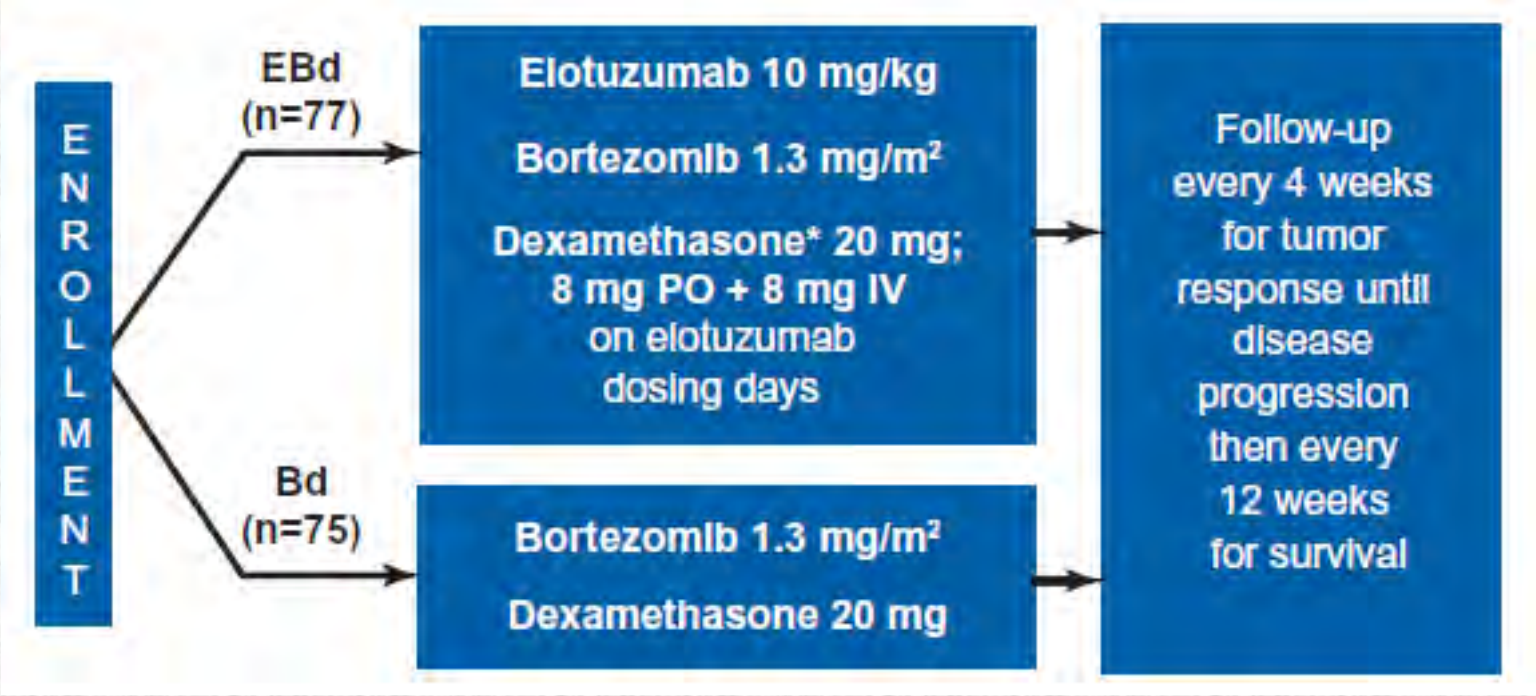
PFS = progression free survival; ORR = overall response rate; TEAE = treatment-emergent adverse event.

Richardson PG et al. ASH 2014: Abstract 2273

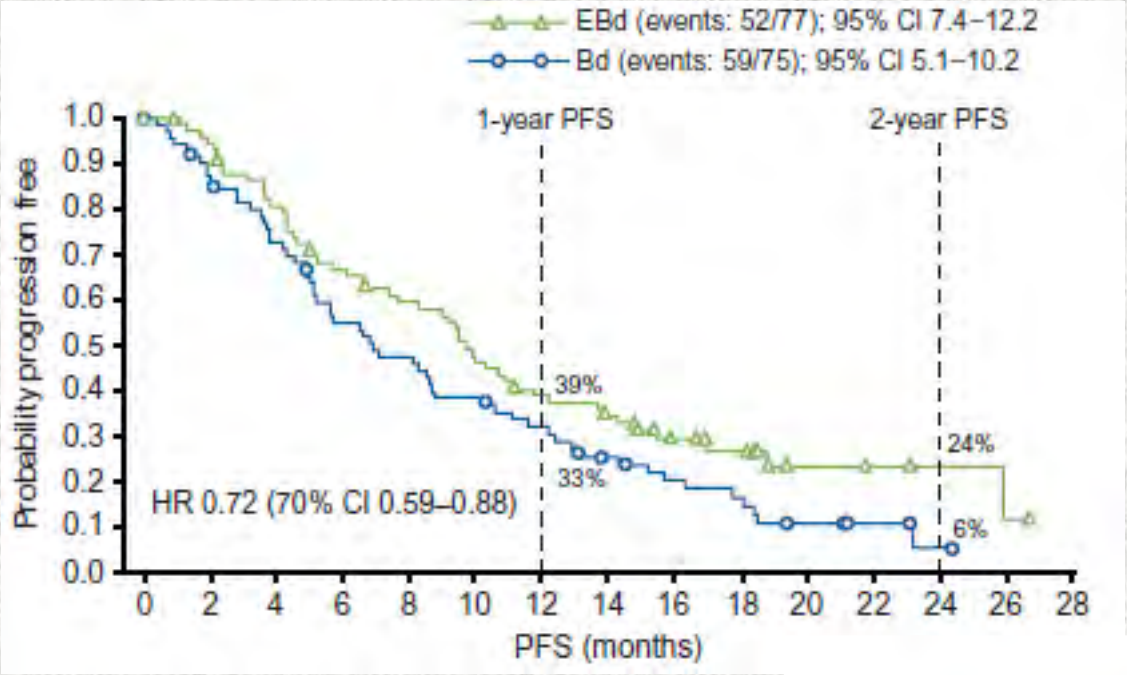
A Randomized Phase 2 Study of Bortezomib/Dexamethasone With or Without Elotuzumab in Patients With Relapsed/Refractory Multiple Myeloma

Andrzej Jakubowiak,[1]* Massimo Offidani,[2] Brigitte Pégourie,[3] Javier De La Rubia,[4] Laurent Garderet,[5] Kamel Laribi,[6] Alberto Bosi,[7] Roberto Marasca,[8] Jacob Laubach,[9] Ann Mohrbacher,[10] Angelo Michele Carella,[11] Anil K. Singhal,[12] L. Claire Tsao,[12] Mark Lynch,[13] Eric Bleickardt,[13] Ying-Ming Jou,[13] Antonio Palumbo[14]

Phase II CA204-009 trial

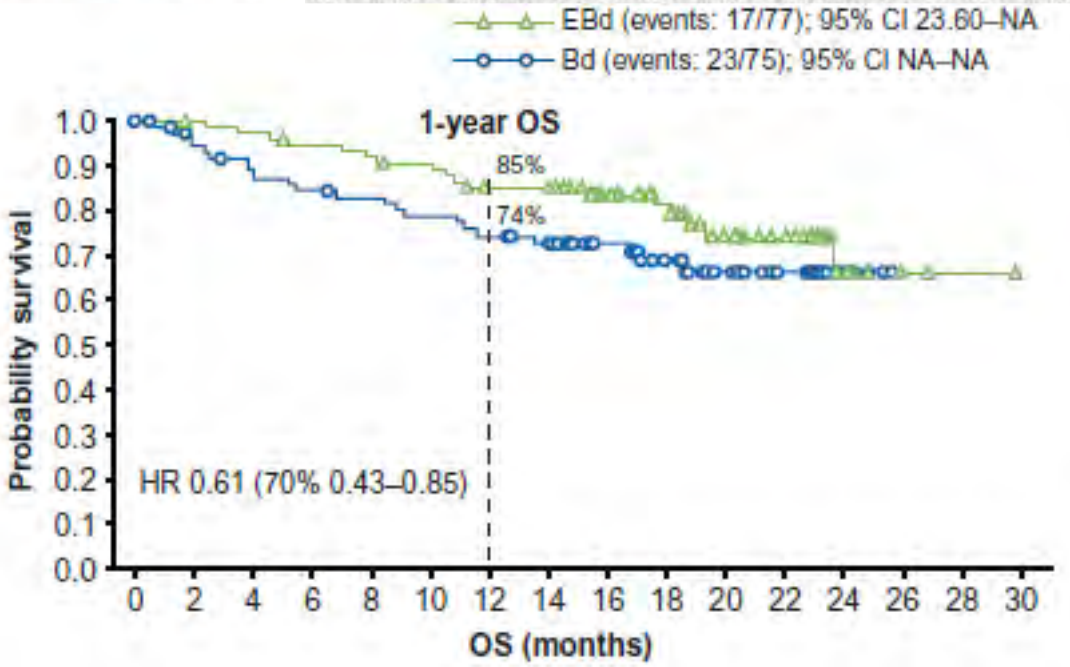


Phase III CA204-009 trial



PFS (median 9.7 *vs* 6.9; p=0.08)

OS



ASCO 2015

ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

- Endpoints:
  - Co-primary: PFS and ORR
  - Other: overall survival (data not yet mature); duration of response, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to Elo administration

Lonial S et al; NEJM, August 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

Baseline Demographics and Disease Characteristics

Characteristic	E-Ld (n=321)	Ld (n=325)
Age (years), median (range)	**67 (37–88)**	**66(38–91)**
≥65 years	187 (58)	183 (56)
Region, %		
Europe	61	60
North America	21	21
Rest of the world	18	19
International Staging System disease stage, n (%)		
I	44	43
II	32	32
III	21	21
Not reported	4	14
Cytogenetics (FISH)		
del(17p)		
Yes	32	32
No	66	67
Not reported	2	1
t(4;14)		
Yes	9	10
No	89	89
Not reported	2	1
1q21		
Yes	46	50
No	53	49
Not reported	2	1

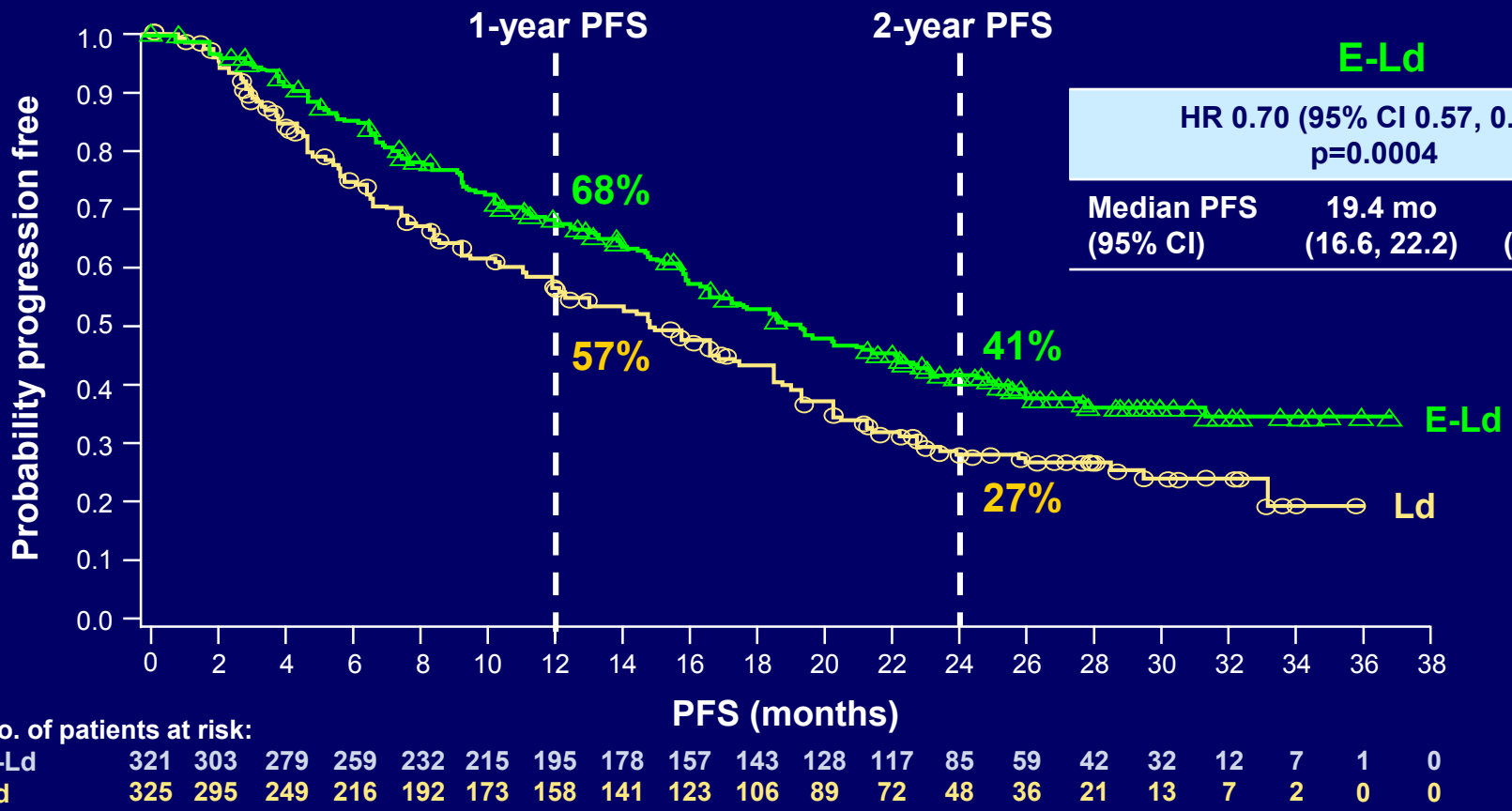
FISH = fluorescence in situ hybridization

Baseline Demographics and Disease Characteristics

Characteristic	E-Ld (n=321)	Ld (n=325)
Prior regimens, median (range)	**2 (1–4)**	**2 (1–4)**
Prior therapies, %		
Bortezomib	68	71
Melphalan*	69	61
Thalidomide	48	48
Lenalidomide†	5	7
Response to most recent line of therapy, %‡		
Refractory	**35**	**35**
Bortezomib refractory	22	21
Thalidomide refractory	9	11
Relapsed	**65**	**65**
Prior stem cell transplantation, %	**52**	**57**

*Oral or intravenous. †Prior lenalidomide was permitted if best response was ≥partial response and patients were not refractory to prior lenalidomide treatment; patients could not receive more than 9 cycles of lenalidomide and had at least 9 months between the last dose of lenalidomide and progression. ‡One patient in the elotuzumab group had an unknown response to the most recent line of therapy

Co-primary Endpoint: Progression-Free Survival

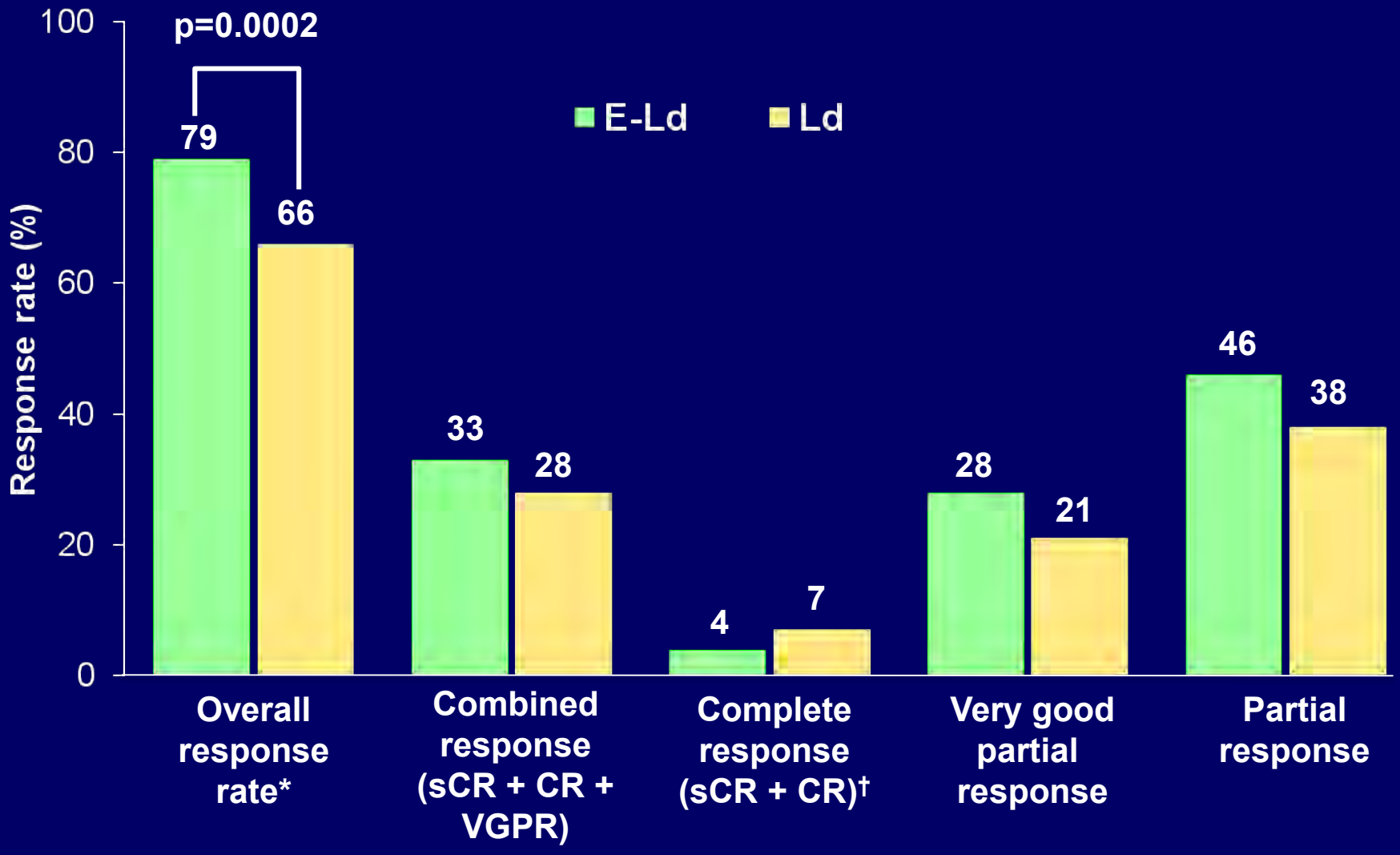


From *N Engl J Med*, Lonial S et al, Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. Copyright © (2015) Massachusetts Medical Society. Reprinted with permission

E-Ld–treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively

PFS analysis used the primary definition of PFS

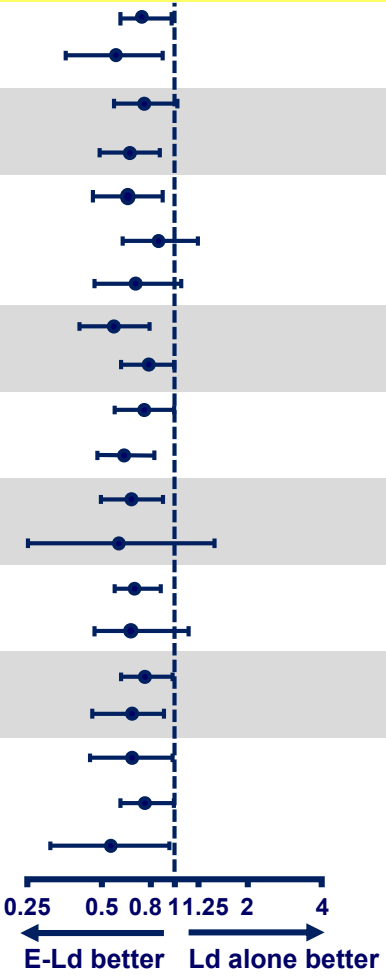
Co-primary Endpoint: Overall Response Rate



*Defined as partial response or better. †Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay

Progression-Free Survival: Subgroup Analysis

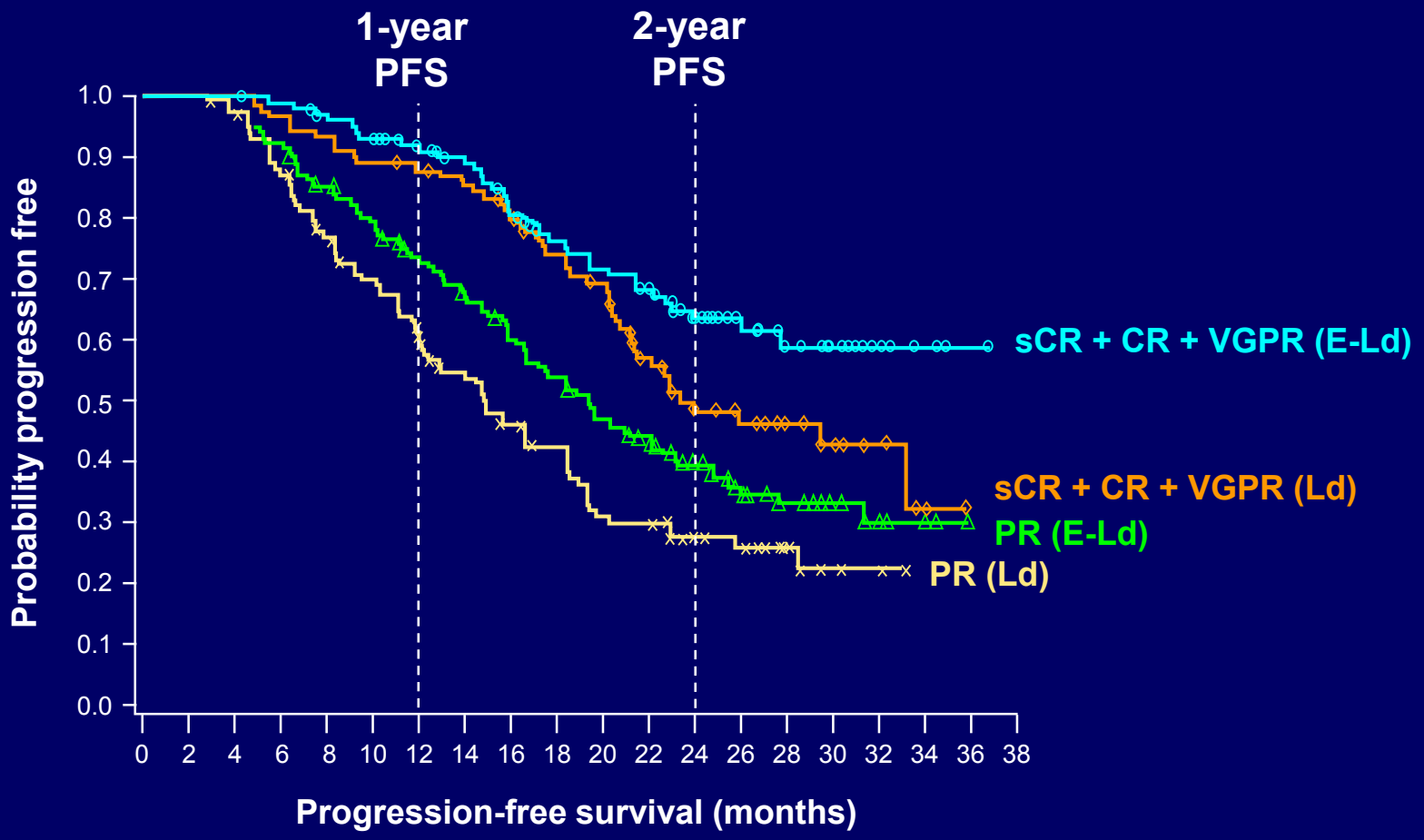
Subgroup	Hazard ratio (95% CI)
Age (<75 years)	0.73 (0.59–0.92)
Age (≥75 years)	0.56 (0.35–0.89)
Age (<65 years)	0.75 (0.55–1.02)
Age (≥65 years)	0.65 (0.50–0.85)
ISS stage (I)	0.63 (0.46–0.87)
ISS stage (II)	0.86 (0.61–1.22)
ISS stage (III)	0.70 (0.47–1.04)
Response to most recent therapy (refractory)	0.56 (0.40–0.78)
Response to most recent therapy (relapsed)	0.77 (0.60–1.00)
Lines of prior therapy (1)	0.75 (0.56–1.00)
Lines prior therapy (2 or 3)	0.65 (0.49–0.87)
Prior IMiD (prior thalidomide only)	0.64 (0.48–0.85)
Prior IMiD (other)	0.59 (0.25–1.40)
Prior bortezomib (yes)	0.68 (0.54–0.86)
Prior bortezomib (no)	0.72 (0.49–1.07)
Prior SCT (yes)	0.75 (0.58–0.99)
Prior SCT (no)	0.63 (0.46–0.86)
del(17p) (yes)	0.65 (0.45–0.94)
1q21 (yes)	0.75 (0.56–0.99)
t(4;14) (yes)	0.53 (0.29–0.95)



PFS benefit in E-Ld group was consistently better across key subgroups

IMiD = immunomodulatory drug; ISS = International Staging System

Progression-Free Survival by Tumor Response



Patients achieving ≥PR showed improved PFS with E-Ld vs Ld alone

Adverse Events Reported in ≥30% of Patients

Adverse event, n (%)	E-Ld (n=318)		Ld (n=317)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Common non-hematologic adverse events				
Fatigue	149 (47)	27 (9)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (0.3)
Muscle spasms	95 (30)	1 (0.3)	84 (27)	3 (1)
Cough	100 (31)	1 (0.3)	57 (18)	0
Common hematologic toxicities				
Lymphopenia	316 (99)	244 (77)	311 (98)	154 (49)
Anemia	306 (96)	60 (19)	301 (95)	67 (21)
Thrombocytopenia	266 (84)	61 (19)	246 (78)	64 (20)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Infections	259 (81)	89 (28)	236 (74)	77 (24)

- **Exposure-adjusted infection rate was 197 (incidence rate per 100 person-years of exposure) in both arms**
- **There was no detriment to overall health-related quality of life with the addition of elotuzumab to Len/Dex**

Infusion Reactions

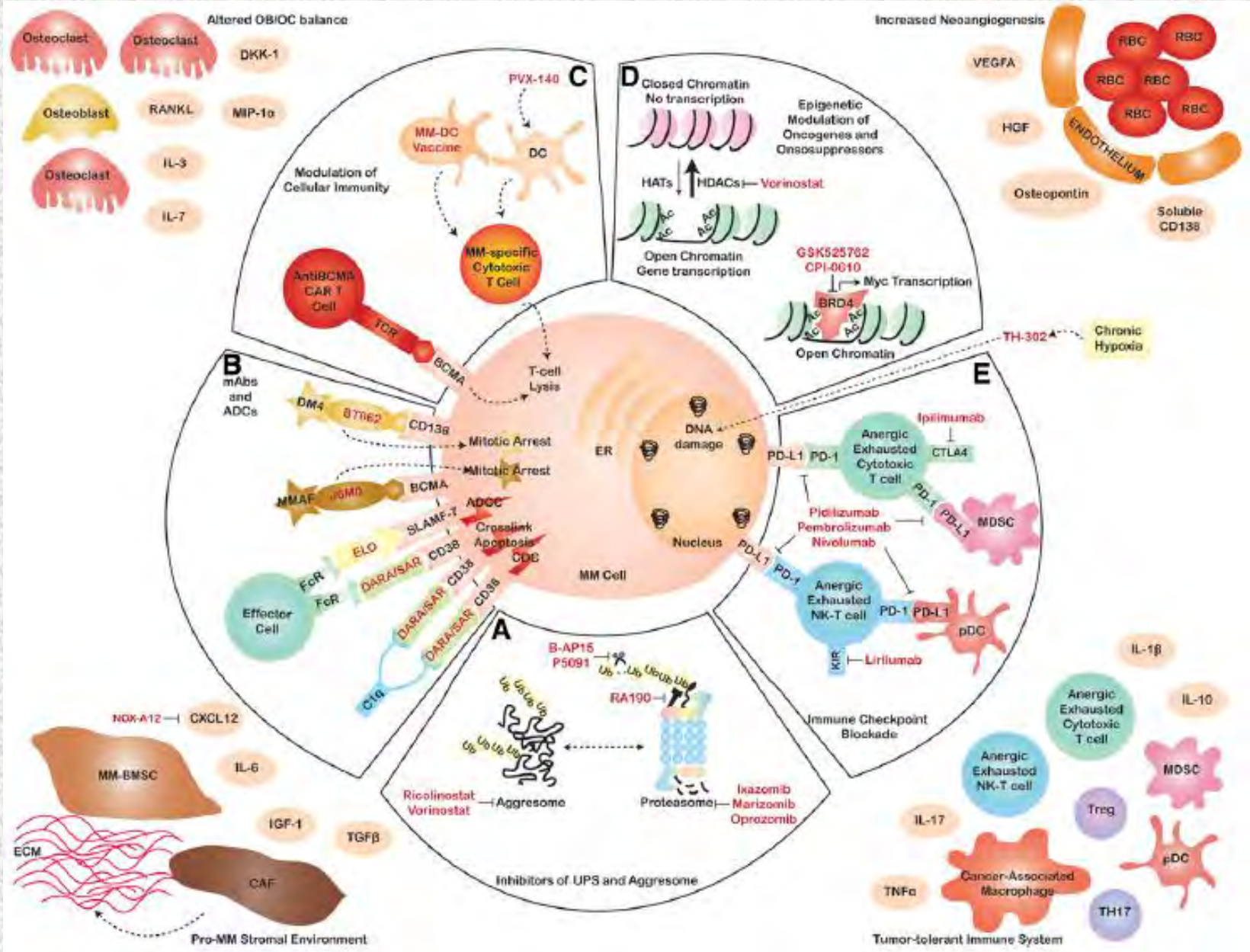
Events, n (%)	E-Ld (n=318)		
	Grade 1/2	Grade 3	Grade 4/5
Infusion reaction	**29 (9)**	**4 (1)**	**0**
Pyrexia	10 (3)	0	0
Chills	4 (1)	0	0
Hypertension	3 (1)	1 (<1)	0

- **Infusion reactions occurred in 10% of patients**
- **70% of infusion reactions occurred with the first dose**
- **No Grade 4 or 5 infusion reactions**
- **Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)**
- **2 (1%) patients discontinued the study due to an infusion reaction**

Summary

- Elotuzumab is a novel immunostimulatory monoclonal antibody (mAb) with a dual mechanism of action elicited via natural killer cells
- In combination with Len/Dex, elotuzumab is the first immunostimulatory mAb demonstrating a significant and clinically meaningful increase in PFS and ORR in a large randomized phase 3 study in patients with RRMM with 1-3 prior lines of therapy
  - 30% reduction in risk of progression or death versus Len/Dex alone
  - Difference in PFS greater at 2 years for E-Ld versus Ld
  - Greater PFS benefit in elotuzumab group consistent across key subgroups, including elderly and high-risk patients
  - Absolute difference in ORR favored elotuzumab group
- No increase in incidence of AEs versus Len/Dex alone
- Elotuzumab, in combination with Len/Dex, represents an important new treatment option for previously treated patients with multiple myeloma

Biomarkers will be necessary to select the appropriate regimen in a given patient (molecularly target therapy)




Grazie!!