MM Therapy
Paradigm Shift (?)

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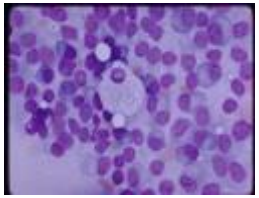
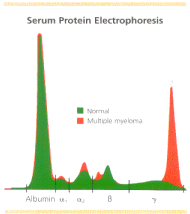
DIRECTOR OF MYELOMA SERVICE

Maryland half marathon

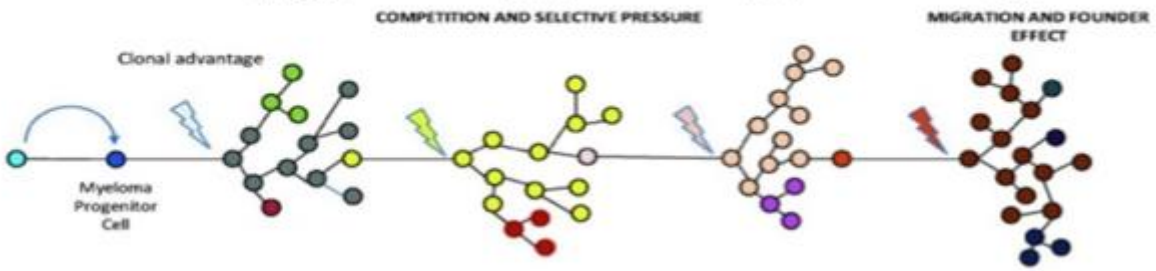
MM

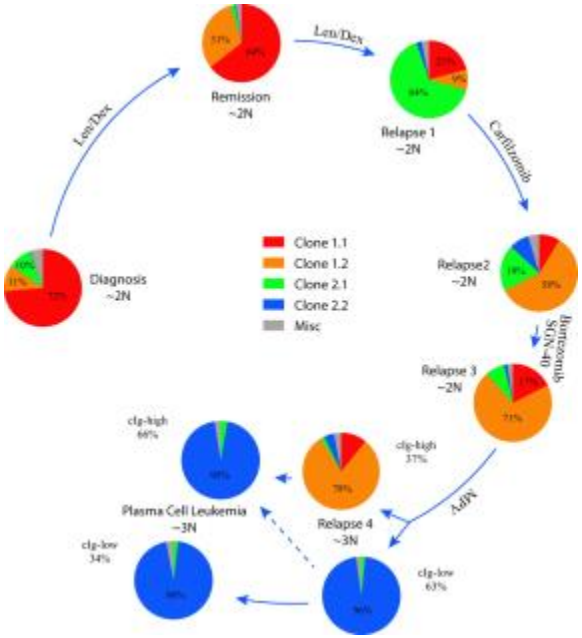


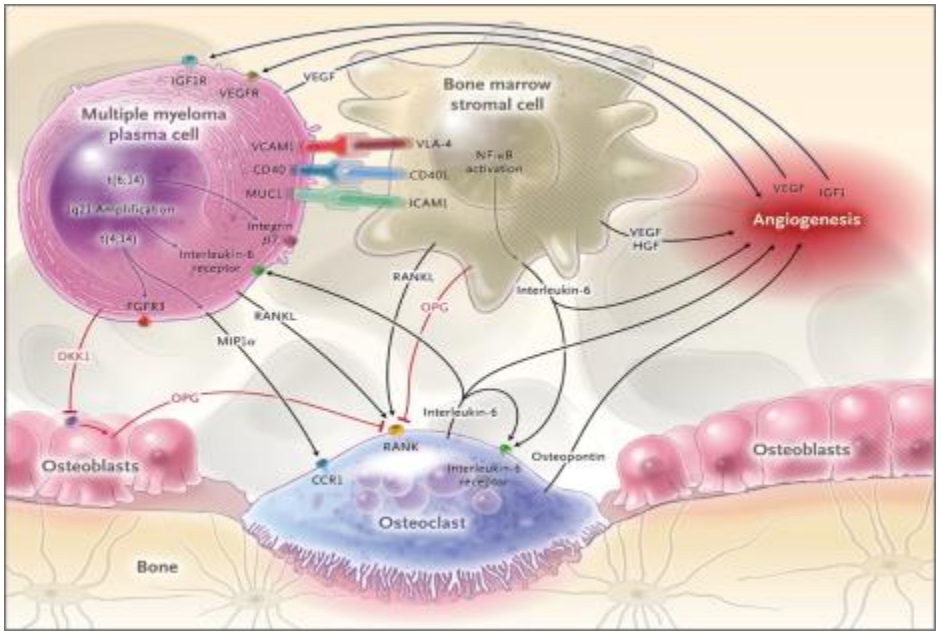


Pre malignant states
MGUS **SMM**

Myeloma defining event





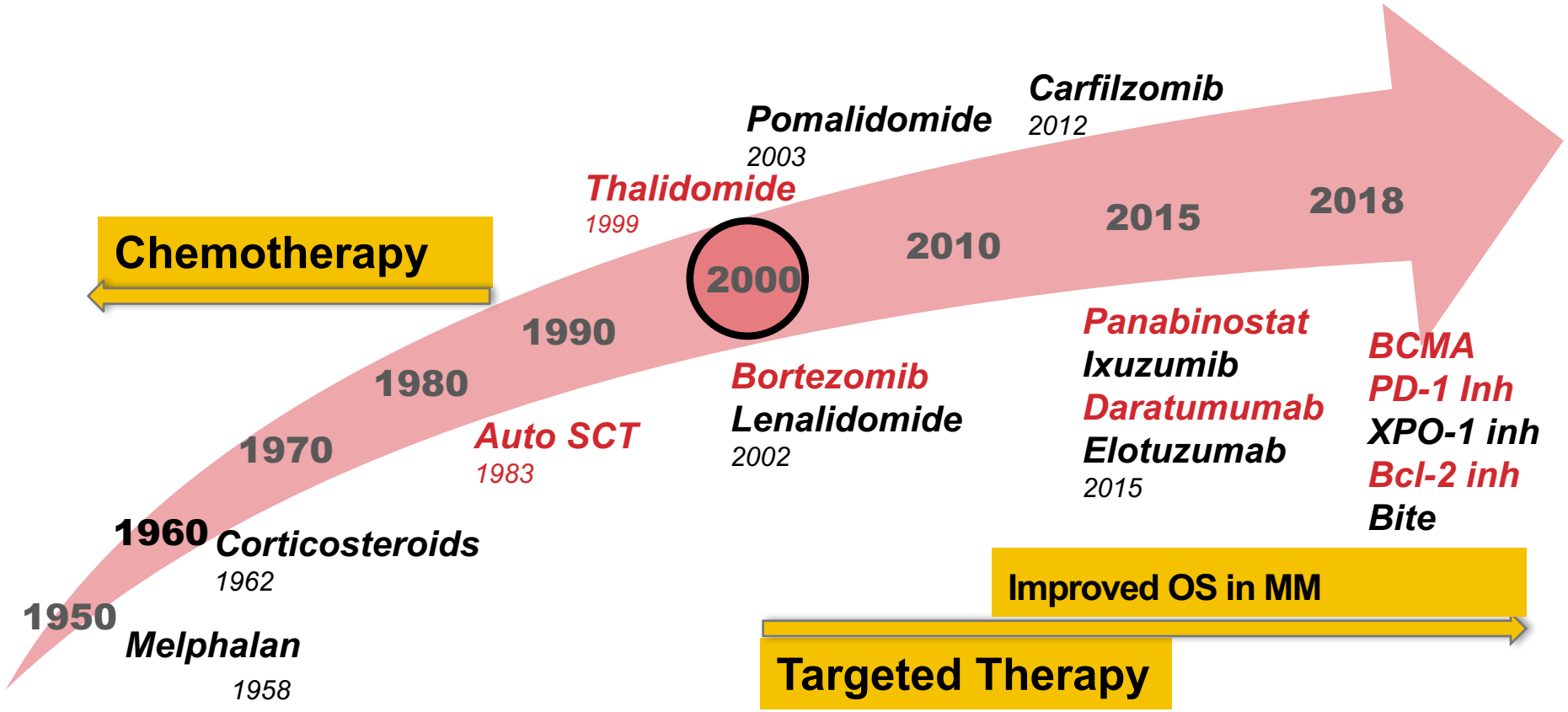


Sub clones; median no.=7

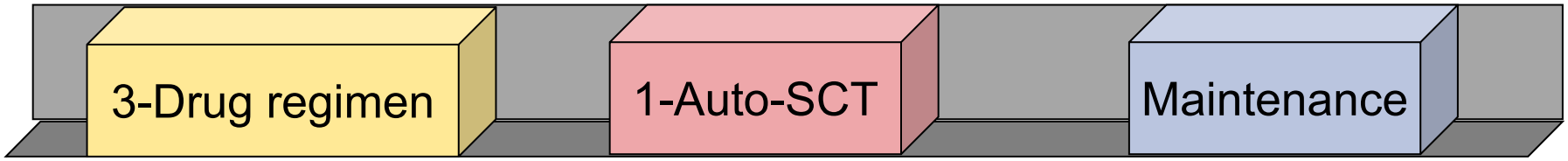
BM environment…Immune effects

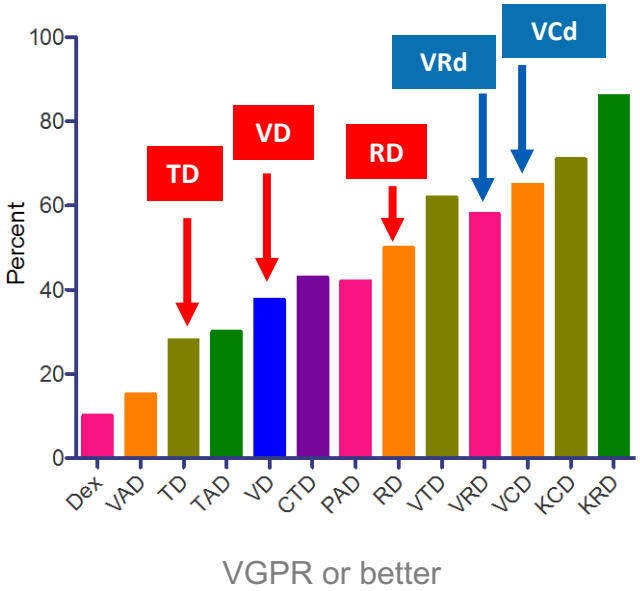
Morgan GJ, et al. Nat Rev Cancer. 2012;12:335; Keats J et al. Blood 2012;120:1067-1076 Palumbo A, Anderson K. N Engl J Med 2011;364:1046

MM Therapy


Chemotherapy
1950
1960
Corticosteroids
1962
Melphalan
1958
1970
1980
Auto SCT
1983
1990
Thalidomide
1999
2000
Bortezomib
Lenalidomide
2002
Pomalidomide
2003
2010
Carfilzomib
2012
2015
Panabinostat
Ixuzumib
Daratumumab
Elotuzumab
2015
2018
BCMA
PD-1 Inh
XPO-1 inh
Bcl-2 inh
Bite
Improved OS in MM
Targeted Therapy

MM Therapy---2018

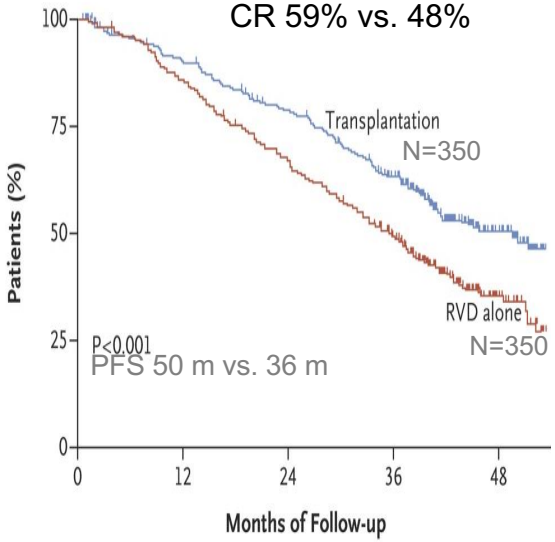




VGPR or better

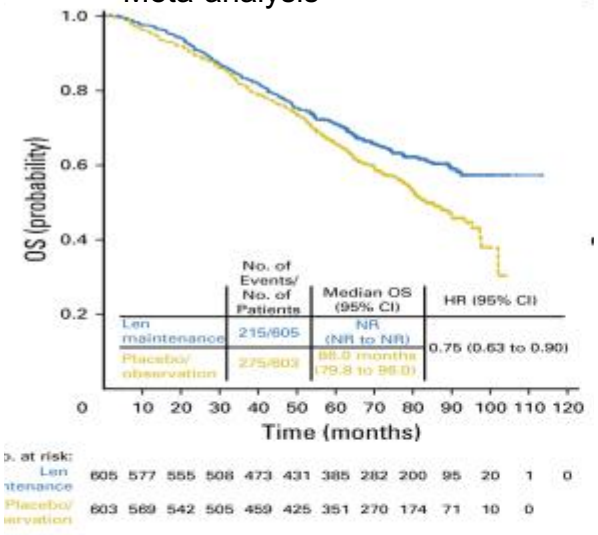
RVD +/- SCT

CR 59% vs. 48%



Maintenance-lenalidomide

Meta-analysis

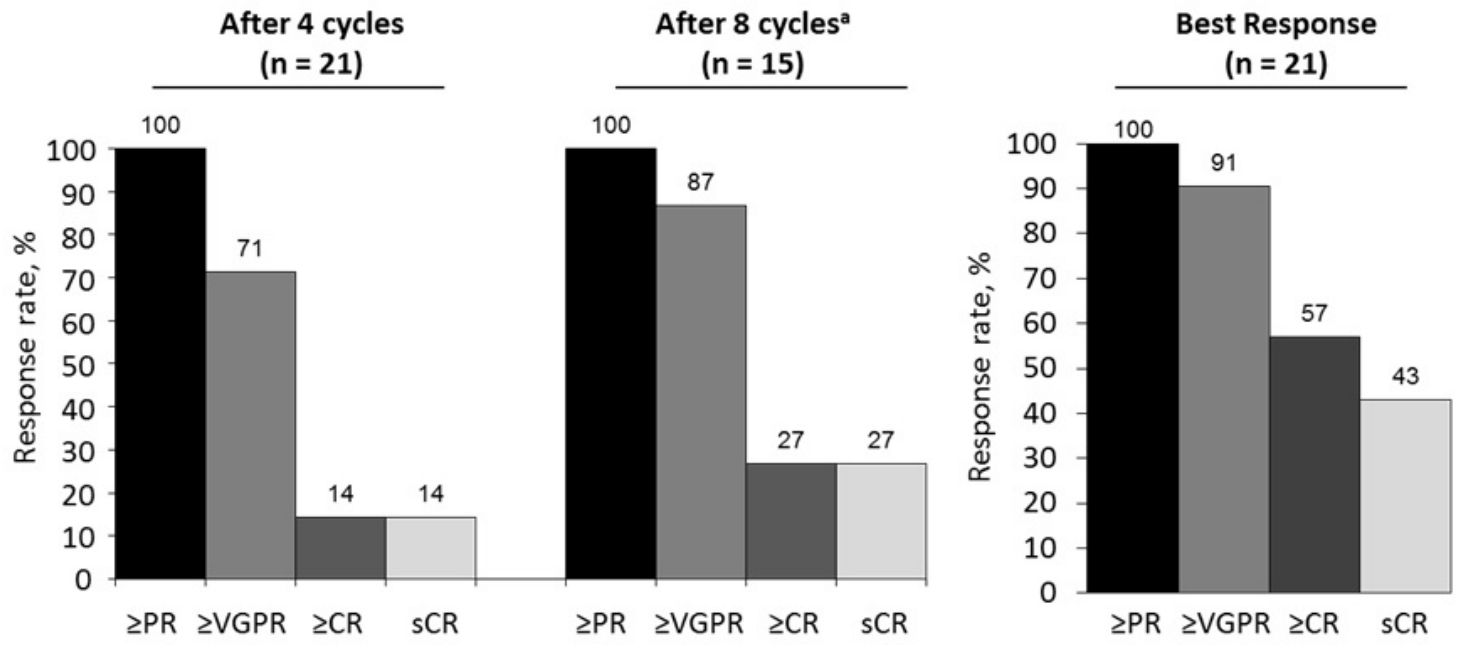


sTaMINA

Post induction + ASCT-1 followed by:	R Maint only n=257	RVD→R n=254	Double ASCT→R n=247
Median PFS, mos	52.2	56.7	56.5
Median OS, mos	83.4	85.7	82.0

McCarthy P; at al. *JCO* 2017, 35, 3279-3289.
BMT CTN0702 STaMINA Trial
Attal M et al. N Engl J Med 2017

Daratumumab Plus KRD In Newly Dx MM



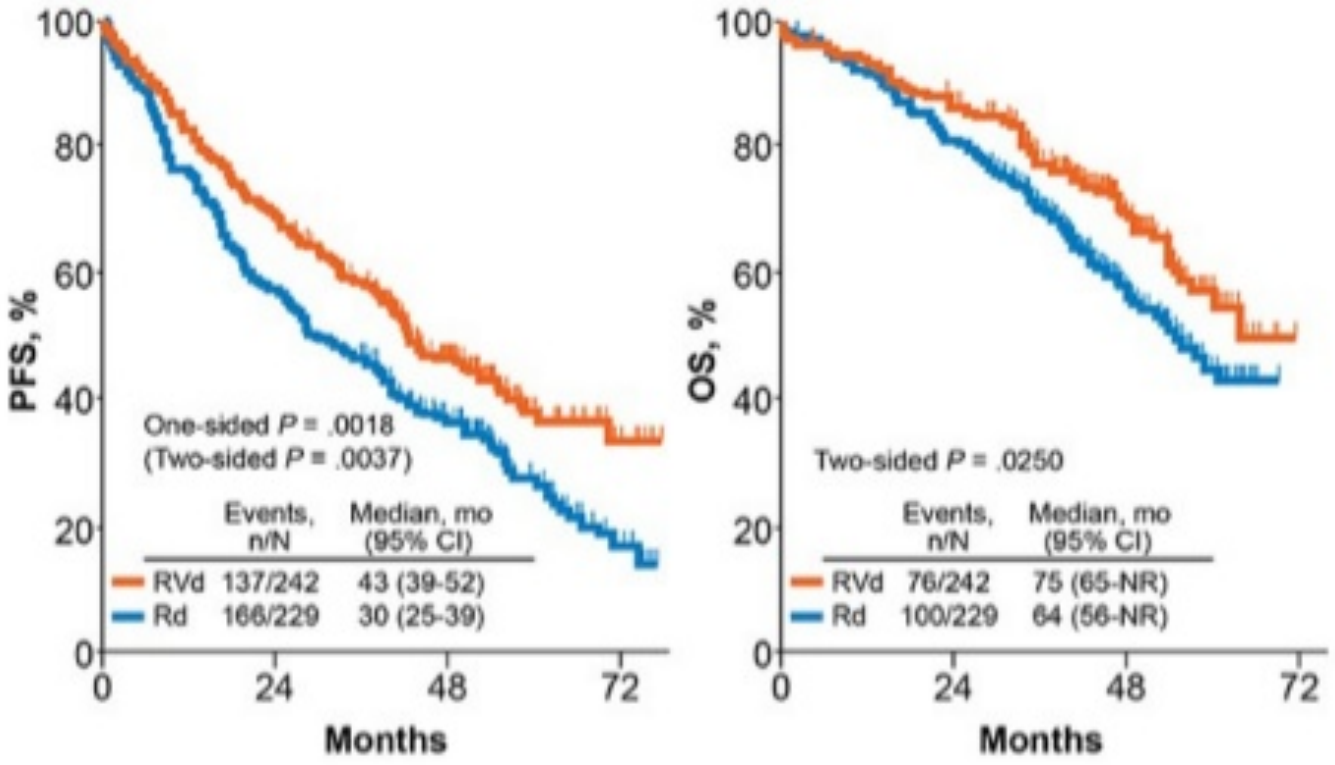
[a]5 patients who proceeded to ASCT before Cycle 8 and 1 patient who discontinued due to progressive disease at Cycle 7 were excluded.

Ajay C, et al. Ash 2017 # 3110

RVD VERSUS RD IN ELDERLY MM NOT ELIGIBLE FOR SCT

N=525

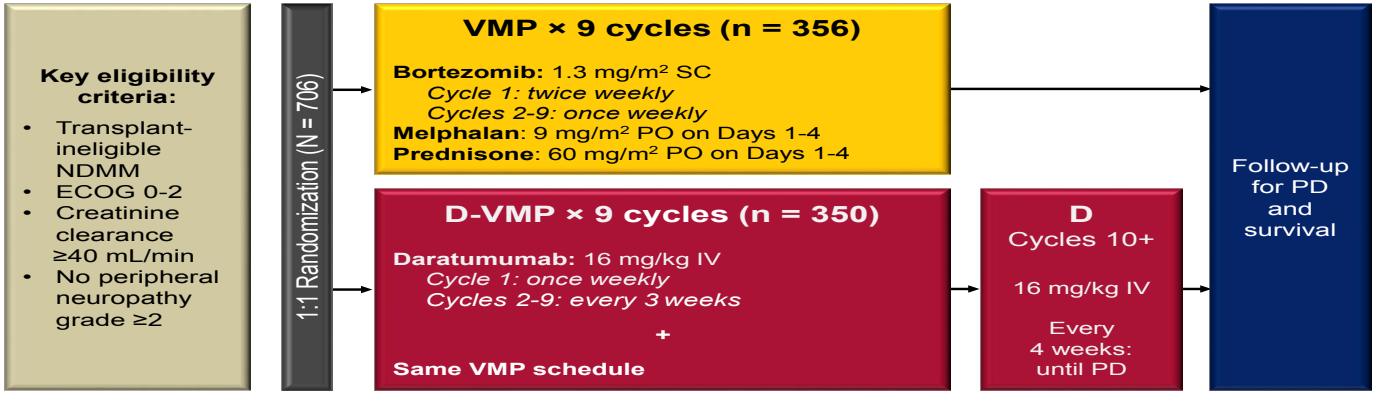
- **Initial therapy:** RVd for eight 21-day cycles vs Rd for six 28-day cycles in patients not intending to proceed to transplant, followed by Rd in both arms

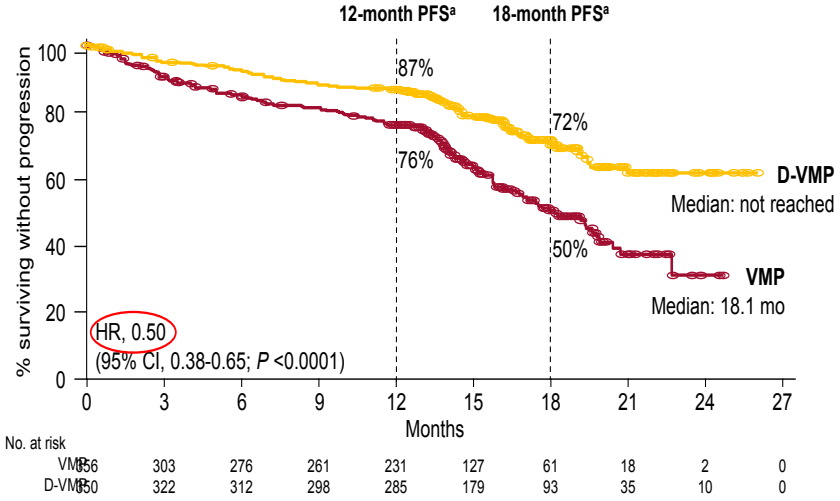


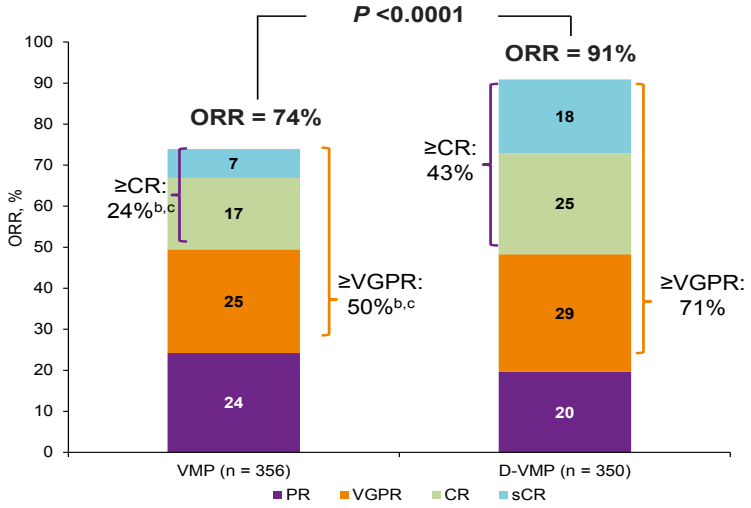
1. Durie B et al. *Lancet*. 2017;389:519-527.

MM Therapy---2018

VMP +/- Daratumumab in NDMM not eligible for SCT







50% reduction in risk of progression

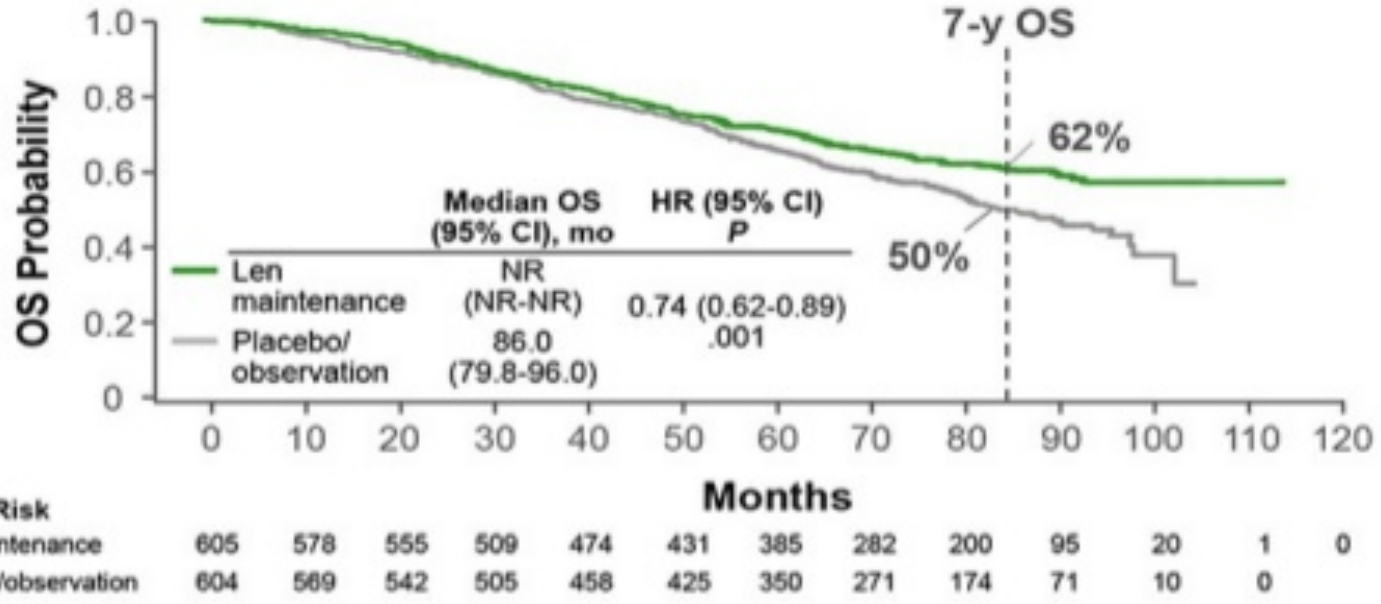
MRD –ve 22% versus 6%

Mateos MV, et al, NEJM 2018

Lenalidomide Maintenance

Meta-analysis

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

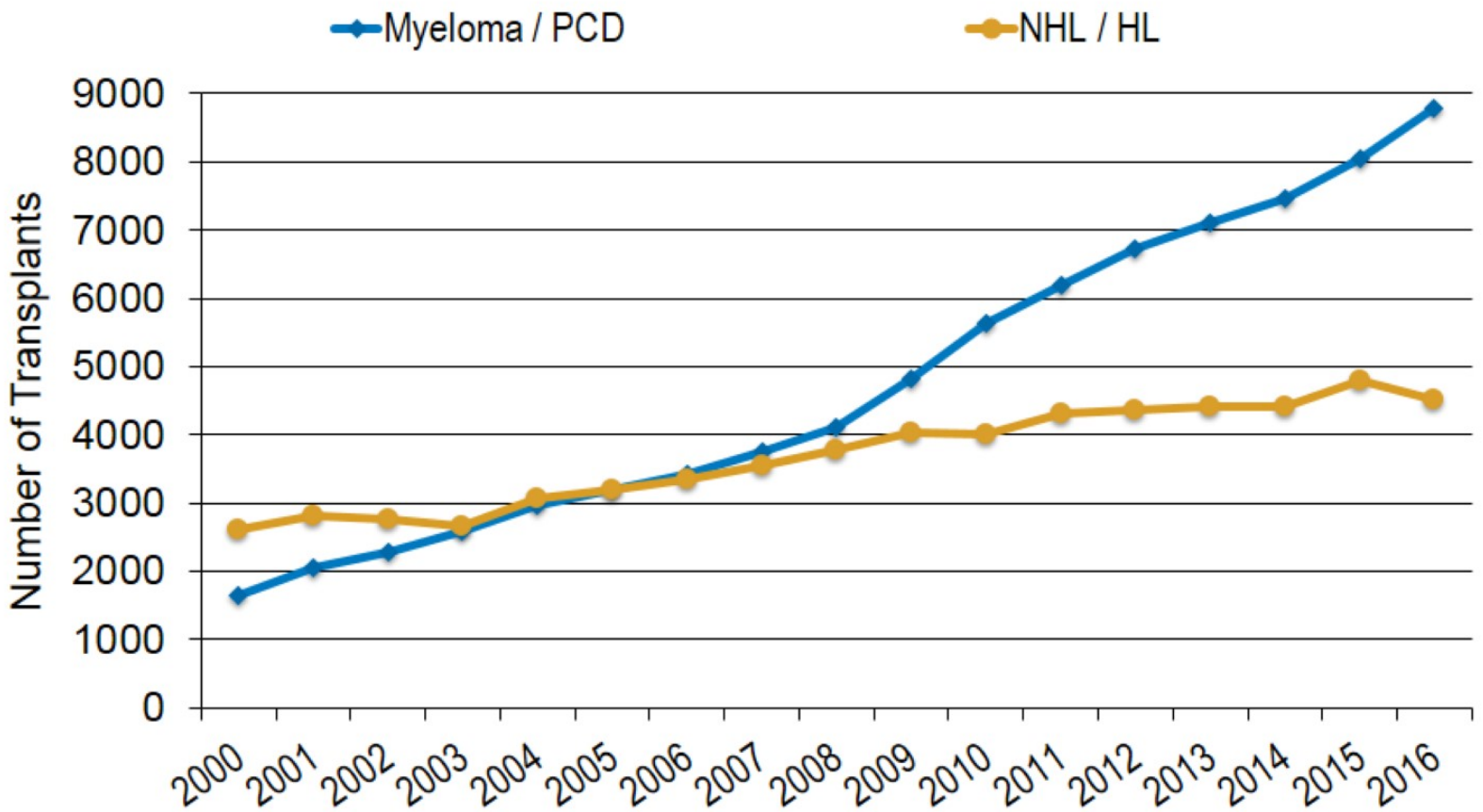


[a] Log-rank test and Cox model stratified by study to assess impact of Len maintenance on OS. Median for len treatment arm was extrapolated to be 115 mo based on median of control arm and HR (median, 86 mo; HR = 0.74).

1. Attal M et al. 2016 American Society of Clinical Oncology Annual Meeting (ASCO 2016). Abstract 8001.

Role of SCT

Trends of Auto SCT in The USA



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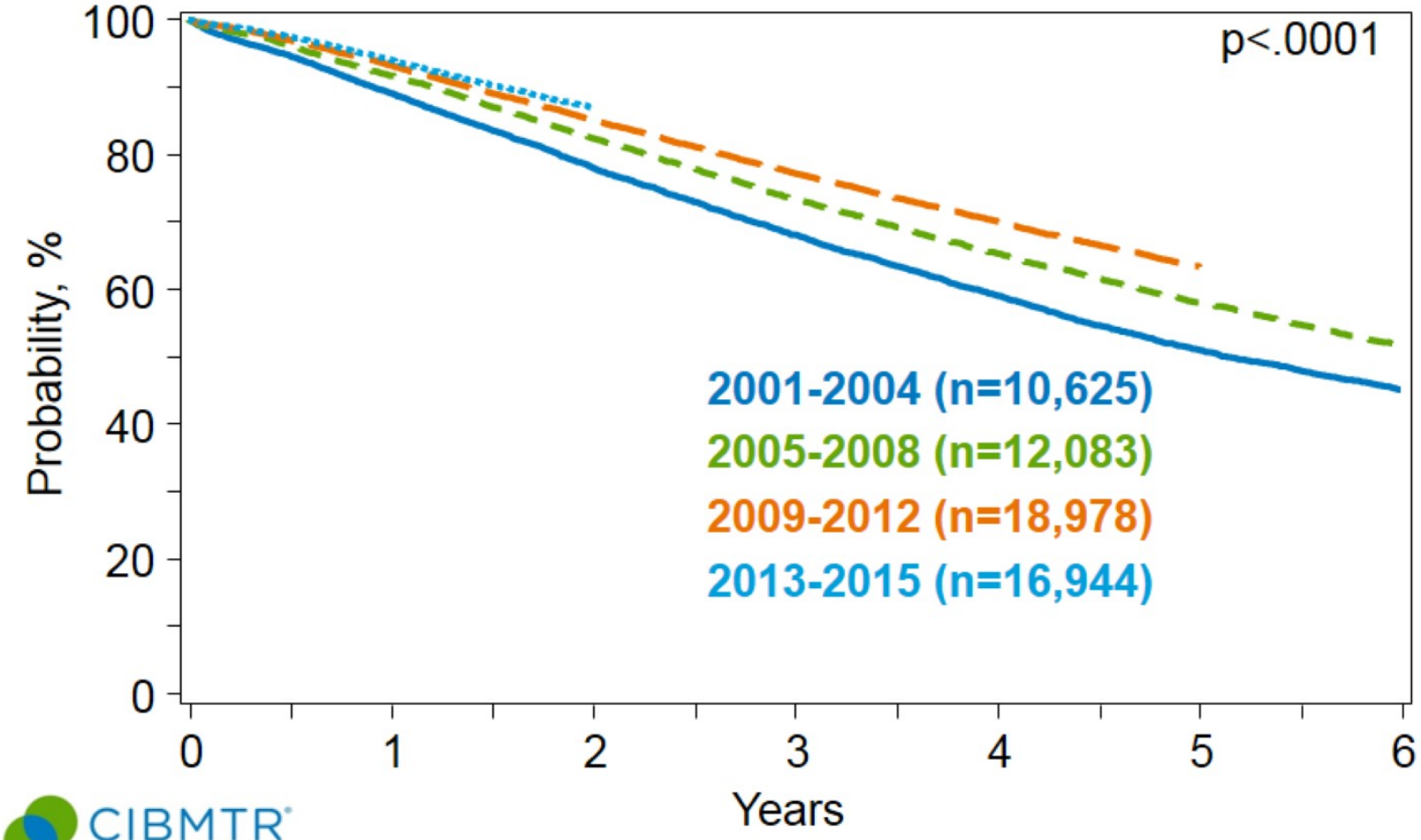
OS after auto-SCT for MM



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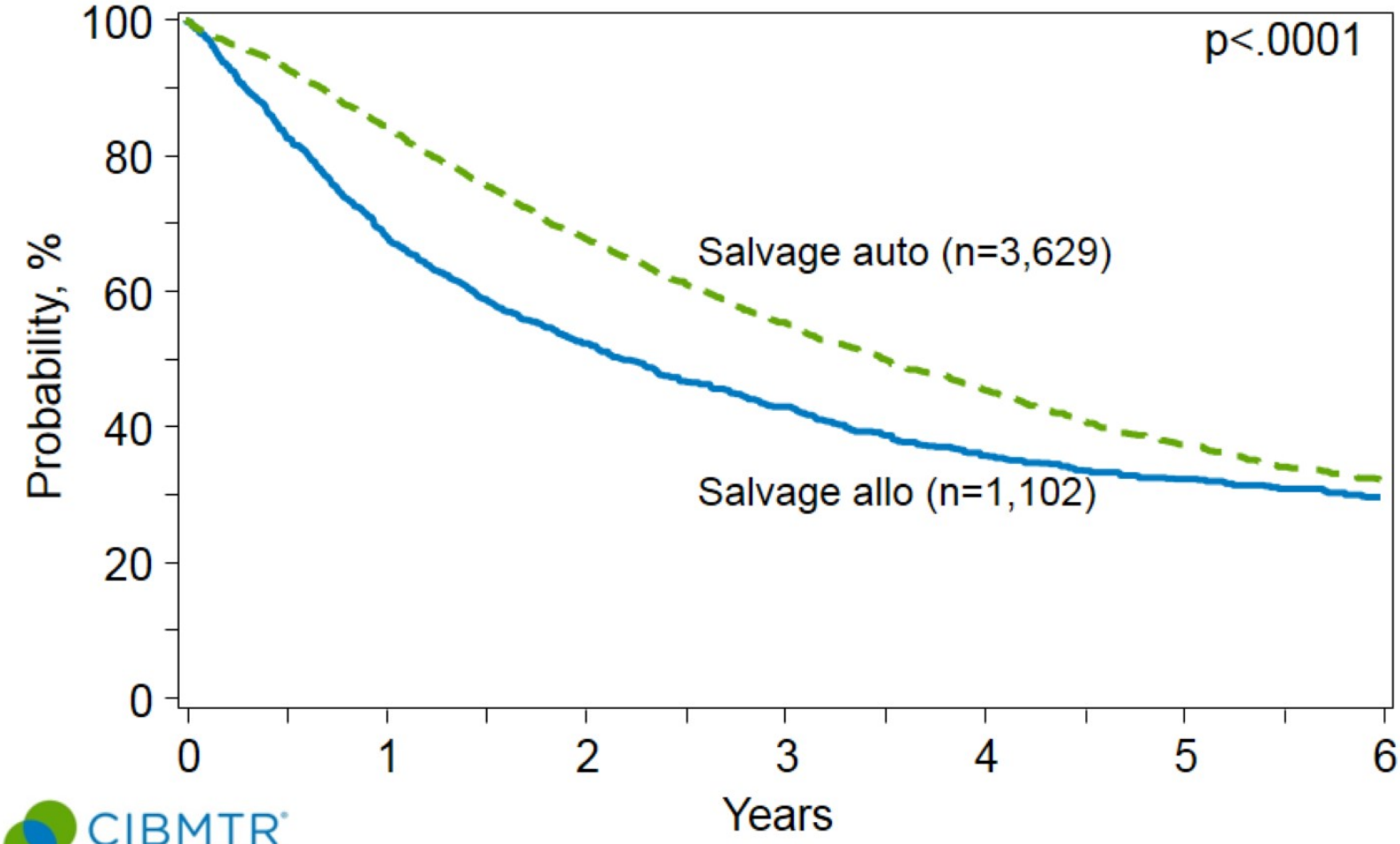
Salvage SCT In MM



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Auto-SCT for Newly Dx MM in the Era of Novel Agents: Meta-analysis

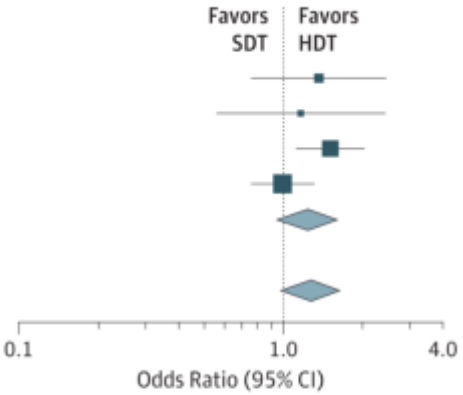
Table 1. Baseline Demographics of Relevant Randomized Clinical Trials

Source	Patients, No.	ISS III, %	High-Risk Cytogenetics, %[a]	Follow-up, mo.	Induction	Conditioning	SDT Regimen	Maintenance (HDT + SDT)
Palumbo et al,[8] 2014	273	23.6	28.8	51.2	RD	MEL 200 × 2	MPR	LEN until progression vs none
Gay et al,[7] 2015	256	29.0	21.8	52	RD	MEL 200 × 2	CRD	LEN + P vs LEN until progression
Attal et al,[5] 2015	700	18.0	12.8	44	RVD	MEL 200	RVD for 8 cycles	LEN for 1 y
Cavo et al,[6] 2016	1192	21.0	25	26	CyBorD	MEL 200 × 1 or 2	VMP for 4 cycles	LEN until progression

JAMA Oncol. 2018;4(3):343-350. doi:10.1001/jamaoncol.2017.4600

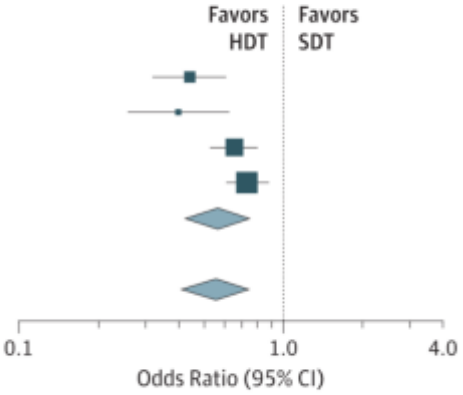
A Complete response

Study	Odds Ratio (95% CI)
Palumbo et al,[8] 2014	1.37 (0.76-2.45)
Gay et al,[7] 2015	1.17 (0.56-2.47)
Attal et al,[5] 2015	1.51 (1.12-2.04)
Cavo et al,[6] 2016	1.00 (0.76-1.32)
Univariate summary, *P*=.11	**1.24 (0.95-1.61)**
Heterogeneity (Q=4.16, P=.24; I^2=38.1%)	
Multivariate summary, *P*=.07	**1.27 (0.98-1.65)**



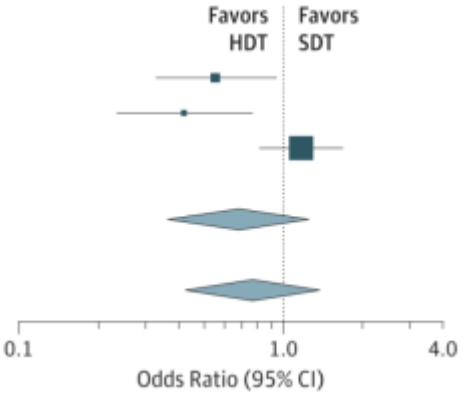
B Progression-free survival

Study	Odds Ratio (95% CI)
Palumbo et al,[8] 2014	0.44 (0.32-0.61)
Gay et al,[7] 2015	0.40 (0.25-0.63)
Attal et al,[5] 2015	0.65 (0.53-0.80)
Cavo et al,[6] 2016	0.73 (0.61-0.88)
Univariate summary, *P*<.001	**0.56 (0.43-0.74)**
Heterogeneity (Q=11.28, P=.01; I^2=77.2%)	
Multivariate summary, *P*<.001	**0.55 (0.41-0.74)**



C Overall survival

Study	Odds Ratio (95% CI)
Palumbo et al,[8] 2014	0.55 (0.32-0.94)
Gay et al,[7] 2015	0.42 (0.23-0.76)
Attal et al,[5] 2015	1.16 (0.80-1.68)
Cavo et al,[6] 2016	
Univariate summary, *P*=.20	**0.67 (0.36-1.24)**
Heterogeneity (Q=10.24, P=.01; I^2=78.7%)	
Multivariate summary, *P*=.36	**0.76 (0.42-1.37)**



Is Transplant Necessary?

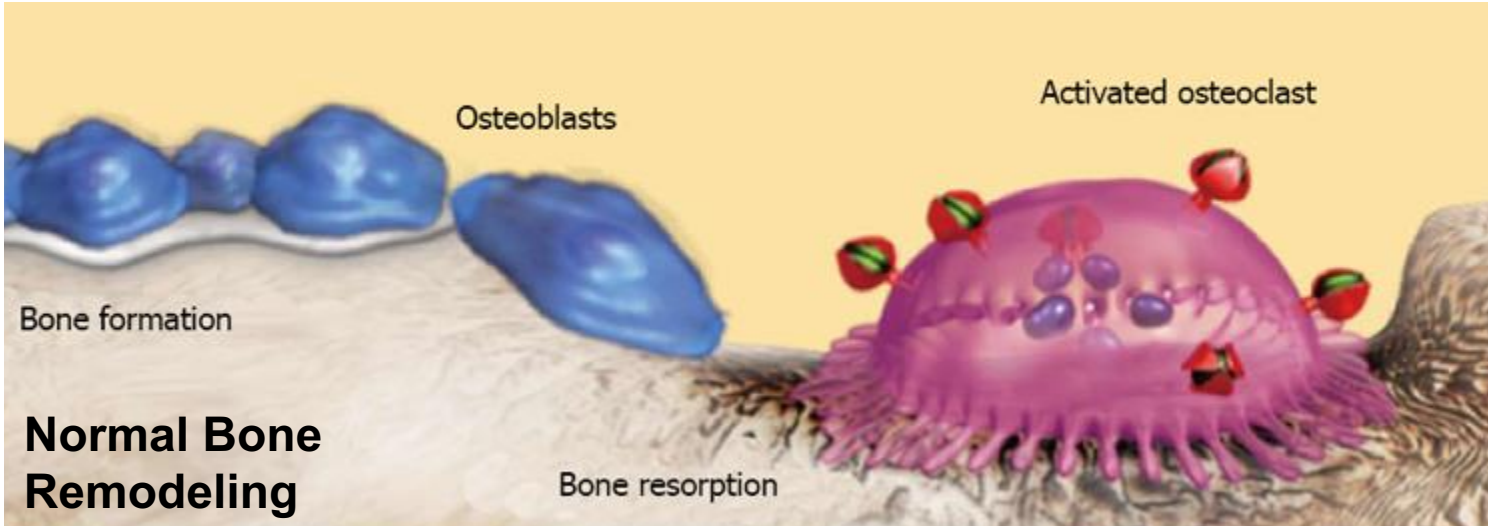
"Upfront" SCT is the standard of care pts < 65 yrs

- ***My Opinion…***
  - SCT
    - Increase CR rate …impact PFS & OS (?)
    - Increase depth of response to molecular level more (?)
    - 1 SCT is adequate with maintenance (2rd one may be beneficial?)
  - Relapse after SCT is salvageable with novel agents…
  - Patients are more fit
  - Salvage SCT
    - Less benefit (?)
    - Not done in 40%

- ***If MRD negativity is achived do we need more therapy???***

BONE DISEASE

BONE DISEASE



Normal Bone Remodeling

<u>Bisphosphonates</u>

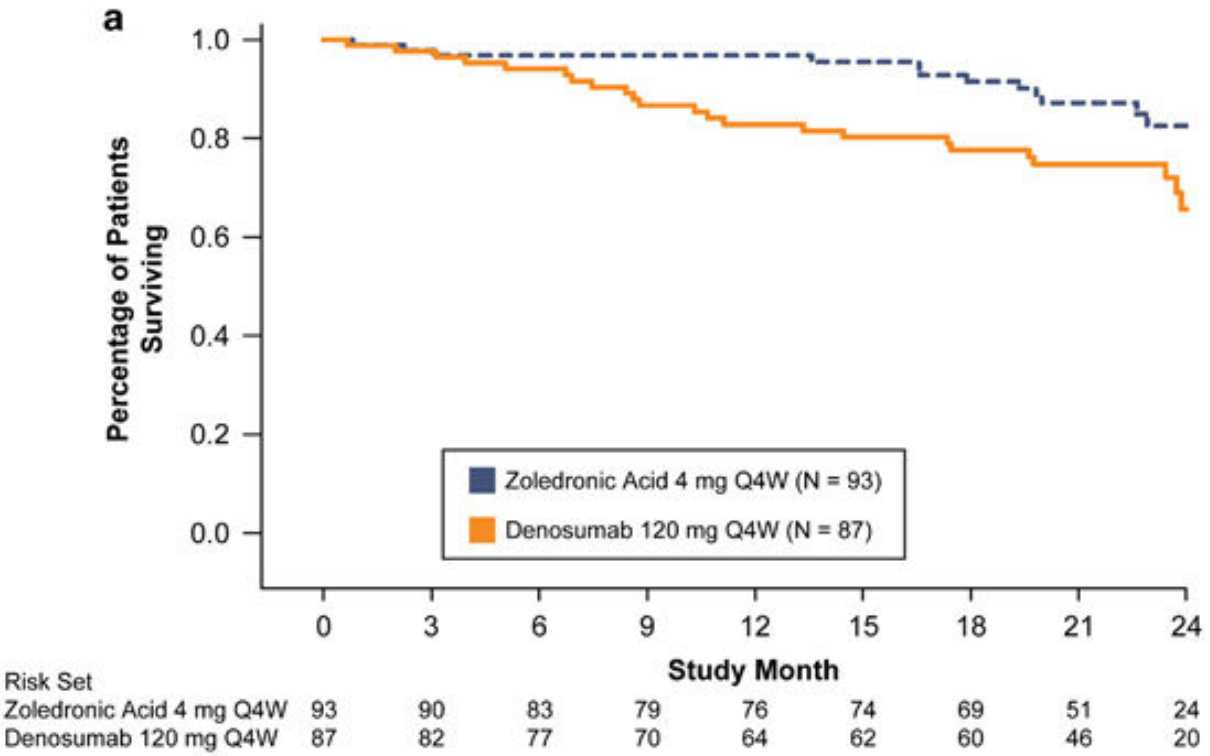
Zoledronic acid
Pamidronate

Rank Ligand Inhibitors

Denosumab

Terpos et al. J Clin Oncol 2013 Jun 20;31(18):2347-57
Morgan GJ, et al Clin Cancer Res. 2013;19:6030-8

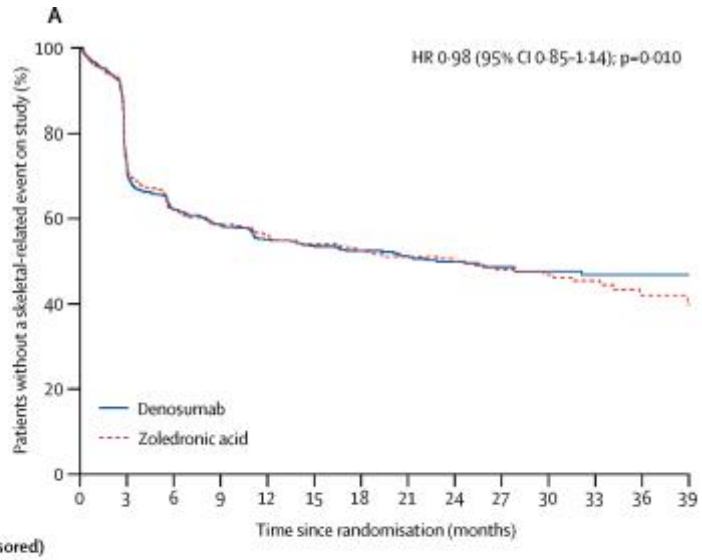
Denosumab vs. Zometa in solid trs & MM(n=1776) OS analysis, MM subset (n=180)



Henry DH, et al. J Clin Oncol. 2011 Mar 20;29(9):1125-32.

Denosumab vs. zometa in newly Dx MM (n=1718) Phase 3

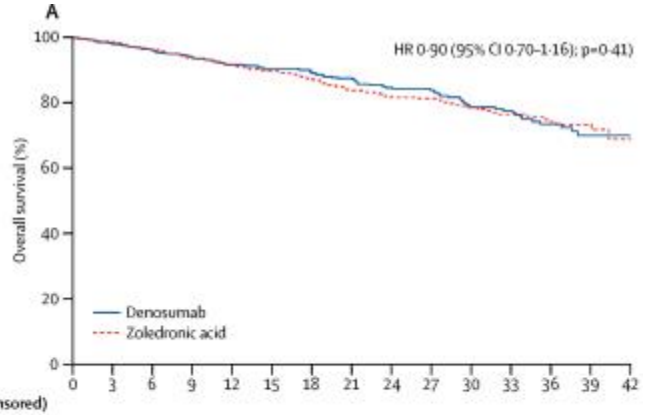
Time to SRE



Number at risk (censored)

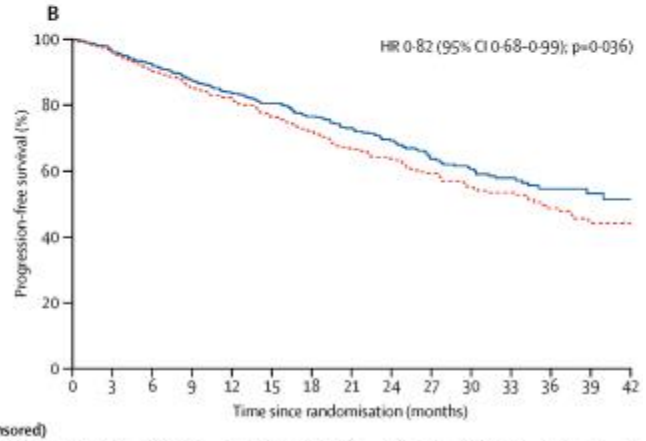
Denosumab	859	583	453	370	303	243	197	160	127	99	77	50	35	22
	(0)	(52)	(49)	(58)	(47)	(53)	(41)	(33)	(29)	(25)	(20)	(26)	(15)	(13)
Zoledronic acid	859	595	450	361	288	239	190	152	125	95	69	48	31	18
	(0)	(34)	(65)	(66)	(59)	(39)	(43)	(33)	(24)	(26)	(24)	(19)	(14)	(12)

OS & PFS



Number at risk (censored)

Denosumab	859	809	737	640	565	477	395	344	288	229	175	130	85	48	19
	(0)	(32)	(58)	(81)	(60)	(81)	(76)	(44)	(45)	(57)	(41)	(43)	(39)	(34)	(29)
Zoledronic acid	859	830	737	652	568	488	414	348	289	233	179	127	87	49	15
	(0)	(17)	(74)	(65)	(71)	(69)	(61)	(52)	(50)	(55)	(47)	(48)	(37)	(37)	(32)



Number at risk (censored)

Denosumab	859	789	703	583	501	411	329	269	214	157	125	82	57	35	14
	(0)	(38)	(55)	(85)	(58)	(73)	(63)	(46)	(42)	(42)	(25)	(38)	(21)	(21)	(20)
Zoledronic acid	859	806	690	584	495	404	324	252	206	159	112	78	53	30	9
	(0)	(22)	(67)	(70)	(66)	(61)	(59)	(49)	(35)	(34)	(37)	(31)	(19)	(19)	(21)

The Lancet Oncology 2018 19, 370-381

BONE DISEASE MANAGEMENT

- Zometa is the standard of care for patients with MM lytic bone disease
- Denosumab is a new standard of care for patients with renal insufficiency & bone disease
  - It may replace “Bisphosphonates” if Survival benefit can be confirmed in other studies.

Thank you