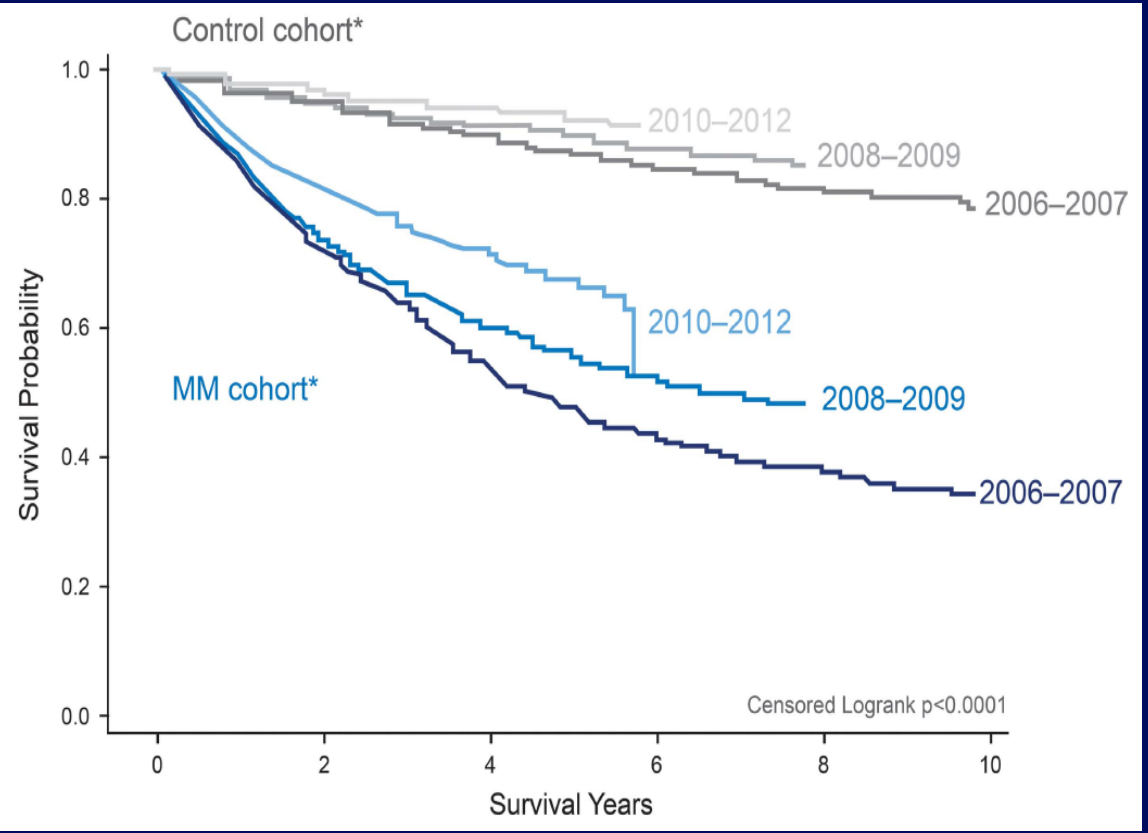
Survival estimates of matched MM patients and controls



Fonseca R, Leukemia 2017

Current IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS

- M protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma-defining events

Smoldering Myeloma

- M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥ 10% to 60%
- No myeloma-defining events

Multiple Myeloma

- Underlying plasma cell proliferative disorder
- AND 1 or more myeloma-defining events:
- ≥ 1 CRAB* feature
- Clonal plasma cells in BM ≥ 60%
- Serum free light chain ratio ≥ 100
- > 1 MRI focal lesion

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

Smoldering Myeloma: High-Risk Criteria

Mayo Clinic (n = 273)

Risk Factors, n	Patients, n (%)	Progression at 5 Yrs, %
1	81 (28)	25
2	114 (42)	51
3	78 (30)	76

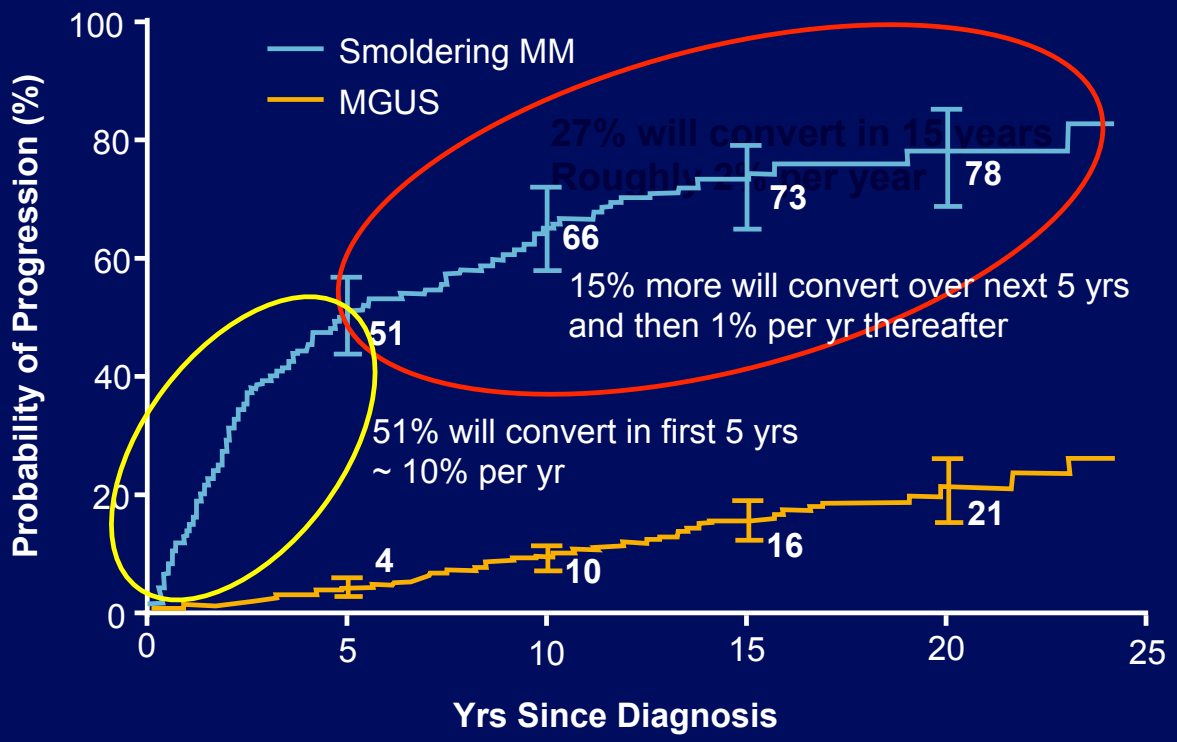
PETHEMA Study Group (n = 89)

Risk Factors, n	Patients, n (%)	Progression at 5 Yrs, %
0	28 (31)	4
1	22 (25)	46
2	39 (44)	72

- Risk Factors
  - Mayo Clinic[1]
    - BMPCs ≥ 10%
    - M-protein ≥ 3 g/dL
    - FLC ratio < 0.125 or > 8
  - PETHEMA[2]
    - ≥ 95% abnormal plasma cells
    - Immunoparesis
  - University of Salamanca[3]
    - BMPCs ≥ 10%
    - High M-protein: IgG ≥ 3 g/dL, IgA ≥ 2 g/dL, or Bence-Jones > 1 g/24 hrs

1. Dispenzieri A, et al. Blood. 2008;111:785-789. 2. Pérez-Persona E, et al. Blood. 2007;110:2586-2592.
3. Mateos MV, et al. N Engl J Med. 2013;369:438-437.

Progression to Symptomatic MM



Kyle RA, et al. N Engl J Med. 2007;356:2582-2590.

Smoldering Myeloma: How to manage

- Current recommendations: Observe or enroll in trial
  - IMWG: If no evidence of end-organ damage, continue with observation (ie, do not treat early)[1]
  - NCCN: Initially observe at 3- to 6-mo intervals or enroll in clinical trial[2]
- *Key: Carefully evaluate patients on a regular basis for evidence of evolving organ damage*
  - *Strongly consider more sensitive imaging (eg, MRI, PET) in patients with negative disease on plain film*
- Evolving data suggest benefit to treating high-risk patients

1. Kyle RA, et al. Leukemia. 2010;24:1121-1127. 2. NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.1.2014.

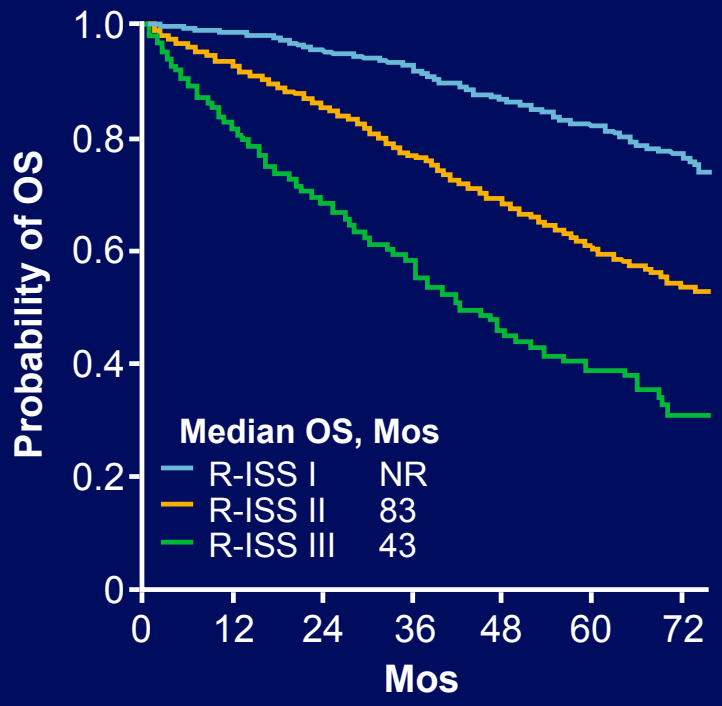
Newly Diagnosed MM: Why Risk Stratify?

- **2 important goals**
  - **Counsel:** Need to provide pt with realistic expectations of prognosis based on currently available treatments
  - **Therapy:** Choose specific therapies based on their differential effects on high-risk vs standard-risk disease

Chng WJ, et al. Leukemia. 2014;28:269-277.

Revised ISS Staging System

ISS Definition	
I	▪ Serum albumin ≥ 3.5 g/dL *AND* ▪ β_2-M < 3.5 mg/L
II	▪ Not stage I or III
III	▪ β_2-M ≥ 5.5 mg/dL
R-ISS Definition	
I	▪ ISS stage I *AND* ▪ Normal LDH ▪ No t(4;14), t(14;16), or del(17p)
II	▪ Not stage I or III
III	▪ ISS stage III *AND* ▪ Serum LDH > ULN *OR* ▪ With t(4;14), t(14;16), or del(17p)



Palumbo A, et al. J Clin Oncol. 2015;33:2863-2869.

mSMART: Classification of Active MM

High Risk	Intermediate Risk*	Standard Risk*†
▪ FISH‡ – del(17p) – t(14;16) – t(14;20) ▪ GEP – High-risk signature	▪ FISH – t(4;14)§ – 1q gain ▪ Cytogenetic del 13 or hypodiploidy ▪ High PC S-phase¶	All others including: ▪ Trisomies ▪ t(11;14)‖ ▪ t(6;14)

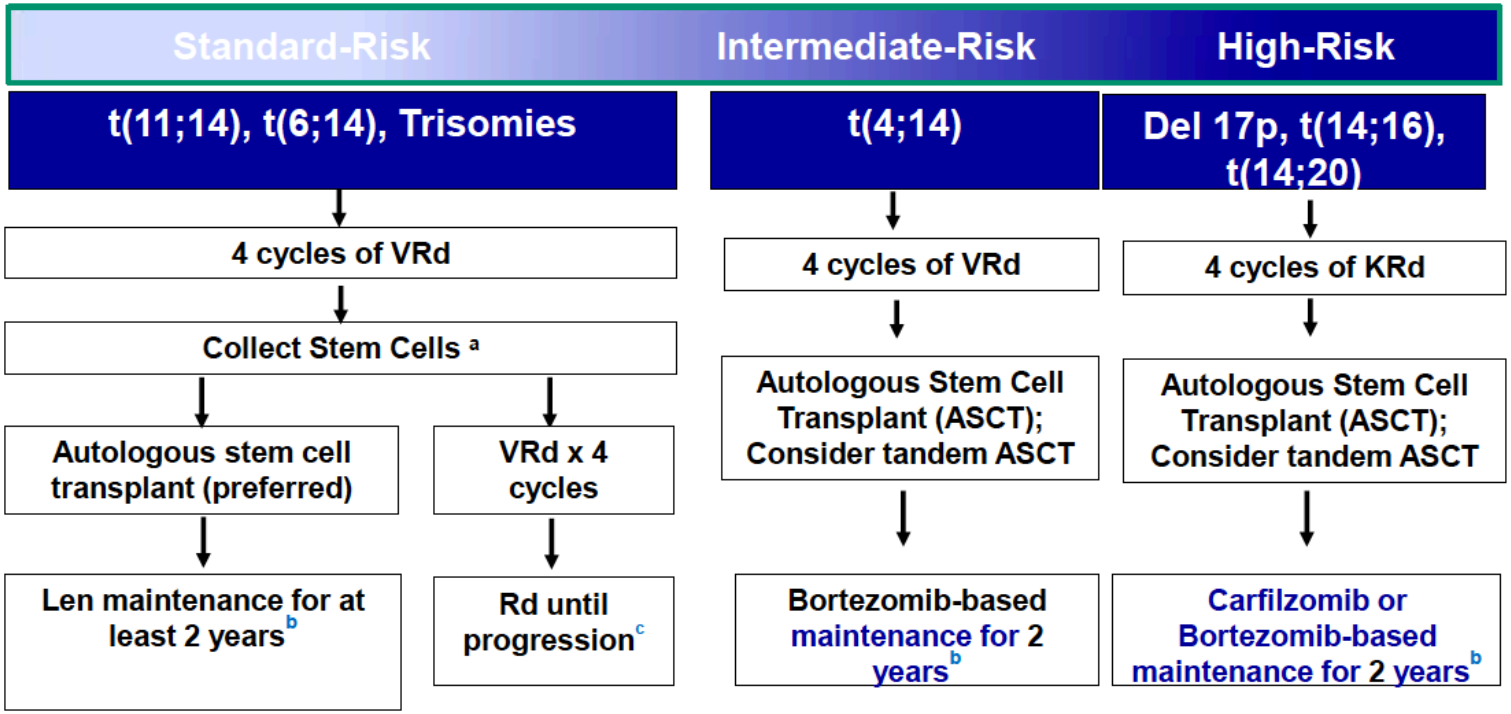
*A subset will be classified as high-risk by GEP.
†LDH > ULN and β_2-M > 5.5 mg/L may indicate worse prognosis.
‡Trisomies may ameliorate.
§Prognosis is worse when associated with high β_2-M and anemia.
‖t(11;14) may be associated with plasma cell leukemia.
¶Cutoffs vary.

Dispenzieri A, et al. Mayo Clin Proc. 2007;82:323-341. Kumar SK, et al. Mayo Clin Proc. 2009;84:1095-1110. Mikhael JR, et al. Mayo Clin Proc. 2013;88:360-376.

MAYO CLINIC

mSMART – Off-Study

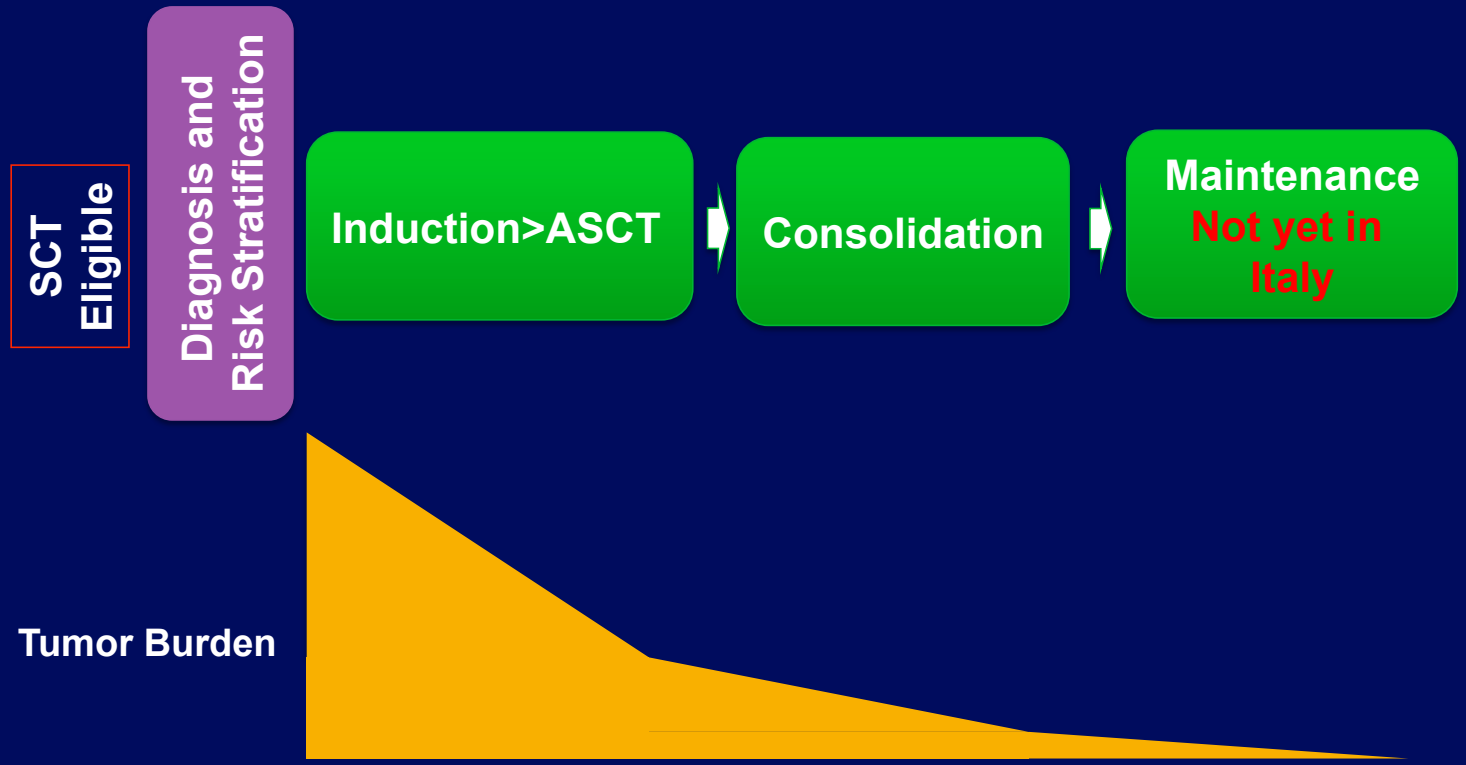
Transplant Eligible



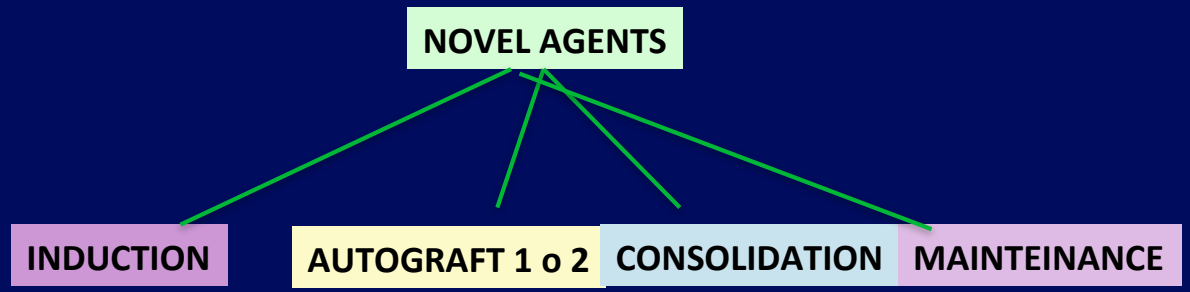
a *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*
b *Duration based on tolerance; consider risks and benefits for treatment beyond 2 years*
c *Continuing Rd for patients responding to Rd and with low toxicities*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed July 2016

Myeloma Treatment Paradigm for pts who are eligible for ASCT



New treatment paradigm for patients who are eligible for ASCT



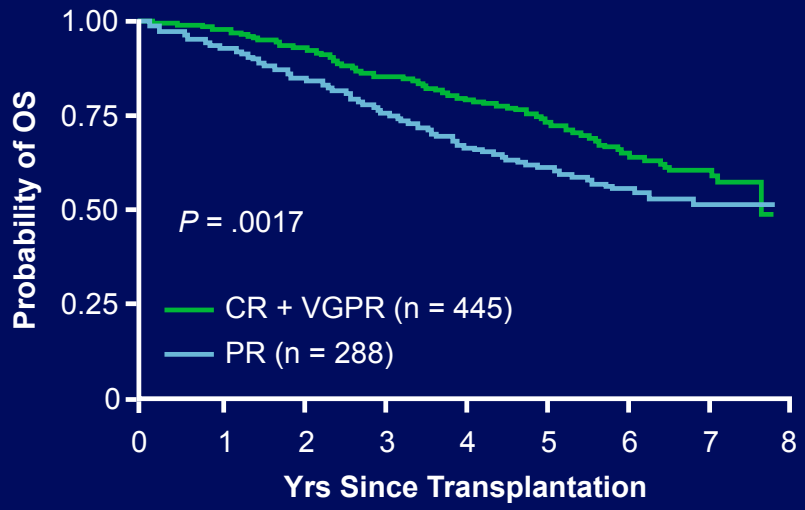
3-drugs bort-based regimens

- **Maximize the depth of response**
- **Minimize the burden of residual tumor cells**

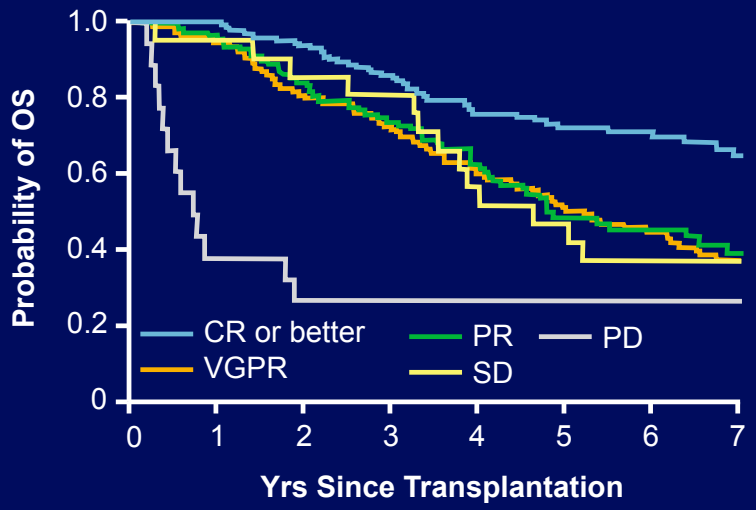
Cavo Blood 2011

Achieving ≥ VGPR or CR Should Be the Goal of Therapy

Achieving ≥ VGPR[1]



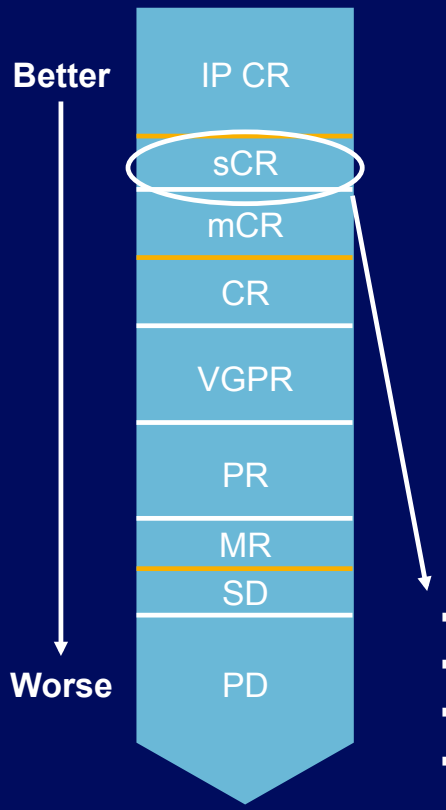
Achieving CR[2]



- Significantly better 5-yr OS in pts with sCR (80%) vs CR (53%) or nCR (47%) ($P < .001$)

1. Harousseau JL, et al. J Clin Oncol. 2009;27:5720-5726.
2. Kapoor P, et al. J Clin Oncol. 2013;31:4529-4535.

Monitoring Disease is Essential: IMWG Myeloma Response Criteria

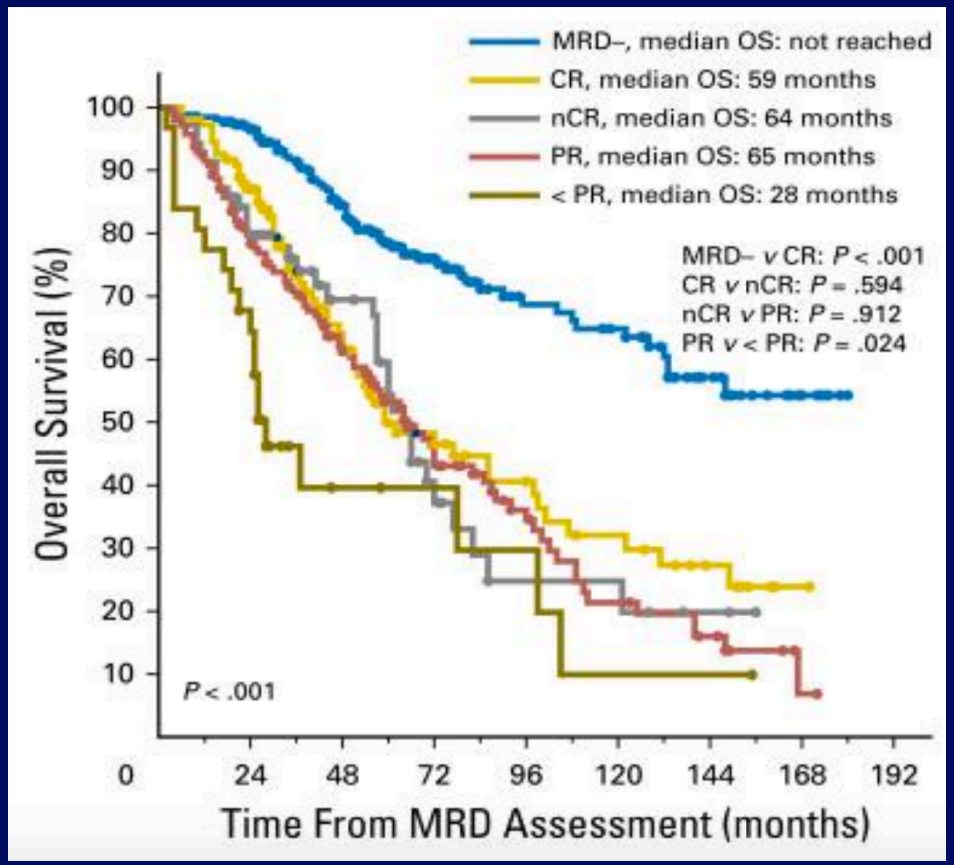


Category	Response Criteria
sCR	Normal FLC ratio; no clonal BM plasma cells
CR	Negative IFX and < 5% BM plasma cells
VGPR	Positive IFX and negative SPEP; ≥ 90% urine protein decrease; urine M-protein level < 100 mg/24 hrs
PR	≥ 50% decrease serum M-protein and ≥ 90% decrease in 24-hr urinary M-protein
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease

- **IP CR: sCR AND BM negative by next gen flow (10^{-6})**
- **sCR: CR AND normal FLC ratio, BM negative by flow, 2 measures**
- **mCR: CR AND negative PCR (10^{-5})**
- **CR: negative IFX; < 5% PC in BM; 2 measures**

Palumbo A, et al. J Clin Oncol. 2014;32:587-600.
Durie BM, et al. Leukemia. 2006;20:1467-1473.

Depth of Response and Survival: MRD Surpasses CR



Lahuerta, JCO 2017

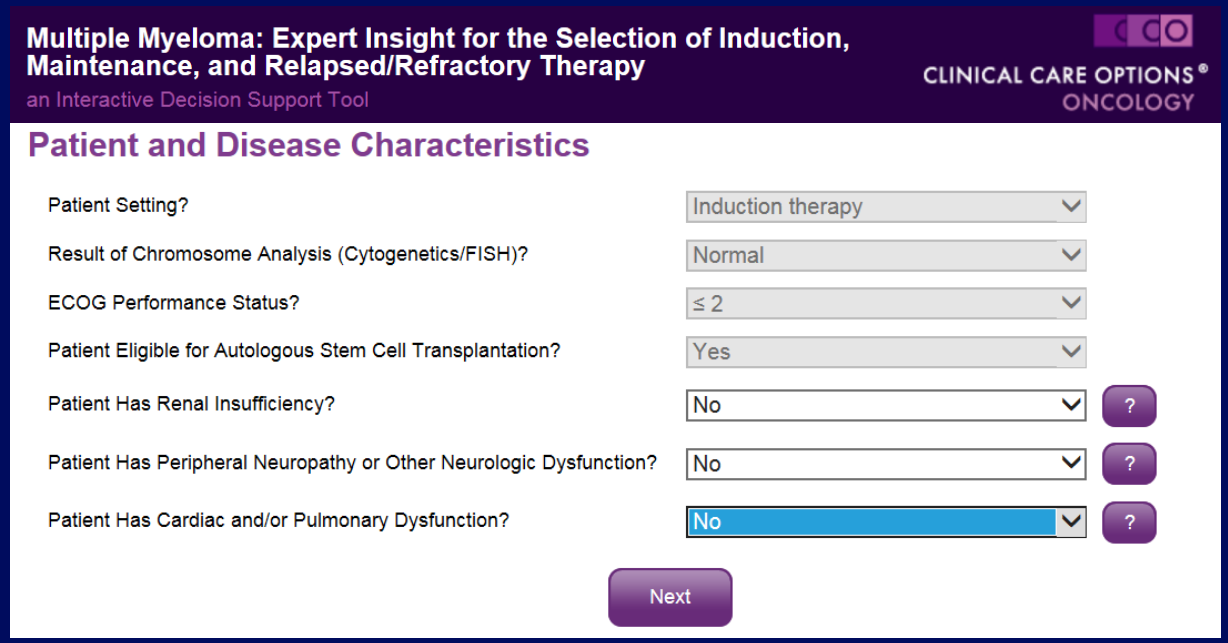
Induction and Maintenance Therapy for Transplantation-Eligible Pts With MM

	NCCN Preferred Regimens	Other NCCN Regimens
Initial therapy (induction) for transplantation-eligible pts (response assessment after cycle 2)	**Category 1** ▪Bort/dox/dex ▪Rd ▪RVd ▪VD ▪VTD **Category 2A** ▪CyBorD	**Category 2A** ▪IRd ▪KRd **Category 2B** ▪Dexamethasone ▪Liposomal dox/vin/dex ▪Thal/dex
Maintenance therapy	**Category 1** ▪Lenalidomide ▪Thalidomide **Category 2A** ▪Bortezomib	**Category 2B** ▪VP ▪VT ▪Interferon ▪Steroids ▪Thal + pred

NCCN. Clinical practice guidelines in oncology: multiple myeloma. v. 3.2016.

Online Treatment Decision Aid for MM

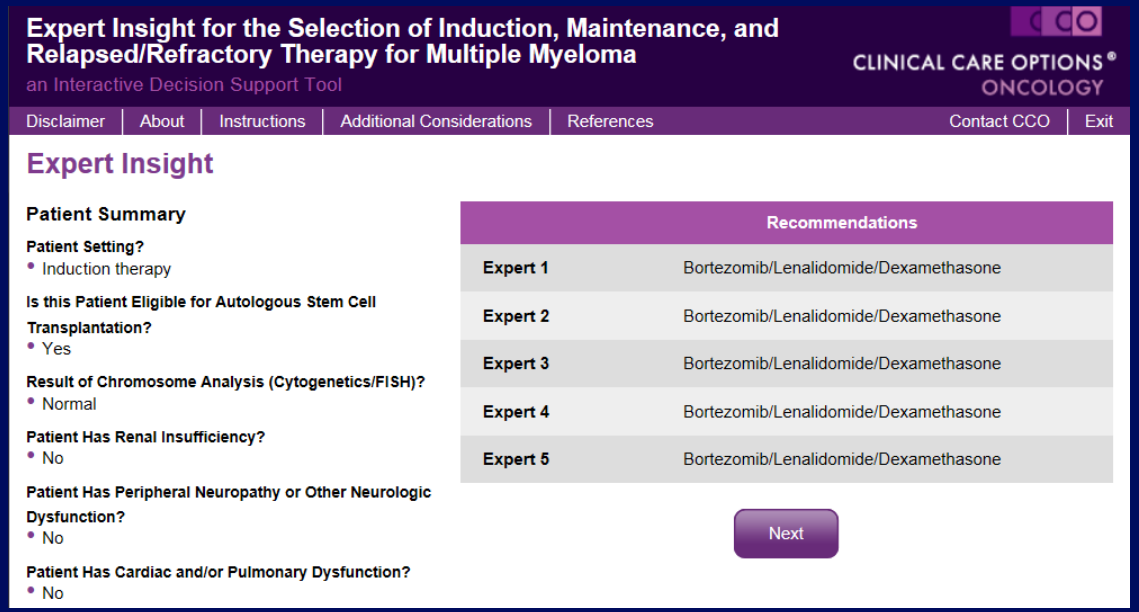
- Developed by 5 MM experts based on key factors to guide therapy
- Users enter specific pt characteristics using dropdown menus



Available at: clinicaloptions.com/MyelomaTool

Case Entry Example: Expert Recommendations

- A 64-yr-old man diagnosed with MM; FISH testing revealed t(11;14) and monosomy 13; ECOG PS 0

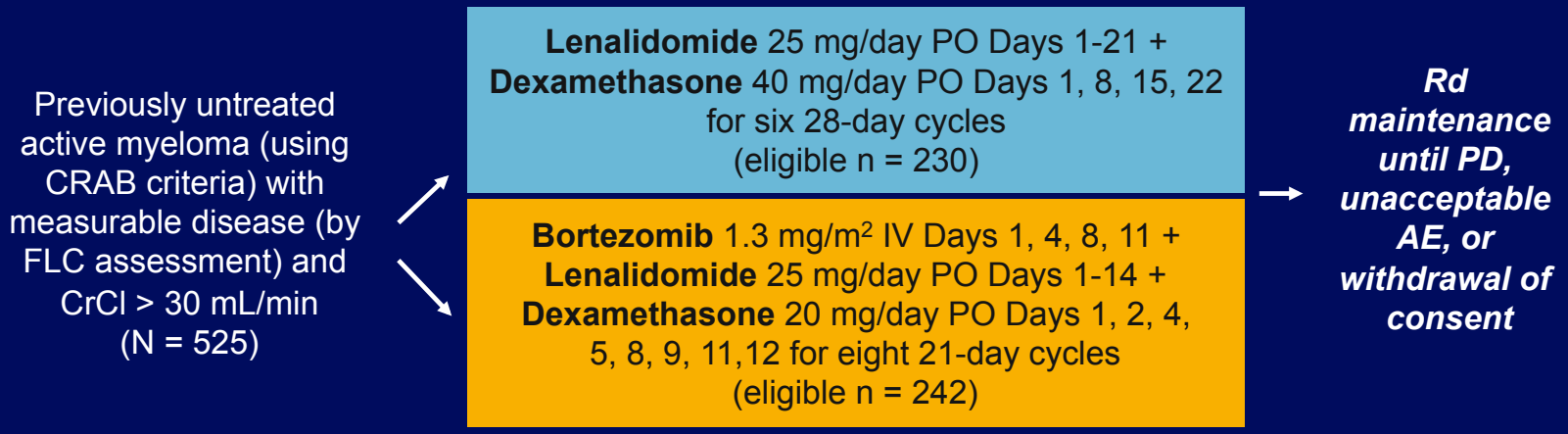


Note: Pt preference and context should always be considered in final treatment decisions

Available at: clinicaloptions.com/MyelomaTool

SWOG S0777: Study Design

- Randomized phase III trial of VRd vs Rd

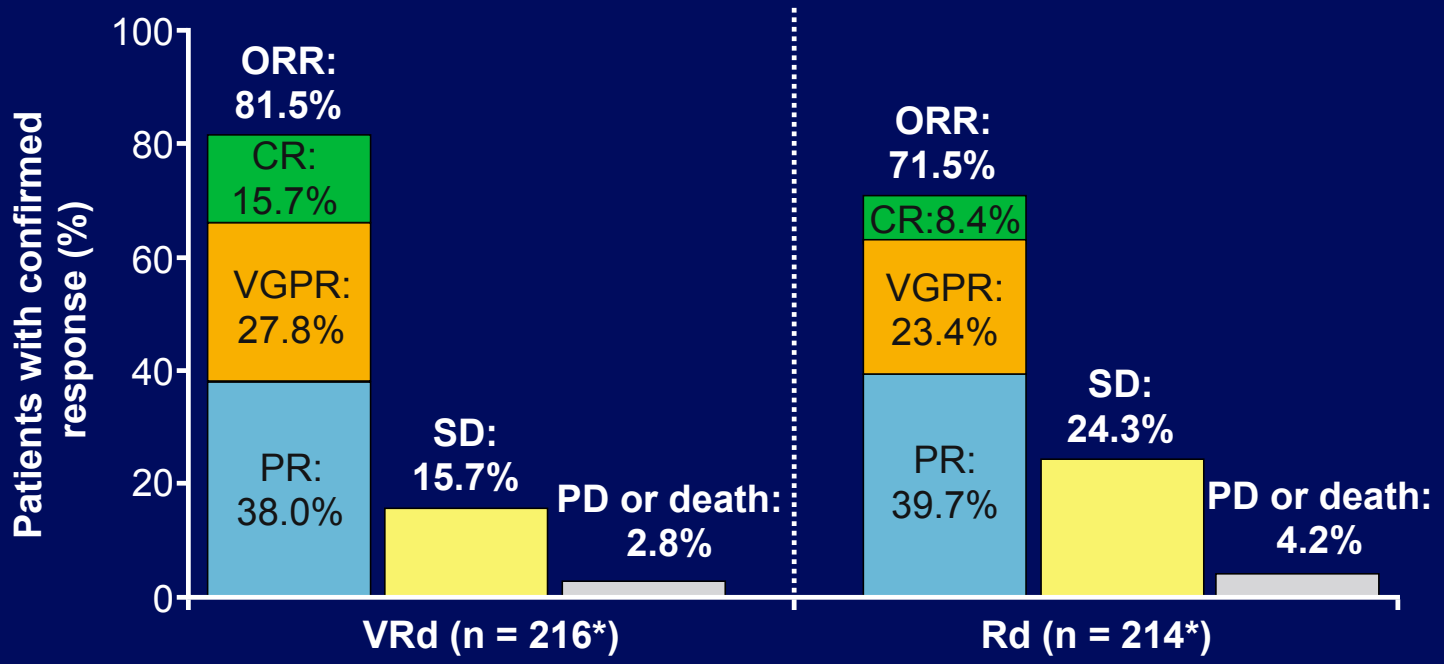


All pts received aspirin 325 mg/day; pts in bortezomib arm received HSV prophylaxis.

- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, safety

Durie BG, et al. Lancet. 2017;389:519-527.

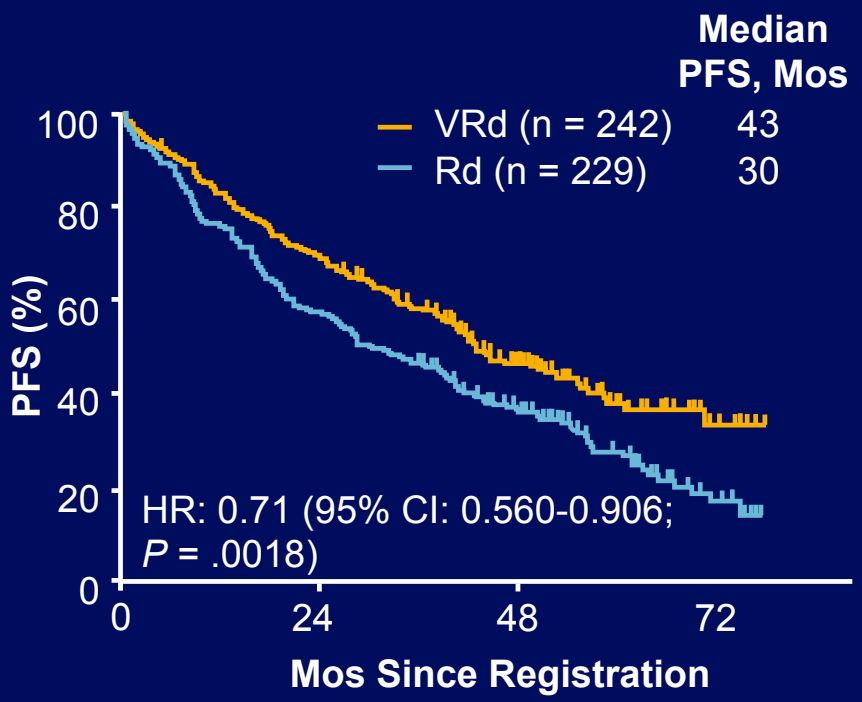
SWOG S0777: Confirmed Response

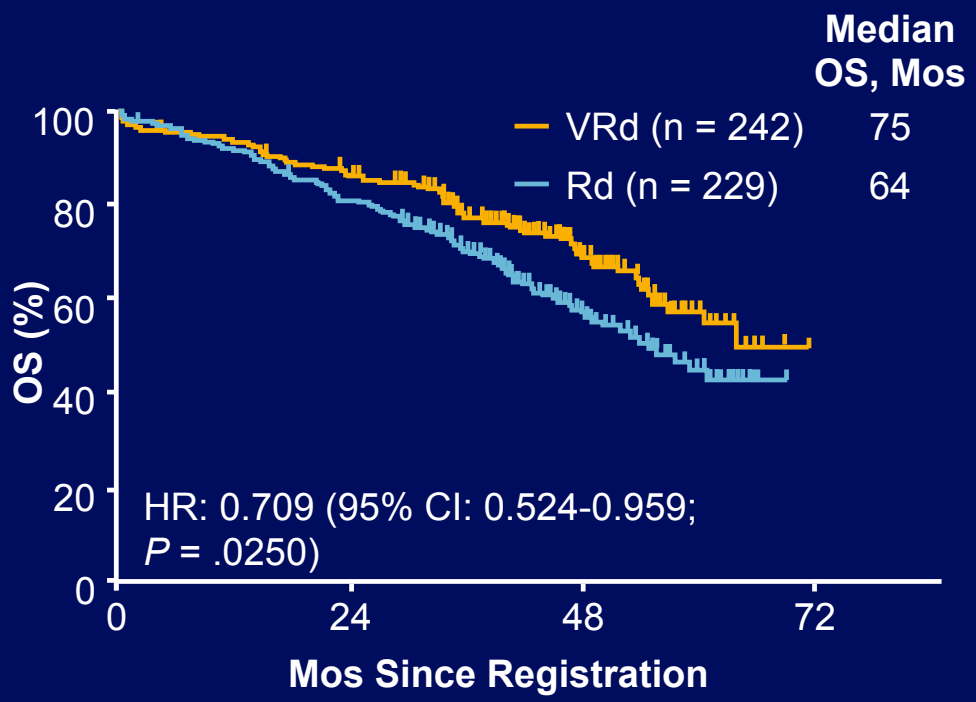


*Assessable.

Durie B, et al. ASH 2015. Abstract 25.

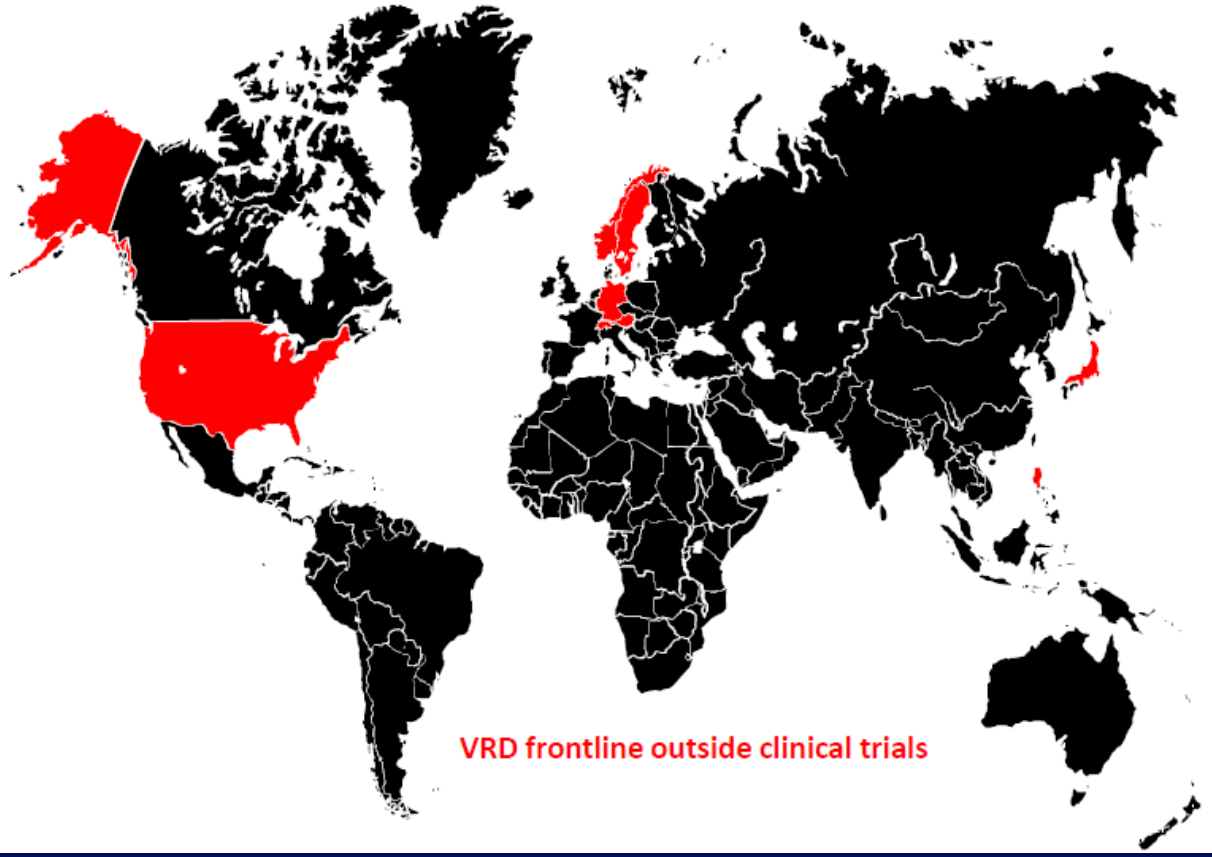
SWOG S0777: PFS, OS





Durie B, et al. Lancet. 2017;389:519-527.

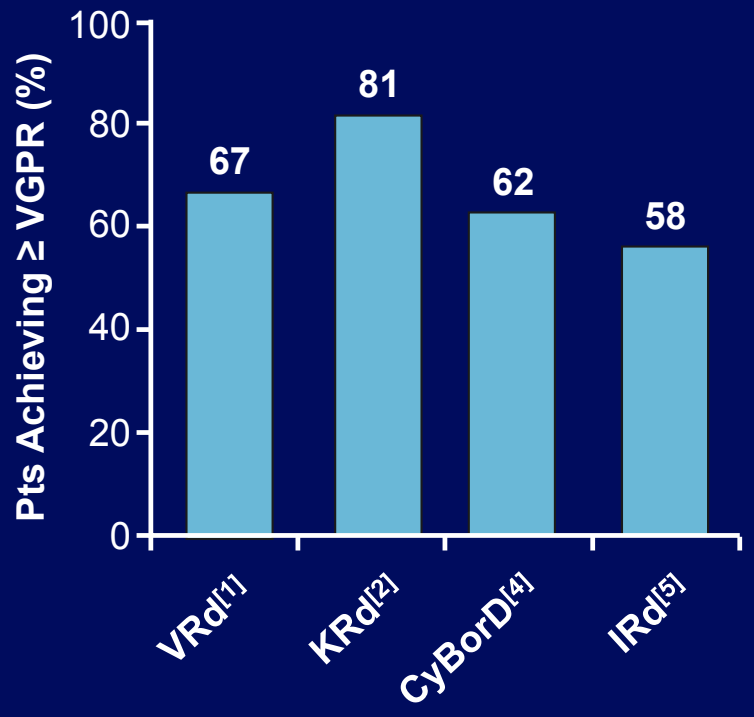
Availability of Novel Combinations



Earlier Phase Studies: Induction Regimens for Transplantation-Eligible Pts

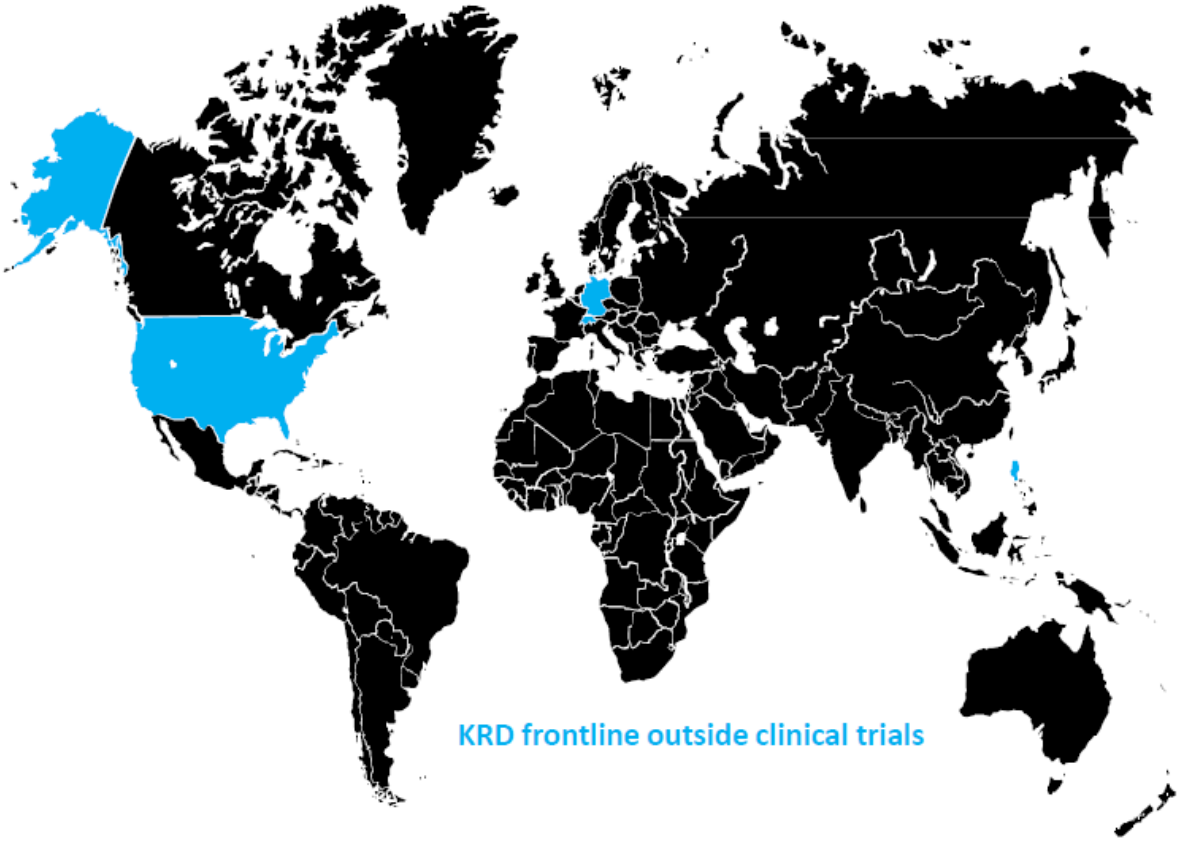
Regimen	Median Total Cycles, n	Survival, %
VRd[1]	10*	18-mo PFS: 75 18-mo OS: 97
KRd[2,3]	12	12-mo PFS: 97 2-yr PFS: 92 3-yr PFS: 79 3-yr OS: 96
CyBorD[4]	4†	5-yr PFS: 42 5-yr OS: 70
IRd[5]	7	12-mo PFS: 88 12-mo OS: 94

*Induction and maintenance; any drug
†Median NR; response after 4 cycles was primary study goal.



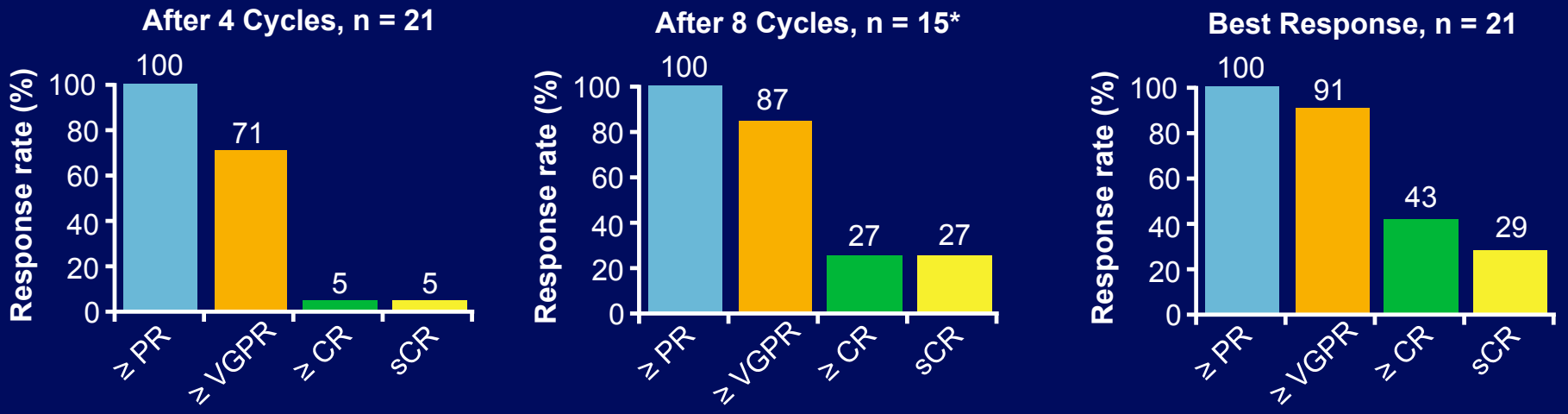
1. Richardson PG, et al. Blood. 2010;116:679-686. 2. Jakubowiak AJ, et al. Blood. 2012;120:1801-1809. 3. Jasielec J, et al. ASH 2013. Abstract 3220. 4. Reeder CB, et al. Br J Haematol. 2014;167: 563-565. 5. Kumar SK, et al. Lancet Oncol. 2014;15:1503-1512.

Availability of Novel Combinations



Daratumumab + KRd in Newly Diagnosed MM: Response

- Median number of treatment cycles: 11.5 (range: 1.0-13.0)



Depth of response improved with duration of treatment

*5 pts who proceeded to ASCT before cycle 8 and 1 pt who discontinued due to PD at cycle 7 were excluded.

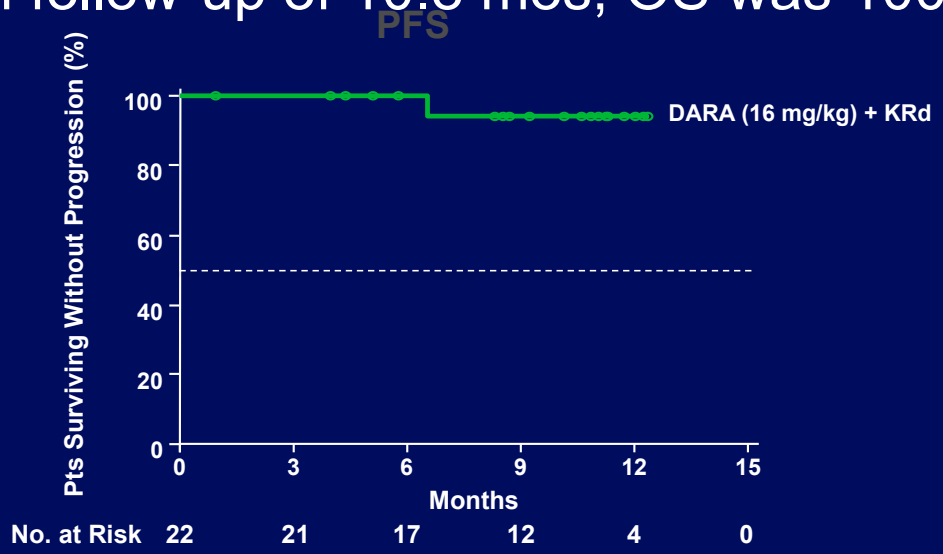
- Median follow-up: 10.8 mos (range: 4.0-12.5)
- OS: 100% at follow-up

Jakubowiak AJ, et al. ASCO 2017. Abstract 8000.

MMY1001: Phase 1b study of Dara + KRd

PFS and os

- 12-month PFS rate was 94%[a]
- With a median follow-up of 10.8 mos, OS was 100%



[a] Kaplan-Meier estimate.

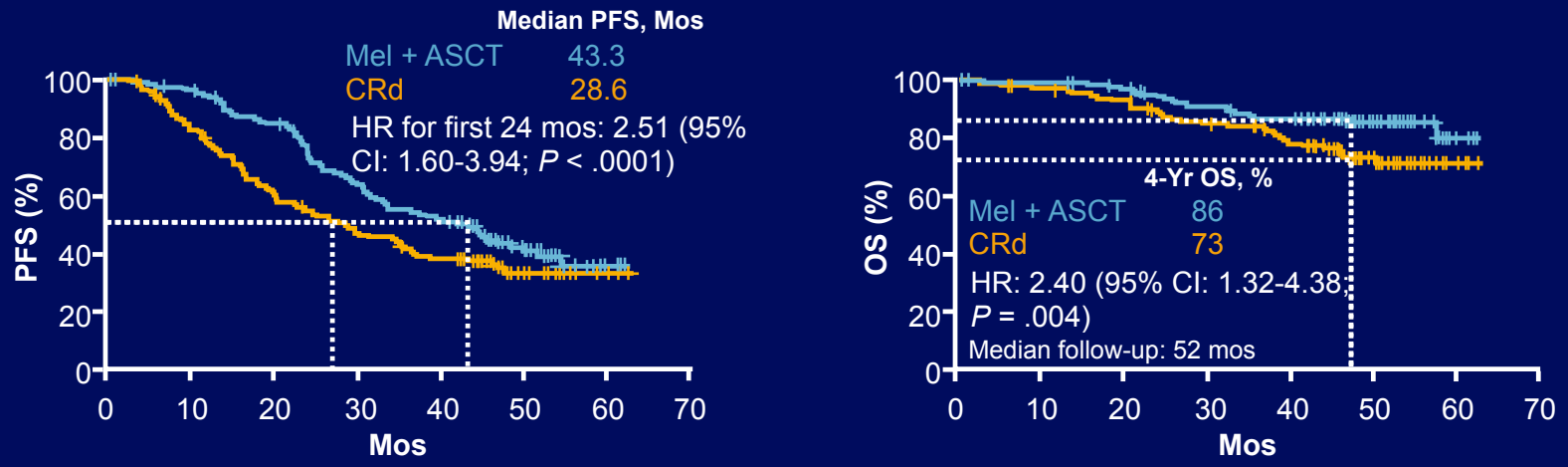
DARA, daratumumab; KRd, carfilzomib, lenalidomide, and dexamethasone; OS, overall survival; PFS, progression-free survival; pt, patient.

Jakubowiak AJ, et al. Daratumumab in Combination With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma (MMY1001): An Open-Label, Phase 1b Study. *ASCO 2017, abstract #8000.*

Autologous Stem Cell Transplantation

Phase III Trial: Rd Induction and Mel + ASCT vs Cyclophosphamide + Rd Consolidation

- Randomized, controlled phase III trial comparing high-dose mel + ASCT (n = 127) vs CRd (n = 129) consolidation in newly diagnosed MM



- Increased grade 3/4 AEs with mel + ASCT vs CRd, but similar serious hematologic (0% vs 2%) and nonhematologic (7% vs 10%) AEs

Gay F, et al. Lancet Oncol. 2015;16:1617-1629.

Phase III IFM/DFCI 2009: Frontline VRd ± ASCT in Younger Pts With MM

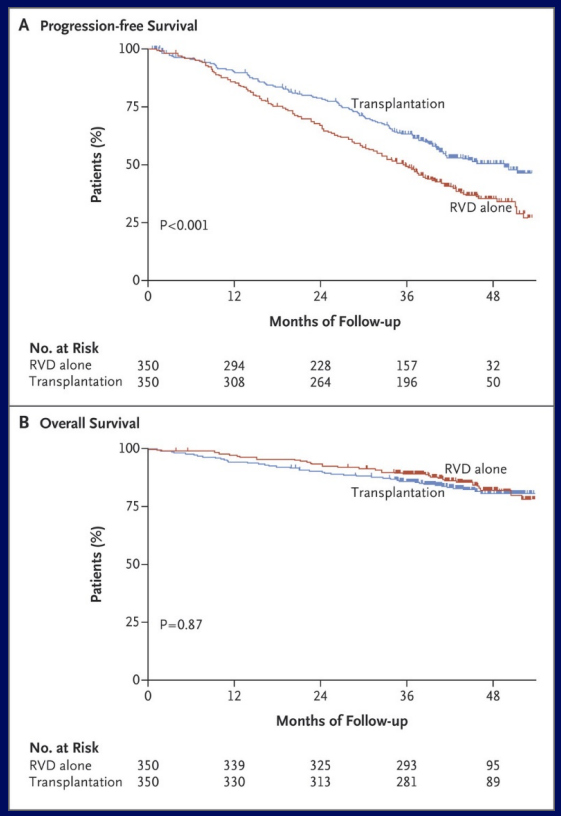
- Previously untreated pts ≤ 65 yrs of age (N = 700)

Outcome	VRd + ASCT (n = 350)	VRd Only (n = 350)	HR (95% CI)	*P* Value
Median PFS, mos	50	36	0.65 (0.53-0.80)	< .001
4-yr OS, %	81	82	1.16 (0.80-1.680	.87
≥ 1 SPM, %	7	6		
ORR, %	98	97		
≥ VGPR, %	88	77		.001

- PFS benefit in ASCT arm uniform across subgroups: age (< 60 or 60-65 yrs), sex, isotype (IgG or IgA or light chain), ISS stage (I or II or III), cytogenetics (standard or high risk)

Attal M, et al. N Engl J Med. 2017;376:1311-1320.

Kaplan–Meier Curves for Progression-free Survival and Overall Survival.

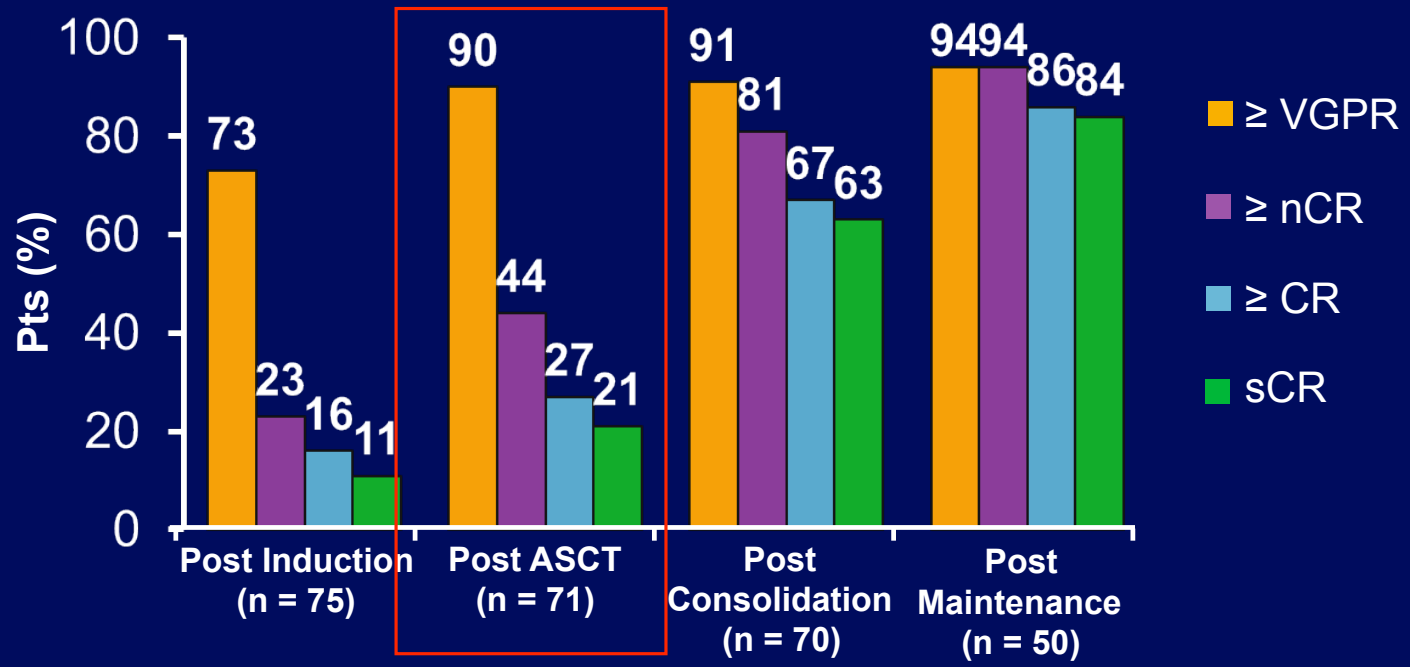


Attal M et al. N Engl J Med 2017;376:1311-1320.

The NEW ENGLAND JOURNAL of MEDICINE

Phase II MMRC Trial: Extended KRd Therapy + ASCT in Pts With Newly Diagnosed Myeloma

- 4 cycles of KRd induction + ASCT, 4 cycles of KRd consolidation, 10 cycles of KRd maintenance



Zimmerman T, et al. ASH 2016. Abstract 675.

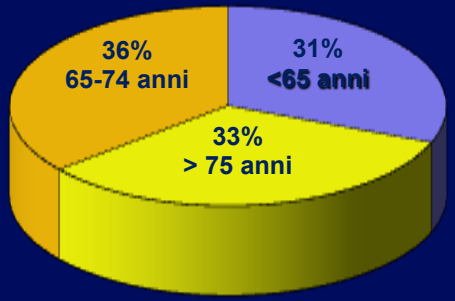
Current Considerations for Initial Treatment of MM in Younger Pts

- 3-drug induction followed by autologous transplantation[1]
- Maintenance therapy post autologous transplantation[2]
- Maximize duration of first response[3,4]
- Assessing depth of response and understanding implications for pt outcome[5]

1. Cavo M, et al. Lancet. 2010;376:2075-2085. 2. McCarthy PL, et al. Expert Rev Hematol. 2014;7:55-66. 3. Palumbo A, et al. N Engl J Med. 2011;364:1046-1060. 4. Lenhers N, et al. ASH 2013. Abstract 3183. 5. Paiva B, et al. Blood. 2012;119:687-691.

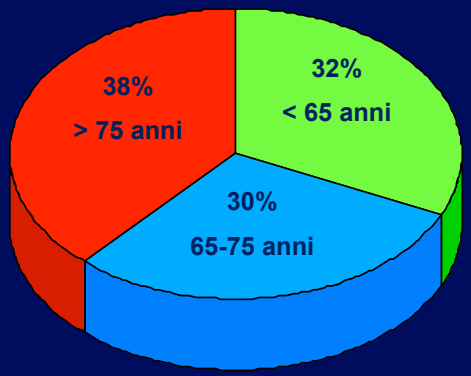
MM: Epidemiologia

INCIDENZA: 8.9/100.000



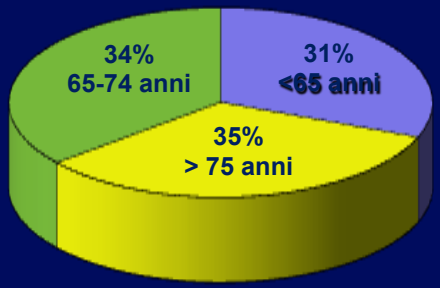
Regione Piemonte 2006

INCIDENZA: 7.3/100.000



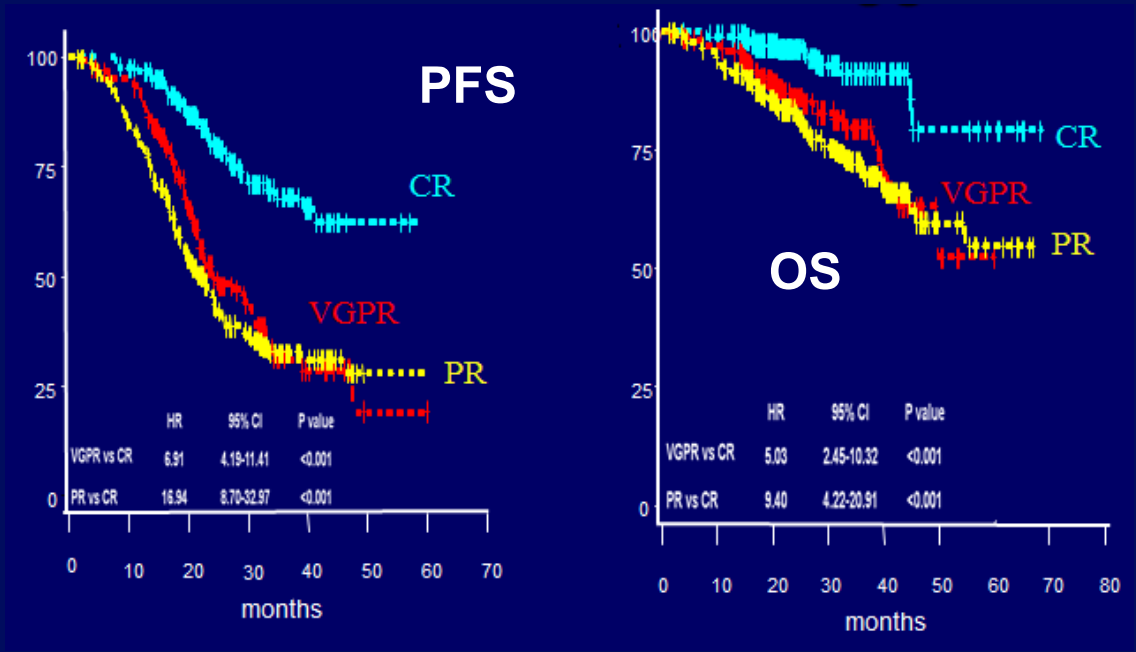
Registro Marchigiano MM 2010

INCIDENZA (nord-centro-sud: 6.1-5-4.3/100.000



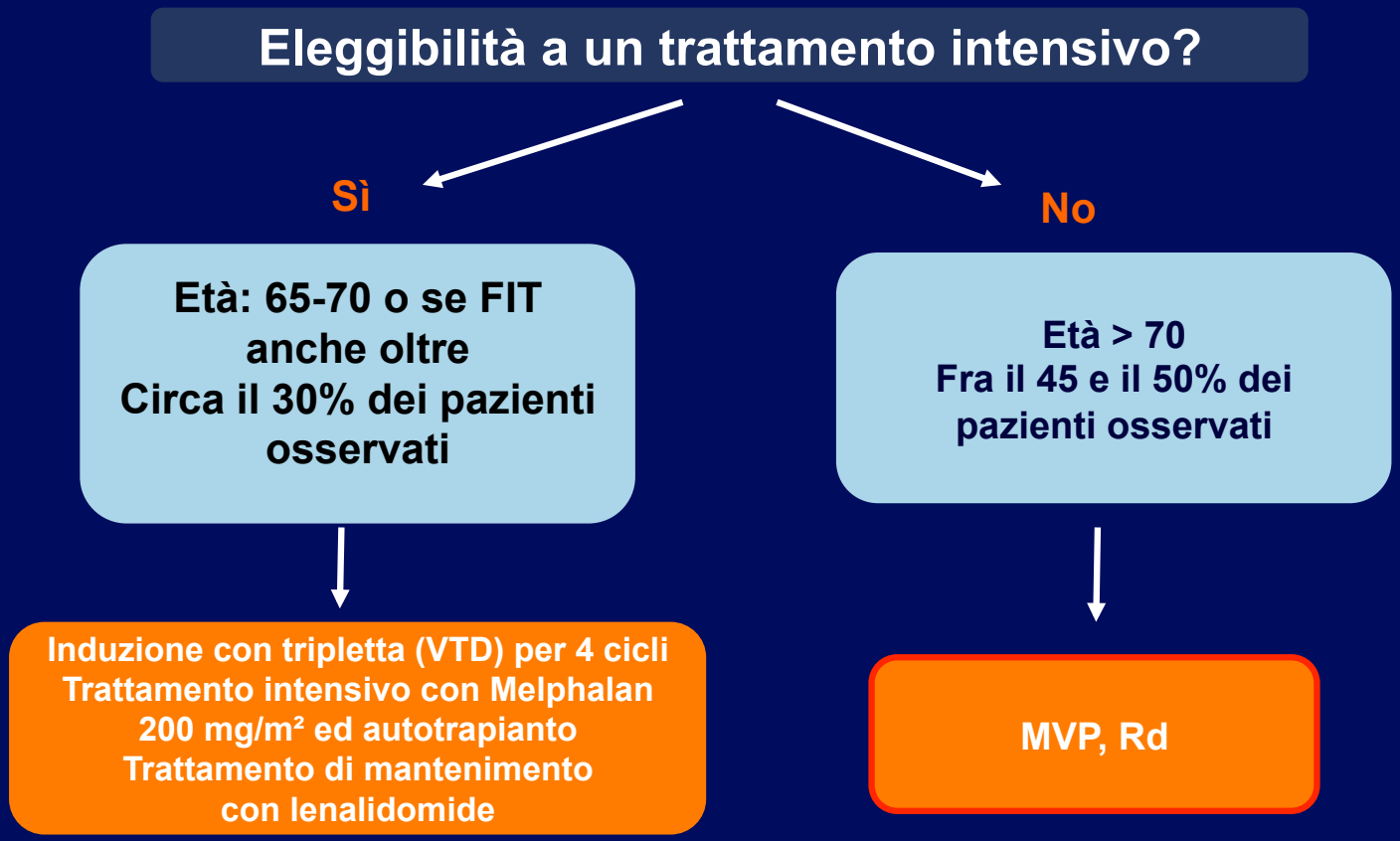
Impact of CR in elderly patients

CR predicts long term outcome



Gay F et al. Blood. 2011 Mar 17;117(11): 3025-31;

Trattamento del paziente > 65 anni



Disease characteristics

Patient's characteristics

Patient's values

TAILORED THERAPY

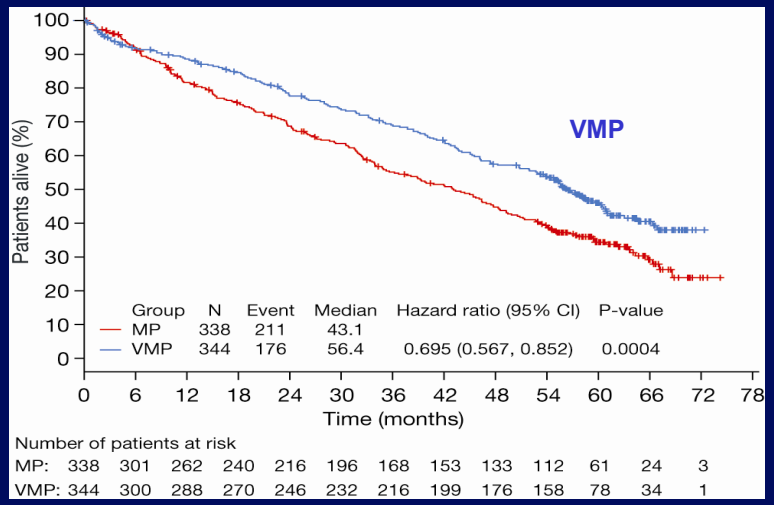
The risks in treating older patients

- **Undertreatment**: making choice based on chronological age only

- **Overtreatment**: making choice considering only response

- **Mistreatment**: making choice non evidence based and non preference based

Overall Survival VMP-MPT



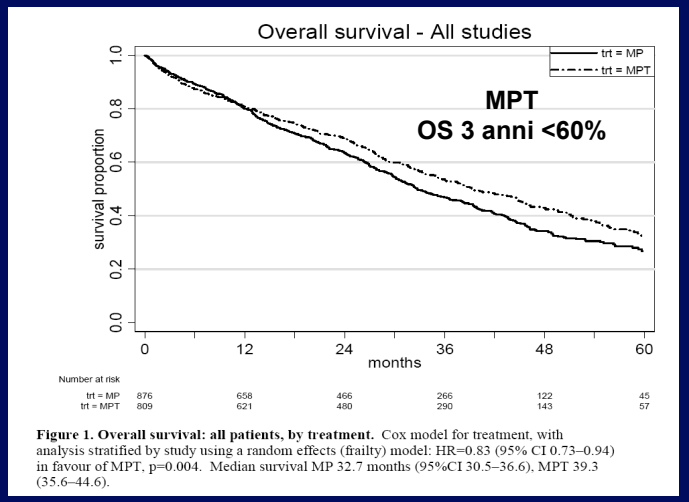


Figure 1. Overall survival: all patients, by treatment. Cox model for treatment, with analysis stratified by study using a random effects (frailty) model: HR=0.83 (95% CI 0.73–0.94) in favour of MPT, p=0.004. Median survival MP 32.7 months (95%CI 30.5–36.6), MPT 39.3 (35.6–44.6).

OS mediana	
VMP	56.4 m
MP	43.1 m

OS mediana	
MPT	39.3 m
MP	32.7 m

VMP vs MP: 13.3 mesi
di beneficio clinico
31% riduzione del rischio di morte

MPT vs MP: 6.6 mesi
di beneficio clinico
17% riduzione del rischio di morte

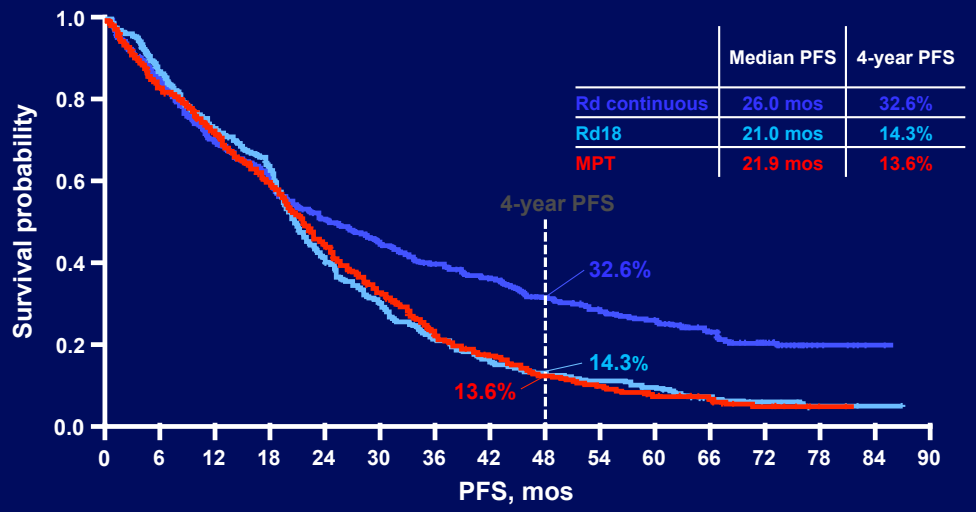
San Miguel et al. ASH 2011 (Abstract 476), oral presentation

FIRST trial: Final PFS

Median follow-up: 67 months

Updated PFS was prolonged with Rd continuous[a]

Results remain consistent nearly 3 years after the original PFS analysis



	Median PFS	4-year PFS
Rd continuous	26.0 mos	32.6%
Rd18	21.0 mos	14.3%
MPT	21.9 mos	13.6%

HR (95% CI)
Rd continuous vs. MPT:
0.69 (0.59–0.79), *P* <0.00001

HR (95% CI)
Rd continuous vs MPT:
0.69 (0.59–0.79), *P* < 0.00001

Facon T, et al. Presented at ASH 2016:abstr 241.

IMPACT OF DEPTH OF RESPONSE ON OUTCOMES

	Rd continuous in FIRST (MM-020)*[1,2]		VMP in VISTA*[1,2]
≥VGPR	48.2%	≥VGPR	41%
DoR	≥VGPR patients: **49.0 months** CR: **59.1 months** PR: **31.5 months**	DoR	CR: **24.0 months** PR: **19.9 months**
TTNT	CR/VGPR: **69.5 months** PR: **49.1 months**	TTNT	CR: **37.8 months for VMP** PR: **25.2 months**

1. Bahlis NJ, *et al. Leukemia* 2017;Epub ahead of print; 2. Facon T, *et al.* Presented at ASH 2016 (Abstract 241).

1. San Miguel JF, *et al. N Engl J Med* 2008;359:906–17; 2. Harousseau J-L, *et al. Blood* 2010;116:3743–50.

FIRST Trial: *Response*[1]

Pts with high-quality response (ie, ≥ VGPR) as best response tended to have faster times to first response across all Tx arms

Median TTR (range), mos[a]	ALL	CR (n = 289)	≥ VGPR (n = 678)	≥ PR (n = 1223)
Rd continuous	1,8	1.0 (0.7-4.7)	1.1 (0.5-8.6)	1.8 (0.5-22.2)
Rd18	1,8	1.0 (0.8-34.8)	1.0 (0.8-34.8)	1.8 (0.8-34.8)
MPT	2,8	1.5 (1.4-9.9)	1.6 (1.3-26.8)	2.8 (1.2-49.7)
VMP (VISTA)	1,4	-	-	-

[a] Pts with response date before randomization date due to data issue were not included.
CR, complete response; MPT, melphalan, prednisone, and thalidomide; PR, partial response; pt, patient; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide and low-dose dexamethasone for 18 cycles; TTR, time to response; VGPR, very good partial response.
Bahlis NJ, et al. *Leukemia*. 2017 Apr 28

1Line Trials NoASCT - Summary

Trial	No. Cycles	Time of treatment (months)	CR	ORR	mPFS
VMP VISTA	8 bw + 5 ow	9,5	30%	70%	21.7m
VMP Gimema	9 ow	9	30%	85%	24.8m
RD	Until Progression	18,4	20%	81%	26m
RD18	18	16,6	14%	73%	21m
MPT	18	15,4	9%	62%	21.9m

La scelta dell'induzione

VMP

- Prima scelta se IR
- Prec TVP o sd trombofilica
- Terapia di durata fissa
- Maggiore possibilità di scelta alla recidiva
- Migliore aderenza al trattamento se pazienti very very old
- Citoriduzione rapida?
- Alti rischi?

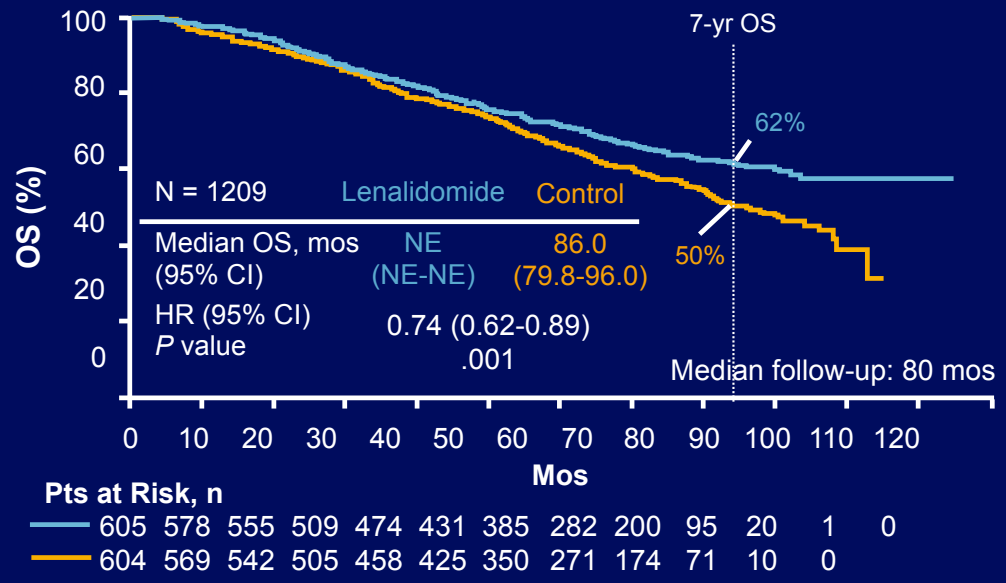
Rd

- PNP
- Logistica (caregiver)
- Terapia orale
- Terapia continuativa
- Meno recidive
- Maggiore probabilità di controllo a lungo termine in particolare nei responsivi
- Meno accessi in ospedale

Duration of Therapy in Multiple Myeloma

Meta-analysis of 3 Phase III Trials: OS With Len Maintenance After High-Dose Melphalan + ASCT

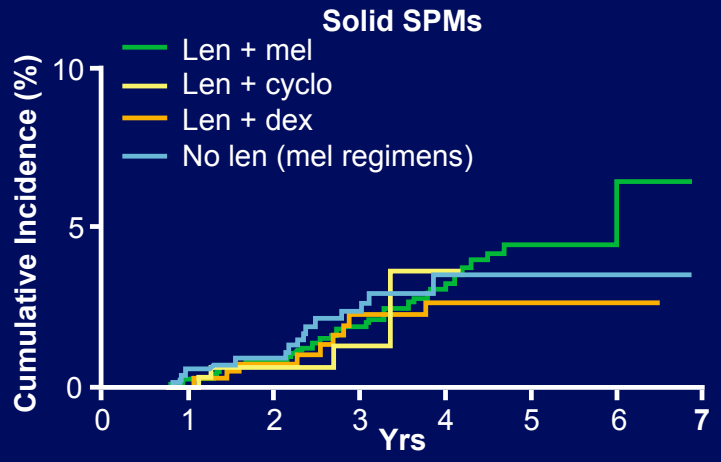
- 26% reduction in risk of death; estimated 2.5-yr increase in median OS

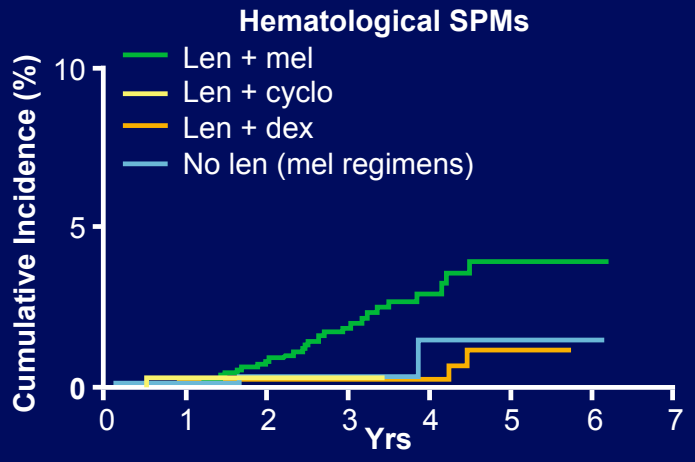


- In February 2017, FDA approved lenalidomide as maintenance therapy for patients with myeloma following ASCT

McCarthy PL, et al. J Clin Oncol. 2017 Jul 25. [Epub ahead of print]

Cumulative Incidence of Second Primary Malignancies by Treatment



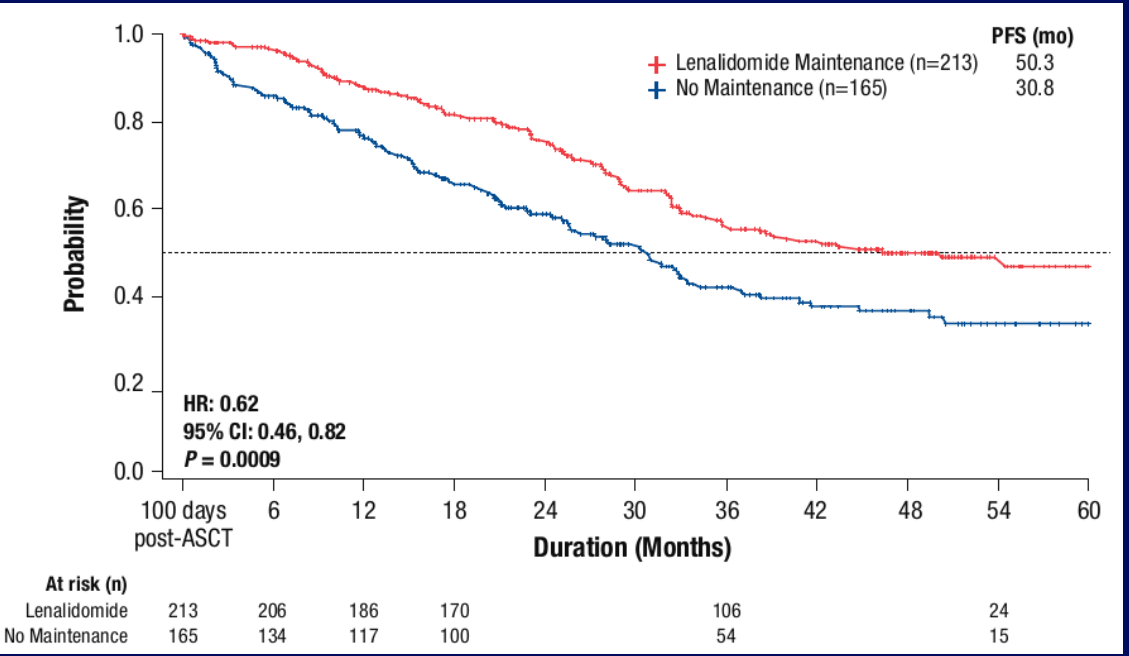


Cumulative Incidence, %	Solid SPMs		Hematologic SPMs	
	3 Yrs	5 Yrs	3 Yrs	5 Yrs
Len + mel	2.7	4.4	1.8	3.9
Len + cyclo	3.5	NE	0.3	NE
Len + dex	2.2	2.6	0.3	1.3
No len	2.9	3.4	0.4	1.4

Palumbo A, et al. Lancet Oncol. 2014;15:333-342.

Connect MM: IMPACT OF post-ASCT Maintenance Tx *PFS*

- PFS was significantly longer in patients treated with lenalidomide maintenance vs no maintenance
  - 3-year PFS rate, 56% with lenalidomide maintenance vs 42% with no maintenance
  - Median PFS in patients with lenalidomide-only maintenance (n = 188) was 54.5 months



ASCT, autologous stem cell transplant; HR, hazard ratio; MM, multiple myeloma; PFS, progression-free survival; Tx, therapy.

Jagannath S, et al. Impact of Post-Autologous Stem Cell Transplant (ASCT) Maintenance Therapy on Outcomes in Patients (Pts) With Newly Diagnosed Multiple Myeloma (NDMM) Using the Large Prospective Community-Based Connect® MM Registry. *ASCO 2017, abstract #8040.*

Maintenance in Myeloma

- PFS advantage[1-3]
- OS improvements?[2]
- Toxicities of treatment
  - Myelosuppression[3]
  - Second primary malignancies[3,4]
  - Quality of life?[5]

- **Which pts benefit from maintenance, which agent(s) to use, duration of therapy still unclear[6]**

1. Attal M, et al. ASH 2013. Abstract 406. 2. McCarthy PL, et al. N Engl J Med. 2012;366:1770-1781.
3. Attal M, et al. N Engl J Med. 2012;366:1782-1791. 4. Palumbo A, et al. Lancet Oncol. 2014;15:333-342.
5. Abonour R, et al. ASH 2016. Abstract 537. 6. Lipe B, et al. Blood Cancer J. 2016;6:e485.

Allogeneic SCT

- Graft-vs-myeloma effect
- Can potentially provide sustained disease control (ie, cure)
- High treatment-related mortality
- Morbidity from GVHD
- **No definite OS advantage vs autologous SCT**
- **Should be offered to high-risk pts in trials**

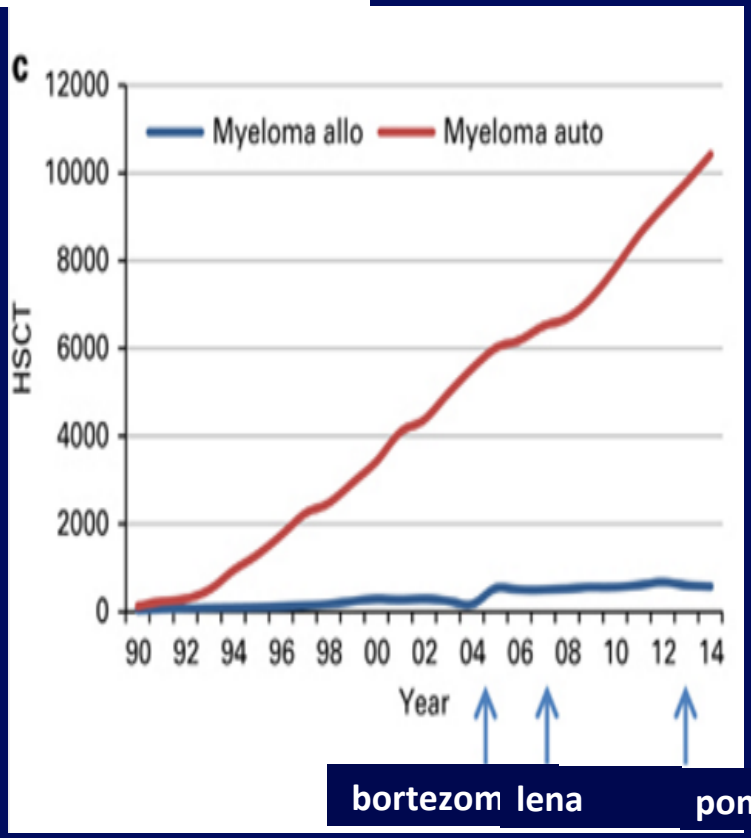
Dhakal B, et al. Bone Marrow Transplant. 2016;51:492-500.

SPECIAL REPORT

Impact of drug development on the use of stem cell transplantation: a report by the European Society for Blood and Marrow Transplantation (EBMT)

JR Passweg[1], H Baldomero[1], P Bader[2], C Bonini[3], S Cesaro[4], P Dreger[5], RF Duarte[6], C Dufour[7], J Kuball[8], D Farge-Bancel[9], A Gennery[10], N Kröger[11], F Lanza[12], A Nagler[13], A Sureda[14] and M Mohty[15] for the European Society for Blood and Marrow Transplantation (EBMT)

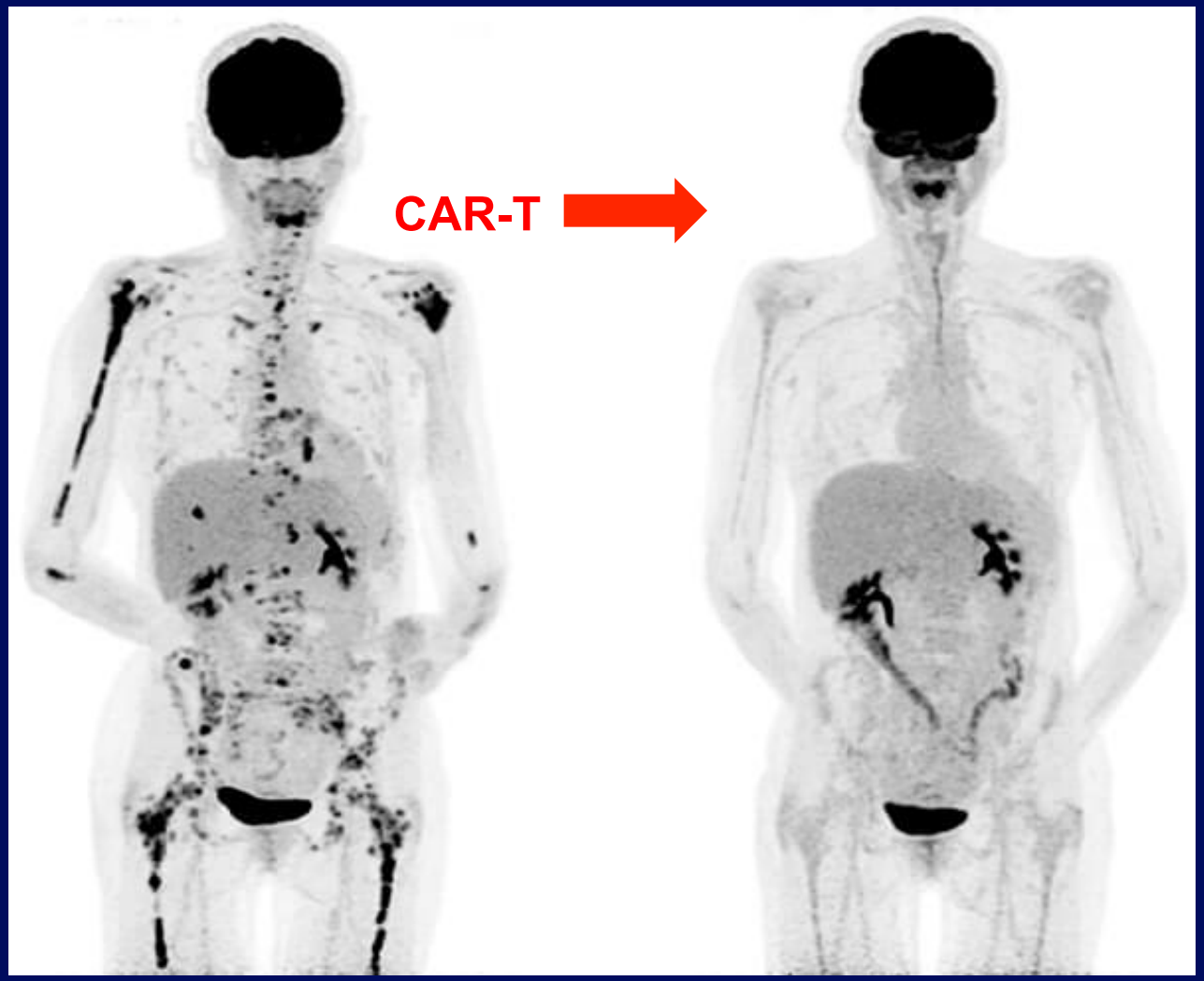
Bone Marrow Transplantation (2016), 1–6



CAR-BCMA T Cells in Myeloma: Response

Pt	Myeloma Type	CAR-BCMA dose (T cells/kg)	Response	Response Duration, weeks
1	κ light chain only	0.3×10^6	PR	2
2	IgA λ	0.3×10^6	SD	6
3	κ light chain only	0.3×10^6	SD	6
4	κ light chain only	1×10^6	SD	12
5	IgG κ	1×10^6	SD	4
6	IgG λ	1×10^6	SD	2
7	IgG λ	3×10^6	SD	7
8	κ light chain only	3×10^6	VGPR	8
9	κ light chain only	3×10^6	SD	16
10	IgA λ	9×10^6	sCR	12+
11	IgG λ	9×10^6	PR	6+
12	IgA λ	3×10^6	SD	2

Ali SA, et al. ASH 2015. Abstract LBA-1.


CAR-T

Conclusions: Myeloma Treatment

- In general, deeper responses translate to longer response duration
- Treat to maximum response, balancing toxicity
- Duration of therapy not clear, but “drug holidays” help with toxicity, quality of life

Future of Myeloma Therapy

- New drugs with different mechanisms of action
- Heterogeneous disease: have to match the mechanism with the biologic abnormality
- Combination regimens may provide possible cure
  - For example, agent generally effective against myeloma with targeted agent for specific subtype
- Effective combinations have to move to upfront setting
- Early intervention may be the key for cure