Updates on the Treatments of Multiple Myeloma and Light-Chain Amyloidosis

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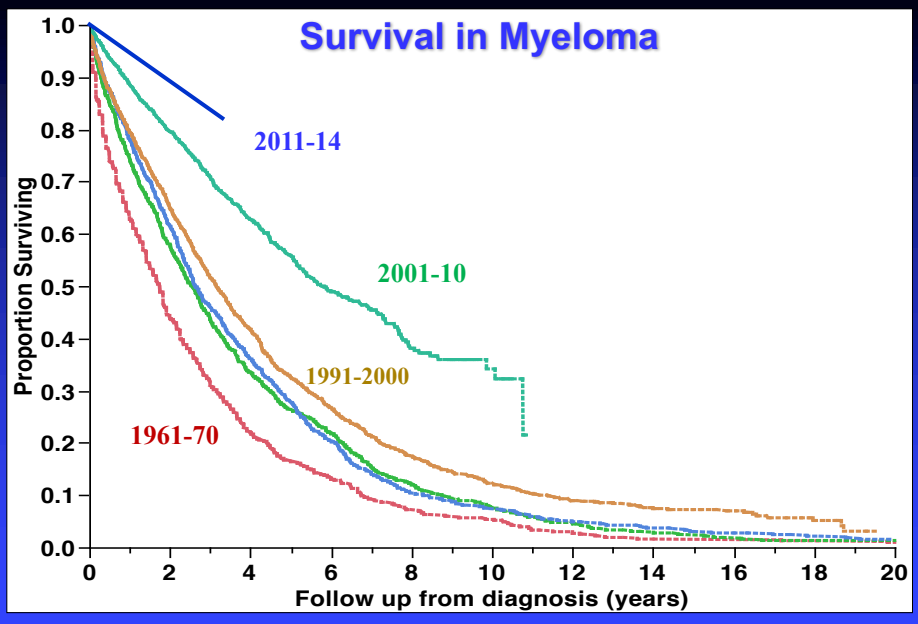


Kumar S. Blood 2008;111: 2516 – 2520; Kumar S. Leukemia (2014) 28, 1122–1128.

Updated 2014 IMWG Criteria for Diagnosis of Multiple Myeloma

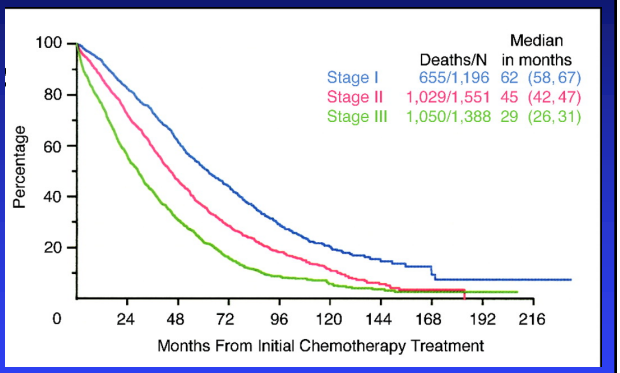
MGUS	Smoldering Myeloma	Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma defining events	▪ Underlying plasma cell proliferative disorder ▪ 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.

International Staging System (ISS)

- Stage I (OS 62 months)
  - B2M < 3.5 mg/L AND
  - Albumin ≥ 3.5
- Stage II (45 months)
  - Not stage I or III
- Stage III (29 months)
  - B2M > 5.5
- 10,000+ patients treated 1981-2002



Greipp et al. J Clin Oncol 2005, 23:3412-3420.

Beyond ISS: Cytogenetics and FISH

- Standard risk
  - normal cytogenetics
  - hyperdiploidy
  - t(11;14)
  - t(6;14)
- Poor risk
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - 1q21 amplification

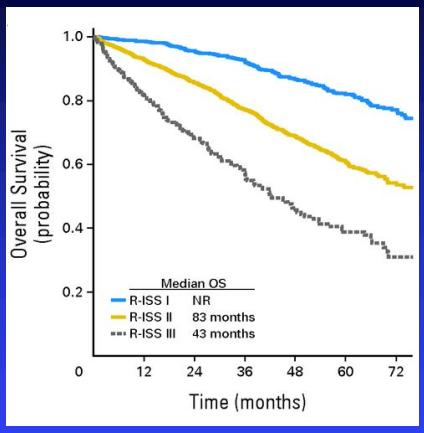
Revised ISS Criteria

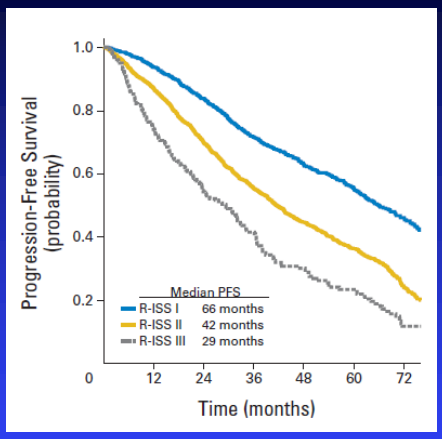
Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and (either high-risk CA by iFISH or high LDH)

Palumbo et al., JCO 2015

Revised ISS Risk Stratification



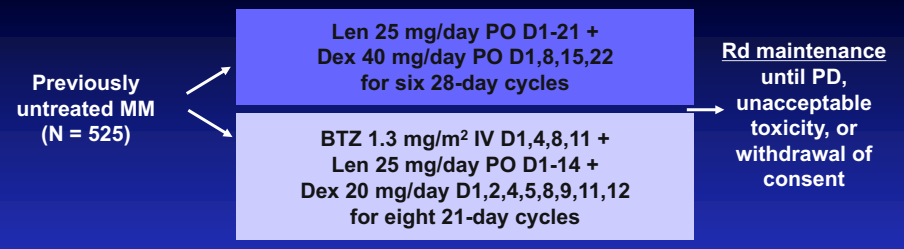


Patients with R-ISS stage I, II, and III had 5-year OS rates of 82%, 62%, and 40%, respectively.

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

Induction Chemotherapy

SWOG S0777: Phase III trial of VRd vs Rd



Survival, Mos	VRd (n = 242)	Rd (n = 229)	HR	*P* Value
Median PFS	43	30	0.712 (0.560 - 0.906)	.0018*
Median OS	75	64	0.709 (0.516 - 0.973)	.025†

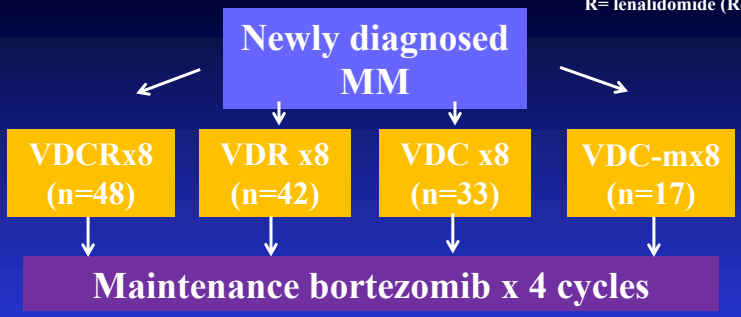
*1-sided *P* value. †2-sided *P* value.

ORR 82% in VRd group v 72% in Rd group; more neuropathy with VRd
PFS and OS increase remained significant when age-adjusted in multivariate analysis

Durie B, et al. Lancet 2017 Feb 4;389(10068):519-527

EVOLUTION Study

V= bortezomib (Velcade)
D= Dexamethasone
C= Cyclophosphamide
R= lenalidomide (Revlimid)



	CR (%)	≥ VGPR (%)	ORR (%)
VDCR	25	58	88
VDR	24	51	85
VDC	22	41	75
VDC-mod	47	53	100

- More hematologic toxicity in VDCR arm
- Similar outcomes but perhaps real comparison should be between VDR vs VDC-mod

Kumar et al, Blood 2012 119:4375-4382

IFM 2013-04 Trial: VCD vs VTD

Table 2. Response to induction

	VTD (n = 169)	VCD (n = 169)	*P* value
Intent to treat			
≥CR	13.0%	8.9%	.22
≥VGPR	66.3%	56.2%	.05
≥PR	92.3%	83.4%	.01
Per protocol	n = 157	n = 154	
≥CR	14.0%	9.1%	.17
≥VGPR	70.7%	60.4%	.05
≥PR	98.7%	90.3%	.001

Primary endpoint:
>=VGPR after 4 cycles induction: 66.3% VTD arm v 56.2% in the VCD arm (P = .05).

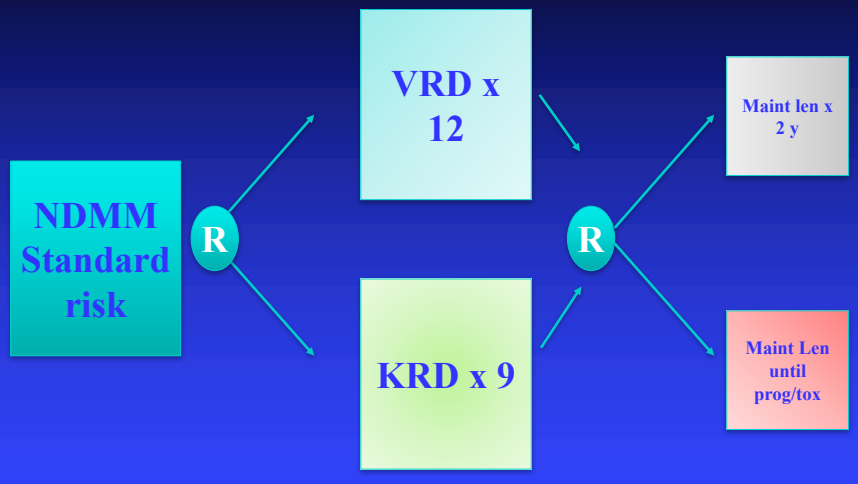
Meta-analysis of 8 prospective clinical trials comparing VCD vs VTD showed the same (Leiba et al, Br J Haematol, 2014)

Moreau et al. Blood. 2016;127(21):2569-2574

Table 4. Safety profile of induction therapy with VTD or VCD

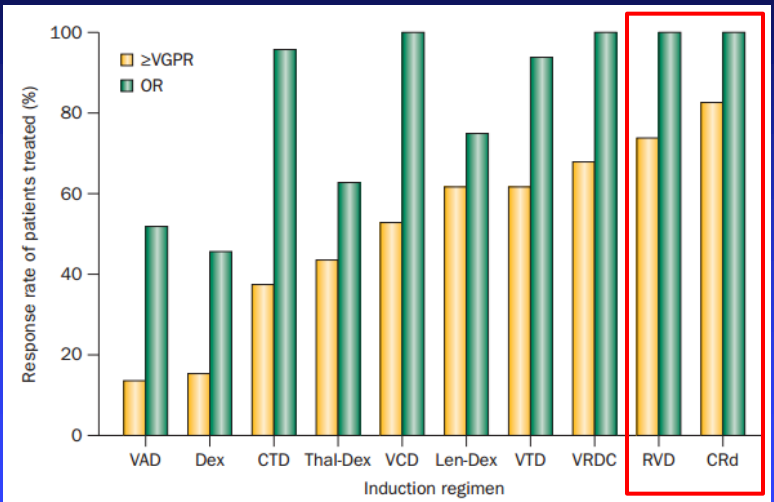
	VTD (n = 169) grade 3-4 (%)	VCD (n = 169) grade 3-4 (%)	*P* value
Any AEs	63.9	68.2	.40
Anemia	4.1	9.5	.05
Neutropenia	18.9	33.1	.003
Infection	7.7	10.1	.45
Thrombocytopenia	4.7	10.6	.04
Thrombosis	1.8	1.8	.99
Cardiac disorders	1.2	0	.16
Cystitis	0	0.6	.32
Gastrointestinal symptoms	5.3	3.5	.42
PN	7.7	2.9	.05
PN grade 2 - 4	21.9	12.9	.008

ENDURANCE Trial (E1A11)



ECOG: NCT01863550

Response Rates of Different Induction Regimens



Mailankody S et al. Nat. Rev. Clin. Oncol. 2015;12:286-95

Stem Cell Transplantation

Is there still a role?

Randomized Trials Comparing Chemotherapy with ASCT

Trial	Age	CR %	PFS (mo)	OS (mo)	Comments
Attal et al. NEJM 1996 N=200	<65	5 vs. 22*	18 vs. 28*	44 vs. 57*	Better CR, PFS and OS with auto
Child et al. NEJM 2003 N=401	<65	8 vs. 44*	20 vs. 32*	42 vs. 54*	Better CR, PFS and OS with auto
Barlogie et al. JCO 2006	<70	11 vs. 11	7-year PFS; 16 vs. 17%	7-year OS: 42 vs. 37%	No difference
Blade et al. Blood 2005	<65	11 vs. 30 *	33 vs. 42	66 vs. 61	Better CR with auto
Fermand et al. JCO 2005	55-65	nCR/CR 20 vs. 36%	19 vs. 25 (p=0.07)	46.6 vs. 47.8	Trend towards better PFS; better QOL

Randomized Transplant Trials in the Novel Era

Group	N	Induction	Comparator	ORR	PFS	OS
Italy NEJM 2014	273	RD x 4	MPR x 6 ASCT x 2	VGPR 63 59	22 mo 43 mo*	65% 4y 81%*
Europe Lancet Oncol 2015	389	RD x 4	CDR x 6 ASCT x2	VGPR 50 54	29 mo 43 mo*	68% 4y 77%*
EMN: ASCO 2016	1198	VCD x 3-4	VMP x 4 ASCT 1 or 2	VGPR 74 85*	44 mo NR (HR 0.73)*	NS (f/u short)

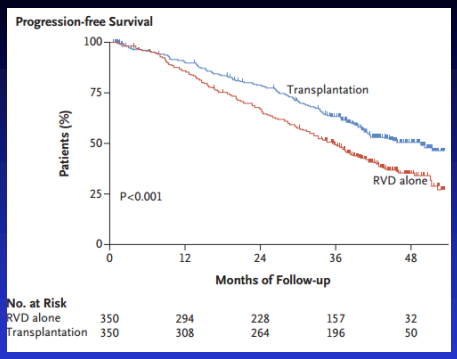
Palumbo et al. N Engl J Med 2014;371:895-905
Gay et al. Lancet Oncol 2015
Cavo et al. J Clin Oncol 34, 2016 (suppl; abstr 8000)

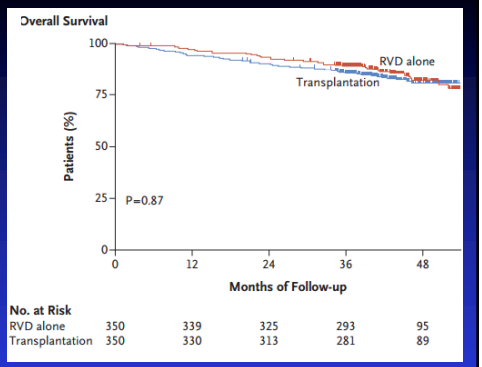
ASCT Up-Front or at Relapse
DFCI/IFM 2009 Trial

Len-Bz-Dex ×3
↓
Stem collection
↓
ASCT
↓
Len-Bz-Dex ×2
↓
Len ×12m (IFM)
Len until relapse (US)

Len-Bz-Dex ×3
↓
Stem collection
↓
Len-Bz-Dex ×5
↓
Len ×12m (IFM)
Len until relapse (US)
⋮
ASCT at relapse

NCI Clinical Trial Identifier NCT01191060.

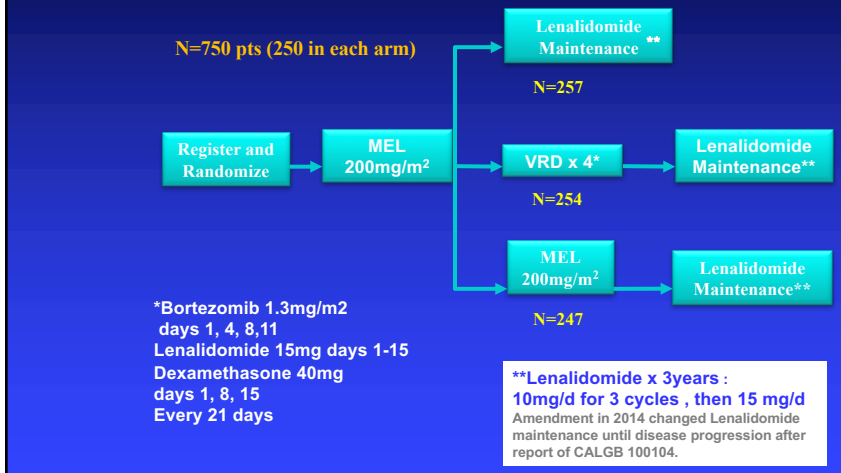




Survival	Early ASCT	Delayed ASCT	HR	*P* Value
Median PFS	50 mo	36 mo	0.65 (0.53 to 0.80)	P<0.001
4-yr OS	81%	82%	1.16 (0.80 to 1.68)	P=0.87
Median OS	NR	NR		

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

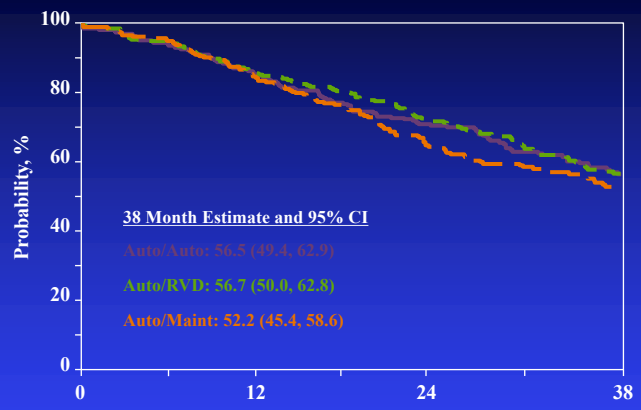
BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents (STAMINA):



*Bortezomib 1.3mg/m2
days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3years :
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

Primary Endpoint: PFS

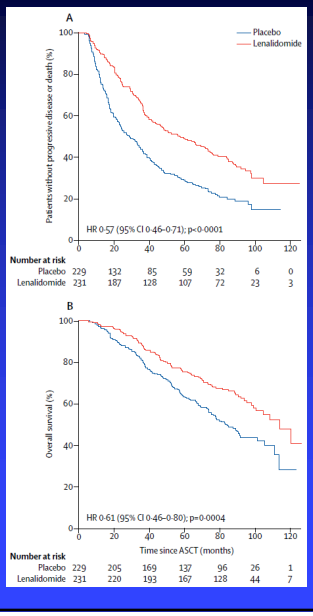


N at risk				
Auto/Auto	247	200	153	87
Auto/RVD	254	215	172	99
Auto/Maint	257	213	158	80

Maintenance Therapy

The case for lenalidomide maintenance

- IFM trial[1]
  - 614 patients
  - Median EFS: 41 vs. 23 months
  - No difference in OS
- CALGB trial[2]
  - 460 patients
  - Median TTP: 57 vs. 29 months (p <0.0001)
  - Median OS: 114 vs. 84 months (p=0.0004)
- Concerns:
  - Low counts
  - Second primary cancers



1. Attal et al, *NEJM* 2012
2. Holstein et al, , *Lancet Oncology* 2017

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JOURNAL OF CLINICAL ONCOLOGY

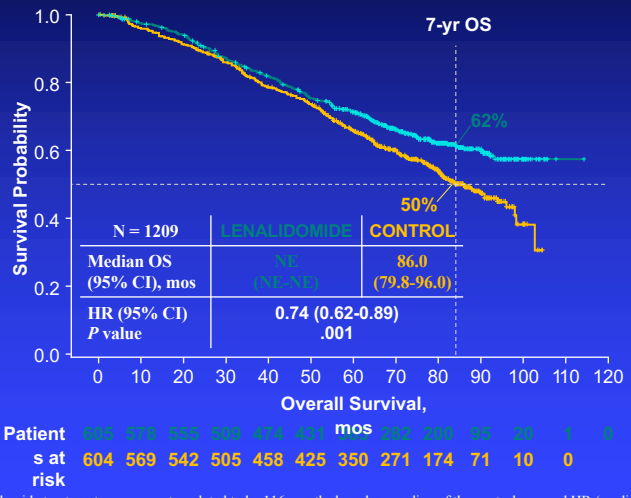
ORIGINAL REPORT

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

Overall Survival: Median Follow-Up of 80 Mo

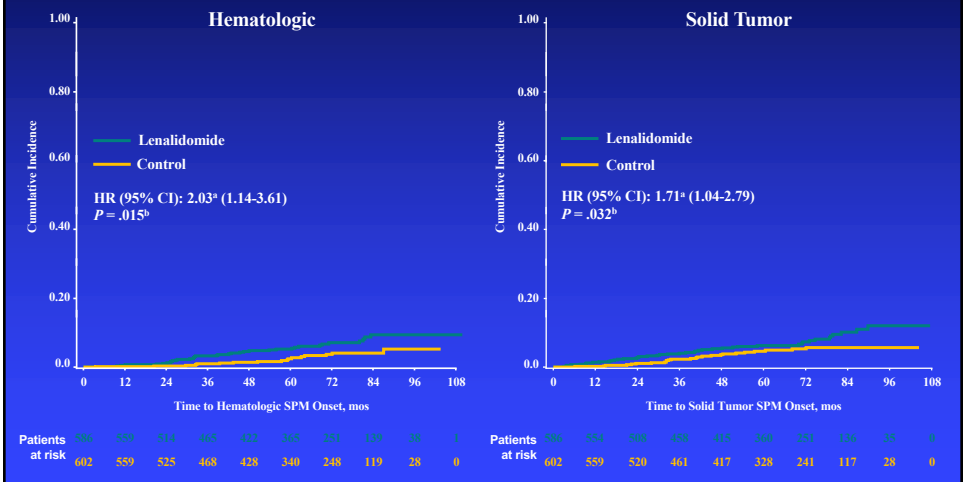
There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival[a]



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

HR, hazard ratio; NE, not estimable; OS, overall survival.

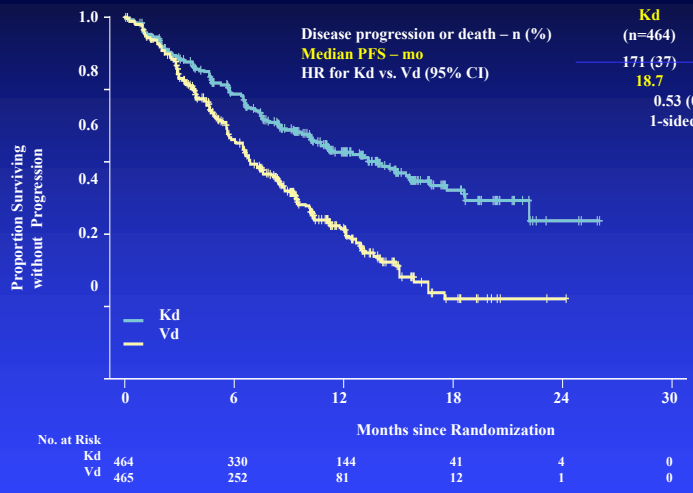
Cumulative Incidence of SPMs



[a] HR based on Cox proportional hazards model. [b] *P* value is based on log-rank test.
SPM, second primary malignancy.

Relapsed Multiple Myeloma

ENDEAVOR: Kd vs Vd
PFS (1-3 Prior Lines)



	Kd (n=464)	Vd (n=465)
Disease progression or death – n (%)	171 (37)	243 (52)
Median PFS – mo	18.7	9.4
HR for Kd vs. Vd (95% CI)	0.53 (0.44–0.65)	
	1-sided *P*<0.0001	

No. at Risk

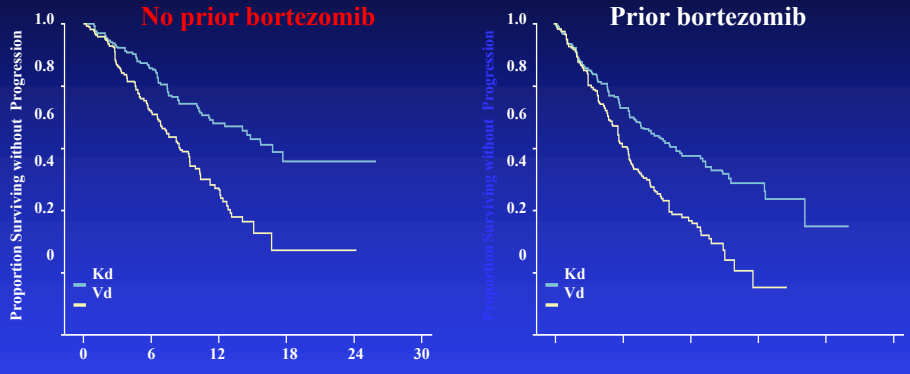
Kd	464	330	144	41	4	0
Vd	465	252	81	12	1	0

- Median follow-up: 11.2 months

27

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

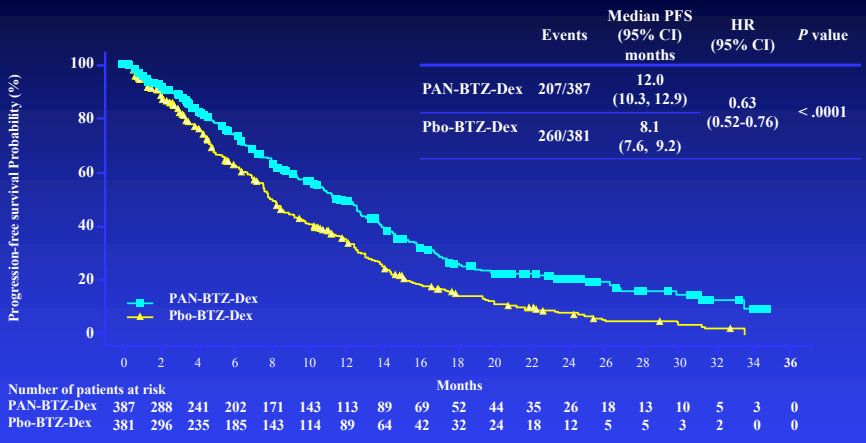
ENDEAVOR
PFS and ORR by Prior Bortezomib Exposure



	Kd (n=214)	Vd (n=213)	1-sided P-value
Median PFS, mo	NE	11.2	
ORR, % (95% CI)	84 (78–88)	65 (59–72)	<0.0001

	Kd (n=250)	Vd (n=252)	1-sided P-value
Median PFS, mo	15.6	8.1	
ORR, % (95% CI)	71 (65–77)	60 (54–66)	0.005

PANORAMA - 1



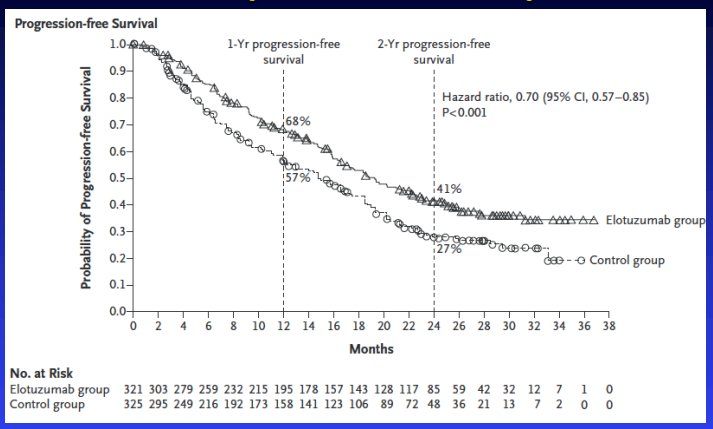
	Events	Median PFS (95% CI) months	HR (95% CI)	*P* value
PAN-BTZ-Dex	207/387	12.0 (10.3, 12.9)	0.63 (0.52-0.76)	< .0001
Pbo-BTZ-Dex	260/381	8.1 (7.6, 9.2)		

Number of patients at risk

PAN-BTZ-Dex	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Pbo-BTZ-Dex	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

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

ELOQUENT-2: Ld vs Eld PFS (1-3 Prior Lines)



No. at Risk

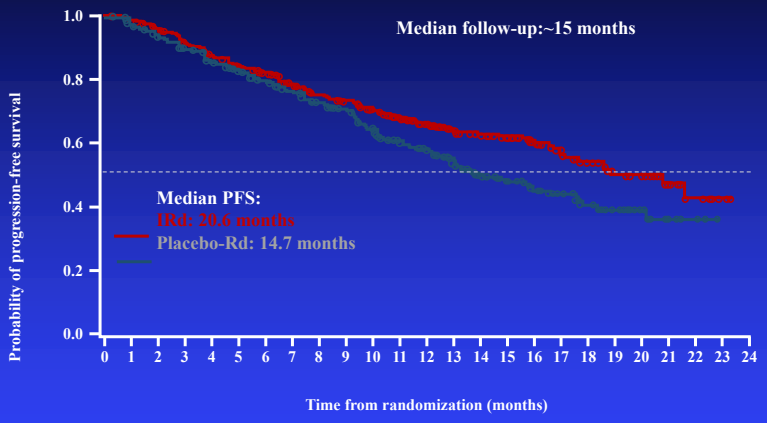
Elotuzumab group	321	303	279	259	232	215	195	178	157	143	128	117	85	59	42	32	12	7	1	0
Control group	325	295	249	216	192	173	158	141	123	106	89	72	48	36	21	13	7	2	0	0

Co-primary endpoint: ORR	E-Ld	Ld
%	79	66
95% CI	74,83	60,71

Median (95% CI) PFS:
E-Ld 19.4 (16.6–22.2) months
Ld 14.9 (12.1–17.2) months
Hazard ratio: 0.70
(95% CI: 0.57 to 0.85 P=0.0004)

Richardson PG et al. Presented at: ASH 2015 (abstr 28).
Lonial SG et al. *N Engl J Med.* 2015;373(7):621-631.

TOURMALINE MM-1: Rd vs IRD
PFS (1-3 Prior Lines)



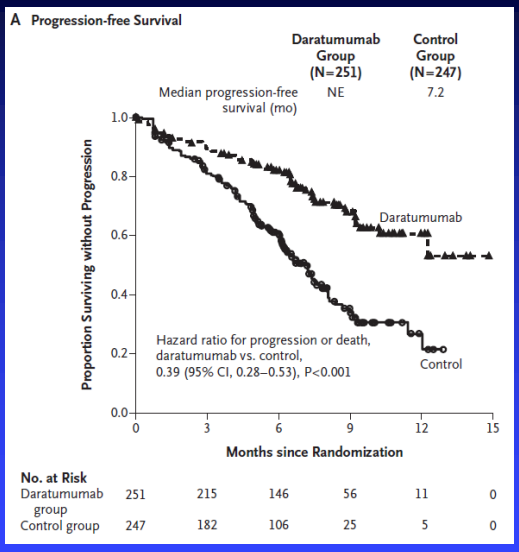
A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events

- Hazard ratio of PFS was 0.82 (95% confidence interval [0.67, 1.0]) for IRd vs Rd
- Estimated median PFS was 20 months in IRd and 15.9 months in Rd

Log-rank test p=0.012
Hazard ratio (95% CI): 0.742 (0.587, 0.939)
Number of events: IRd 129; placebo-Rd 157

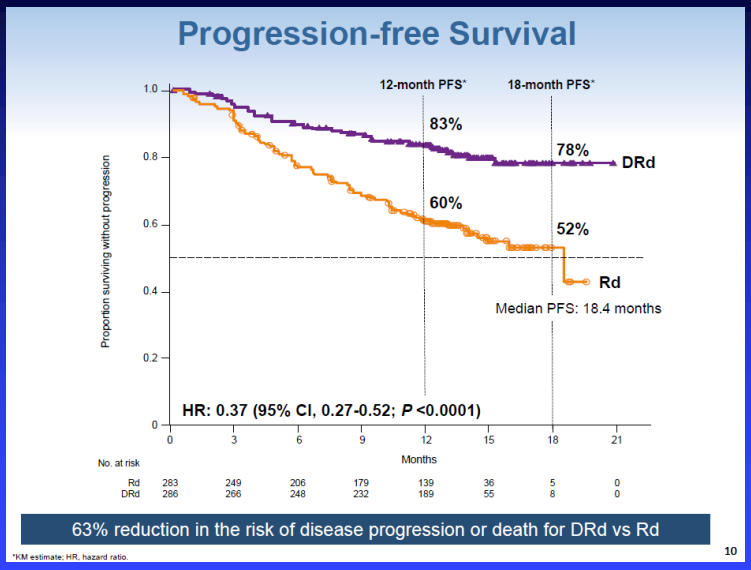
Moreau P. et al., Presented at ASH 2015 (abstr 727).

CASTOR: Vd vs Dara-Vd



Palumbo et al. N Engl J Med 2016; 375:754-766

POLLUX: Rd vs Dara-Rd



Dimopoulos et al., N Engl J Med 2016; 375:1319-133

Early Relapse: SO which to choose? 2017

- 1st relapse off treatment
  - Elo/RD
- 1st Relapse on Maintenance:
  - Bortezomib maintenance (Imid + (elo/carfil/ixaz) or Carfil + cyclo)
  - Lenalidomide maintenace (PI + (len/pom/cyclo))
- 2nd and Subsequent Relapse
  - Lenalidomide sensitive
    - Elo/Rev/Dex
    - Ixazomib/Rev/Dex
    - Dara/RD
  - Bortezomib sensitive
    - V/Pom/dex
    - V/Cyclo/dex
    - Dara/VD
  - Lenalidomide/Bortezomib resistant (double refractory):
    - Carfil/Cyclophophamide/Dex
    - Pomalidomide + Carfilzomib + Dex or Pom + cyclo + dex
    - Daratumumab (also for Quad refractory)

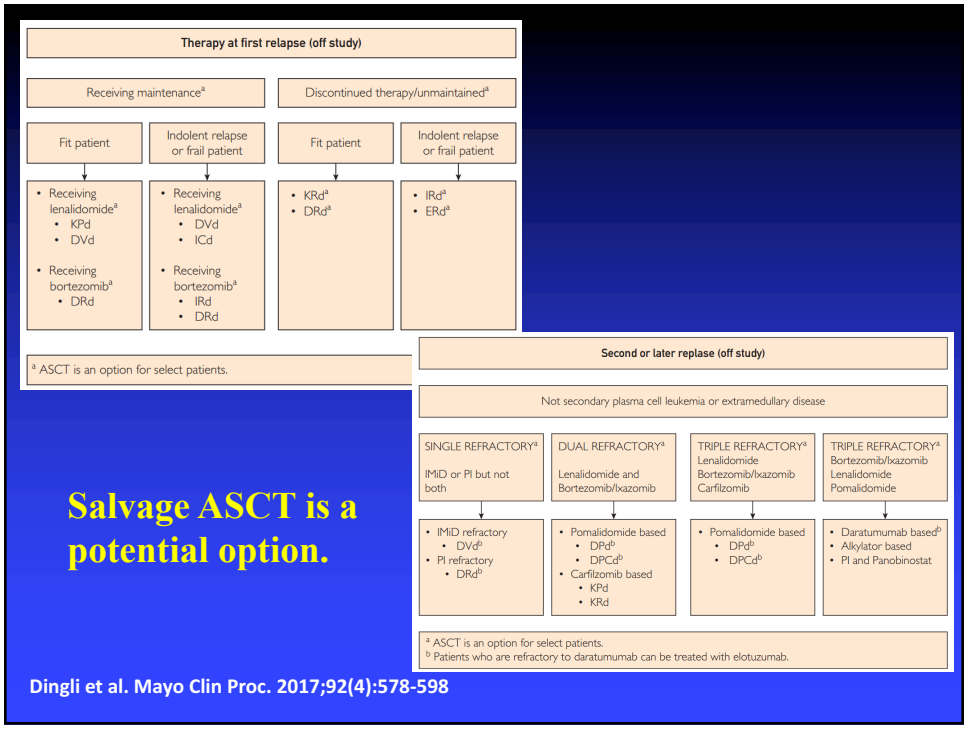
Side effects

QOL: PO vs IV

Respo nse depth

Refrac tory

Courtesy of Nina Shah



Salvage ASCT is a potential option.

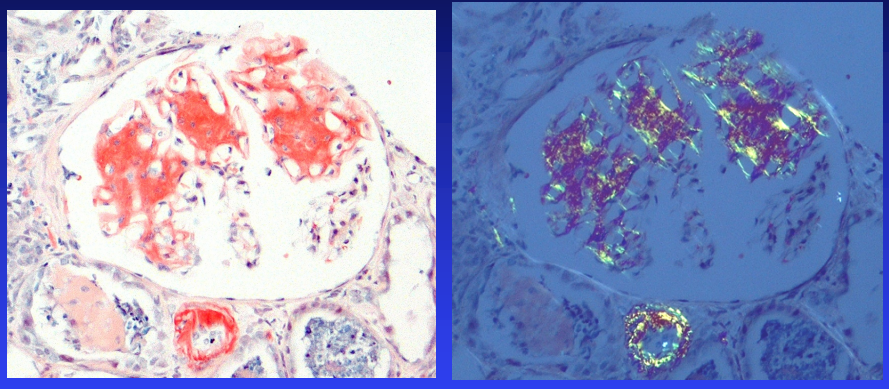
Dingli et al. Mayo Clin Proc. 2017;92(4):578-598

The Landscape of Myeloma Treatment

	Induction: VRD (?)	Transplant (Mel 200)	Maintenance (LEN)	Salvage
current	VD RD VTD CyBorD		?Velcade	Velcade Revlimid Carfilzomib Pomalidomide Panobinostat Ixazomib Elotuzumab Daratumumab
future	KRD	Cell therapy	Ixazomib Len +Ixa Vaccines	Oprozomib Bendamustine Isatuximab CAR-T Pembrolizumab Venetoclax Nelfinavir

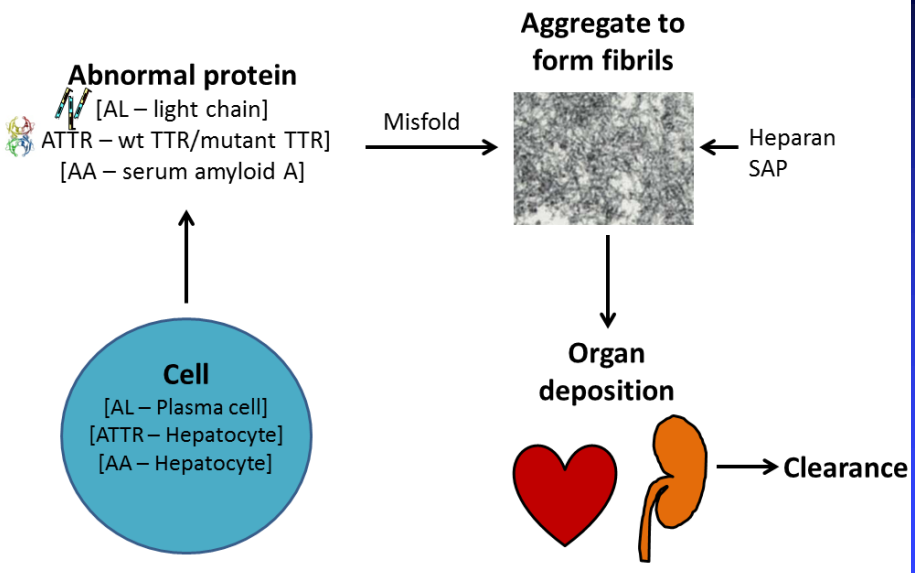
Updates on Systemic Light-Chain Amyloidosis

Diagnosis of Amyloid: Congo Red Stain



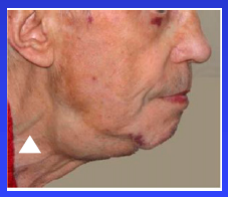
Comenzo et al. Blood 2009

Pathology of Amyloid Deposition



When to think of amyloidosis

- **Signs & Symptoms of AL**
  - **Increased TTE wall thickness and low voltage EKG (different from HCM and HTN)**
  - **Advanced diastolic dysfunction without hypertension**
  - **Severely increased (>15-16 mm) wall thickness on TTE (LVPWd, IVSd)**
  - Lethargy, fatigue, weight loss
  - Peripheral edema
  - Diarrhea/constipation
  - Peripheral/autonomic neuropathy
  - **Postural hypotension**
  - **New onset proteinuria (please check U/A)**
  - Hepatomegaly or splenomegaly

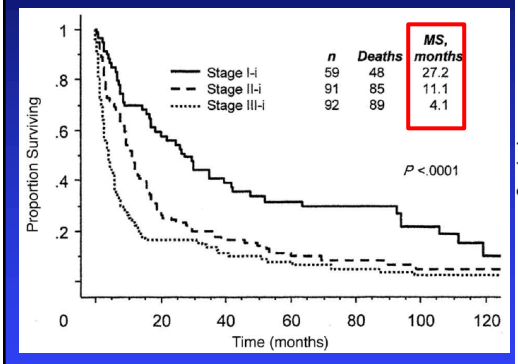


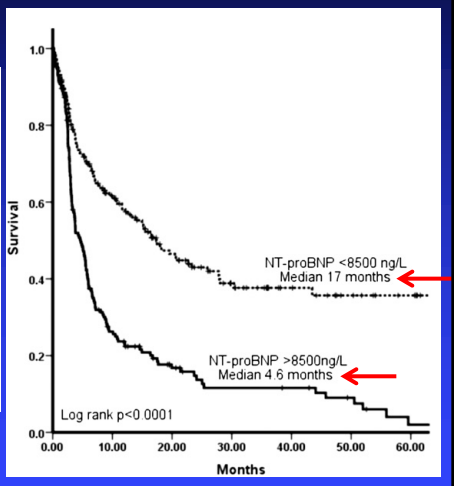
Merlini et al. Blood. 2013.

Work-up for Systemic AL Amyloidosis

- Diagnostic bx
  - involved organ bx
  - surrogate site – abd fat, rectal, gingival
- History & physical
- Chem1, CBC, PT/PTT/INR
- Bone marrow biopsy and aspirate
  - CD138-selected FISH or cIg-FISH
- SFLC, immunoglobulins, SPEP with IFE, UPEP with IFE
- Skeletal survey, PET/CT, MRI Total spine/pelvis or low-dose CT
- Biomarkers:
  - NT-proBNP, Troponin
  - 24-Urine for UTP, GFR
- ? Mass spec

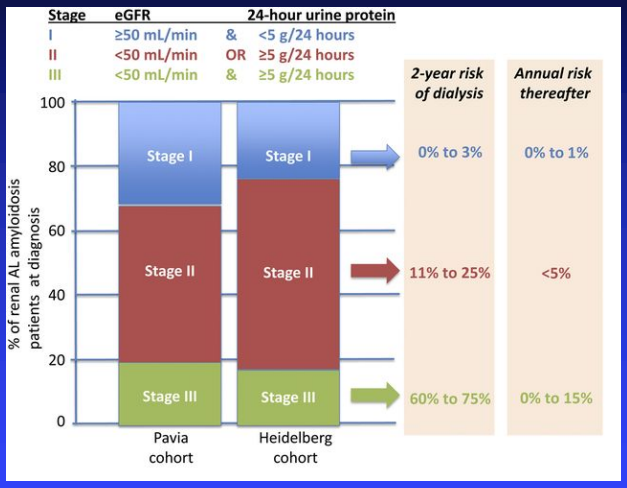
Contributor to Overall Survival: Cardiac Staging





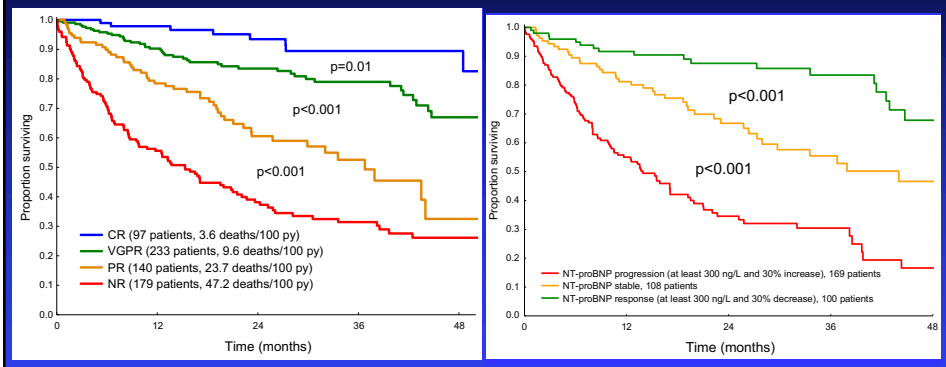
Dispenzieri et al. J Clin Oncol. 2004.
Wechalekar et al. Blood. 2013.

Contributor to Renal Survival: Renal Staging



Palladini et al. Blood 2014.
Dispenzieri et al. Blood 2014.

Goals of Treatment: Hematologic & Cardiac Responses



Depth of hematologic response and organ response predicts for improved survival.

Palladini et al. J Clin Oncol 2012
Comenzo et al. Leukemia 2012

Hematologic response criteria

Table 3. Hematologic response and progression criteria

Response category	*Criteria*
Complete	Normalization of the free light chain levels and ratio, negative serum and urine immunofixation
Very good partial	Reduction in the dFLC to <40 mg/l
Partial	A greater than 50% reduction in the dFLC
No response	Less than a PR
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double) From PR, 50% increase in serum M protein to >0.5 g/dl or 50% increase in urine M protein to >200 mg/day (a visible peak must be present) Free light chain increase of 50% to >100 mg/l

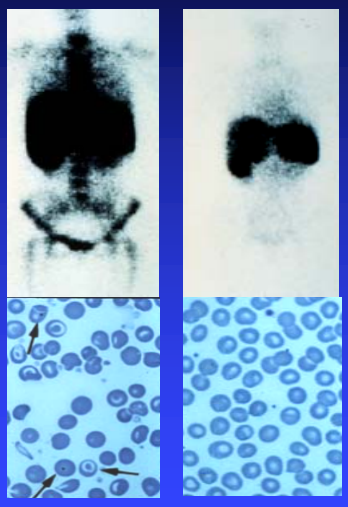
Abbreviations: CR, complete response; dFLC, difference between iFLC and uninvolved FLC; FLC, free light chain; PR, partial response.

The general goal for hematologic response is VGPR or CR.

Comenzo et al. Leukemia 2012

Hematologic CR allows for resorption of amyloid deposits

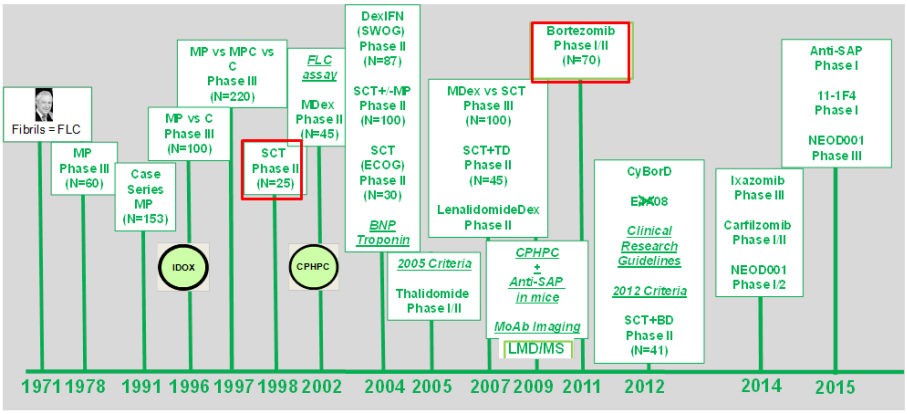
Pre-SCT



Post-SCT

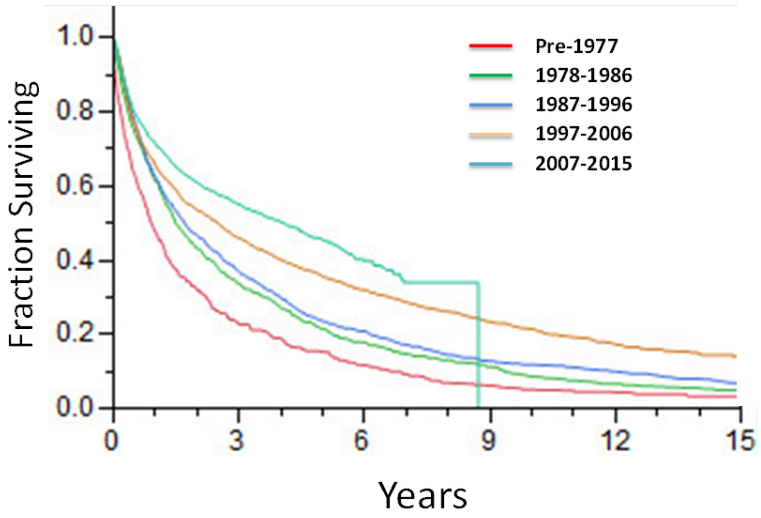
Courtesy of Ray Comenzo

Advances in Systemic AL Amyloidosis



Courtesy of Ray Comenzo

Survival of AL patients over time (n=5030)



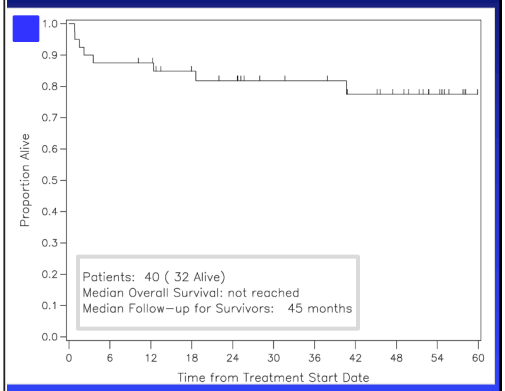
Courtesy of Angela Dispenzieri
Unpublished data of AL amyloidosis patients seen at Mayo Clinic

After RA-SCT for newly dx AL pt, Bortezomib/Dex Consolidation

Table 3. Hematological and organ responses

ITT	*Months post SCT*		
	2–3	*12*	*24*
	N = 40	*N = 38[a]*	*N = 30[b]*
CR	11 (27%)	22 (58%)	12 (40%)
PR	7 (18%)	8 (21%)	6 (20%)
SD	18 (45%)	—	—
PD	—	1 (3%)	4 (13%)
% with ⩾1 OR (ITT)		21 (55%)	21 (70%)
[c]Heart		53% (9/17)	56% (5/9)
[c]Kidney		52% (12/23)	87% (13/15)
[c]Liver/GI		60% (3/5)	60% (3/5)
[c]NS		100% (4/4)	100% (4/4)

Abbreviations: CR, complete hematological response; GI, gastrointestinal; ITT, intention-to-treat; OR, organ response; PD, disease progression; PR, partial response; SD, stable disease. NS response was based on clinical parameters.[14] [a]Two ongoing. [b]10 ongoing. [c]Evaluable patients.

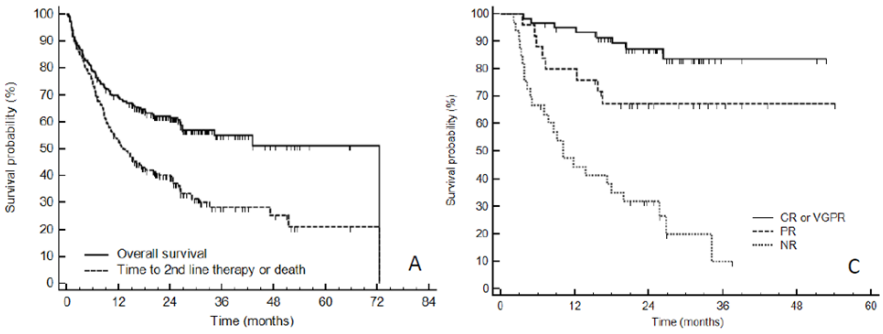


Leukemia 2013;27:823

Only 25% of patients are eligible for ASCT

Mayo Clin Proc. 2015;90(8):1054-1081
Blood. 2002;99:4276-4282

CyBorD Upfront in AL Amyloidosis



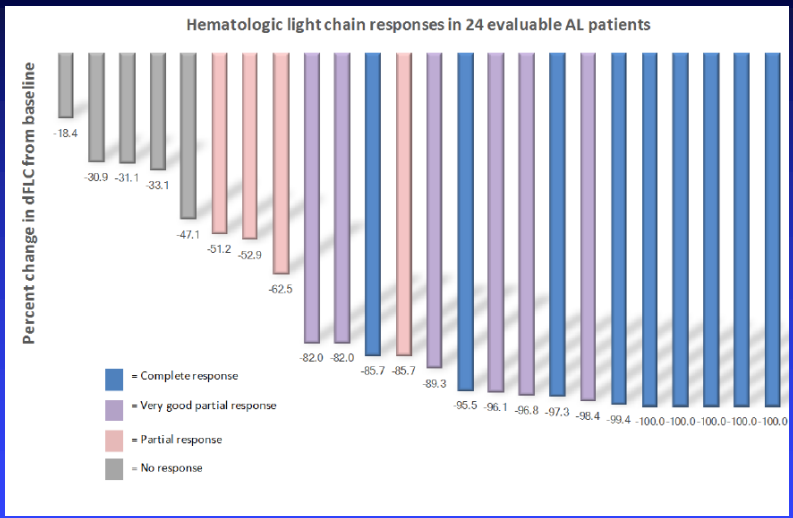
Heme RR = 62%, 43% ≥ VGPR.

Cardiac response = 17% , Renal response in 25%

Advanced cardiac stage III patients: Heme CR 42%, ≥VGPR 23%, median OS 7 mo

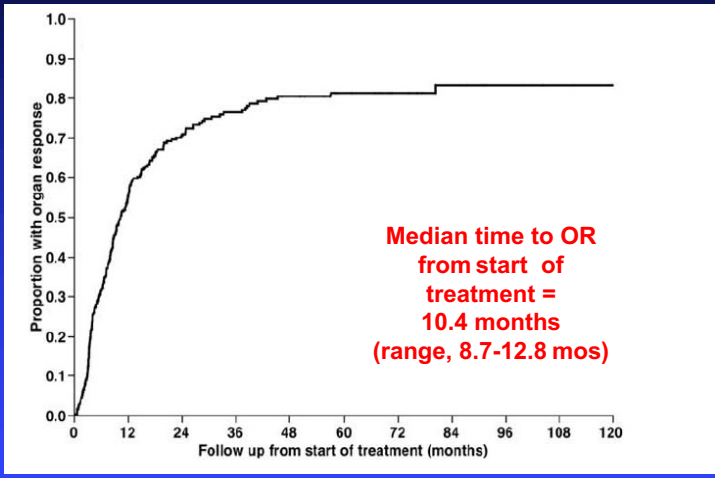
Palladini et al., Blood 2015.

Daratumumab in AL Amyloidosis



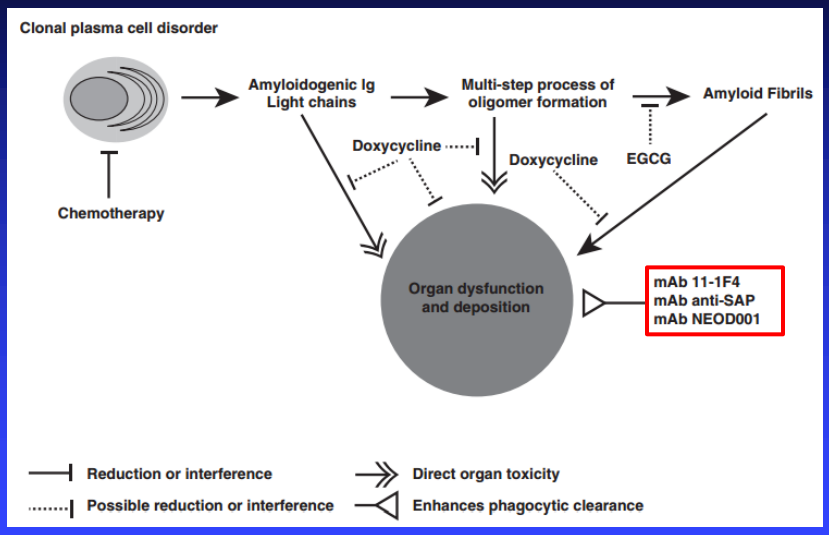
Kaufman et al, Blood. 2017, 130:900-902.

Kinetics of Organ Response



Kauffman et al, Am J Hematol. 2015 Mar;90(3):181-6.

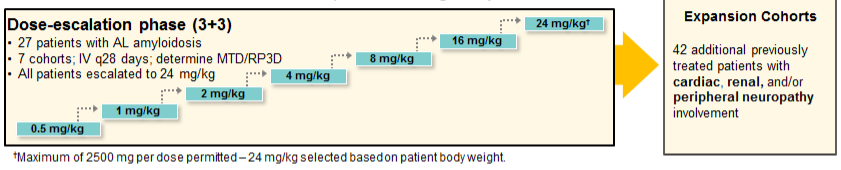
Emerging anti-amyloid agents



Weiss et al, Blood. 2016;127(19):2275-2280

NEOD001 Phase 1/2 Trial (N = 69) Design

• Previous PC-directed treatment and persistent organ dysfunction



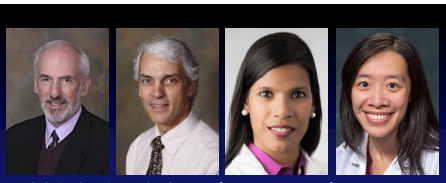
†Maximum of 2500 mg per dose permitted – 24 mg/kg selected based on patient body weight.

Primary objectives	• Evaluate the safety and tolerability of NEOD001 (NCT01707264) • Determine MTD or recommended dose for future clinical study of NEOD001
Secondary objectives	• Evaluate the serum PK of NEOD001 • Assess the immunogenicity of NEOD001 • Evaluate organ response (cardiac, renal, peripheral neuropathy)

Organ	Measurement of Response	Organ Response	Median Time to Initial Response
Cardiac	NT-proBNP	19/36 (53%)	2 months
Renal	24-UTP	23/36 (64%)	4 months
Nerves	NIS-LL	9/11 (82%)	Organ response at month 10

Gertz et al, ASH 2016.

UCSF Clinical Trials



Amyloidosis

- [Ph2b] Renal AL amyloidosis and NEOD001 (RAIN) (Persistent renal dysfunction despite heme remission) (open Winter 2017)
- [Ph3] CyBorD +/- DARA (Newly diagnosed) (open Winter 2017)
- [Ph2] Len/Elo/Dex +/- Cyclophosphamide (Relapsed AL) (open Winter 2018)

Multiple Myeloma

- [Ph2] IRD for consolidation post ASCT followed by Ixa/LEN (open)
- [Ph1] Carfilzomib + Isatuximab (open)
- [Ph1] CD46-ADC in RRMM (Late 2018)
- [Ph3] RVd +/- DARA in newly diagnosed MM (GRIFFIN) (open)

Immunotherapy in Multiple Myeloma

- [Ph1] BCMA CAR-T BB21217 (open)
- [Ph1] BCMA CAR-T BB2121 (future)
- Dendritic cell vaccines (future)