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September 9th, 2021

„Maintenance strategies for MM“

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NCT UK HD

Disclosures

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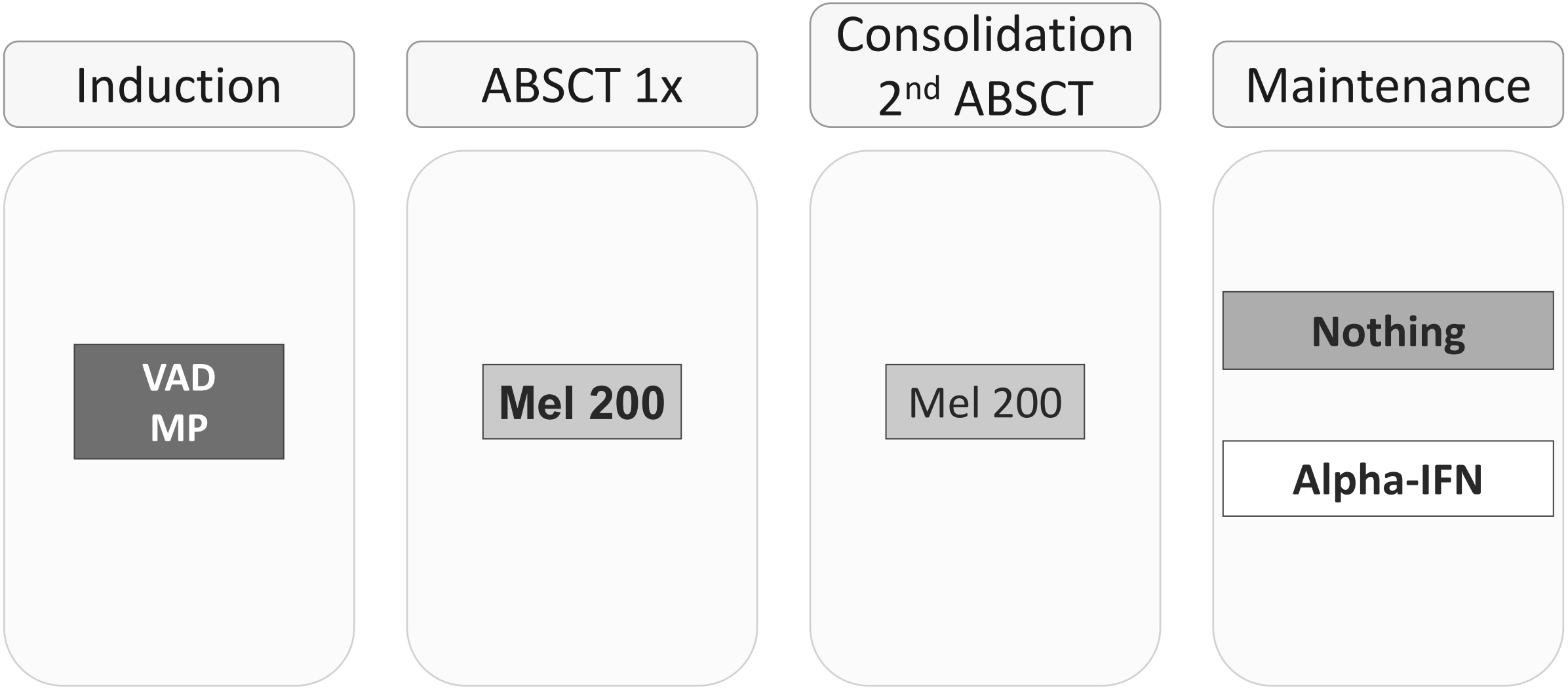
UNIVERSITÄTS KLINIKUM HEIDELBERG

Disclosures

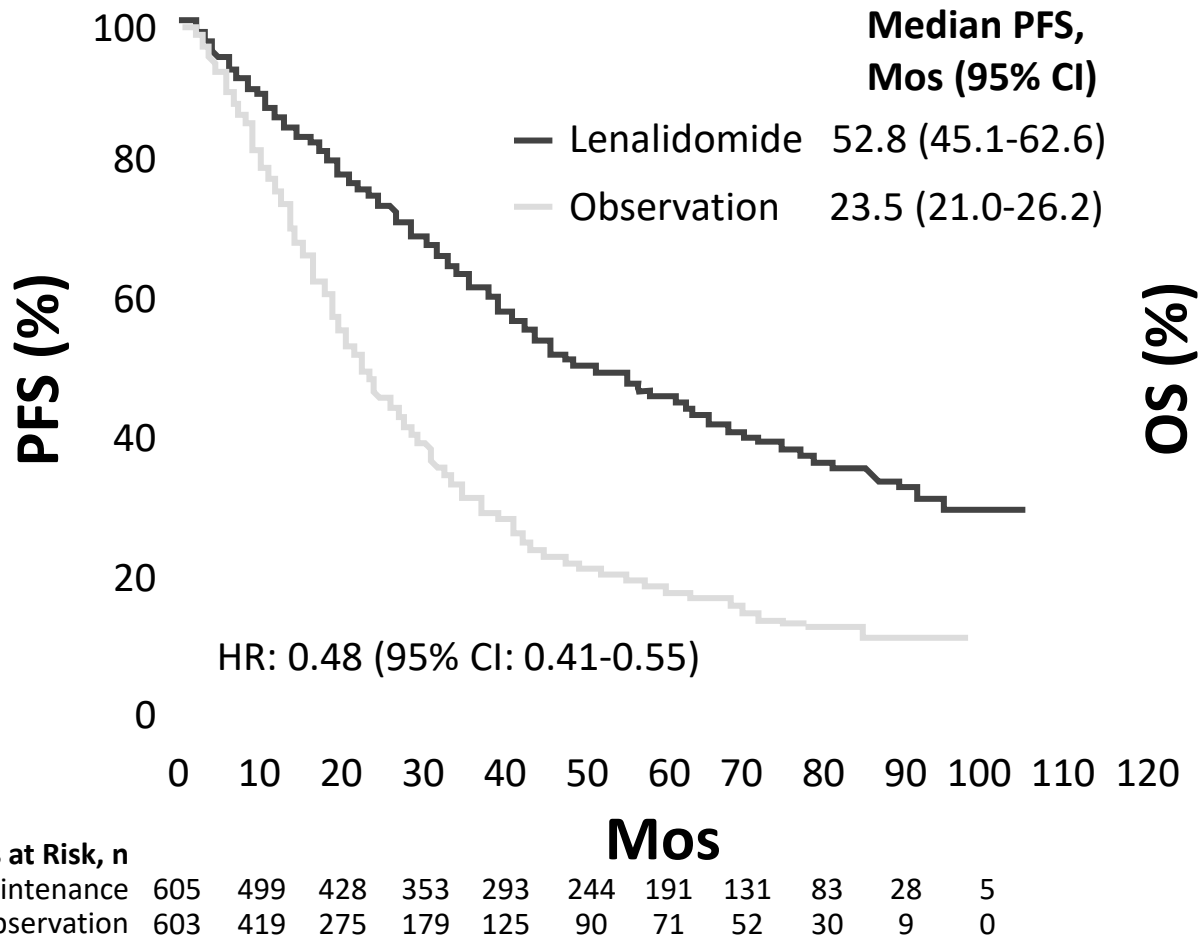
- Honoraria
  - Amgen, BMS, Celgene, Chugai, GSK, Janssen, Novartis, Omnia Med Deutschland, Sanofi
- Consulting or advisory role
  - Adaptive Biotechnology, Amgen, BMS, Celgene, Millenium Pharmaceuticals Inc., Molecular Partners AG Zürich, Janssen, Sanofi, Takeda
- Research funding
  - Amgen, BMS, Celgene, Chugai, Janssen, Incyte, Merck Sharp and Dohme (MSD), Molecular Partners AG Zürich, Mundipharma, Novartis, Sanofi, Takeda
- Travel, accommodations, expenses
  - Amgen, BMS, Celgene, Chugai, GSK, Janssen, Novartis, Takeda, Omnia Med Deutschland, Sanofi

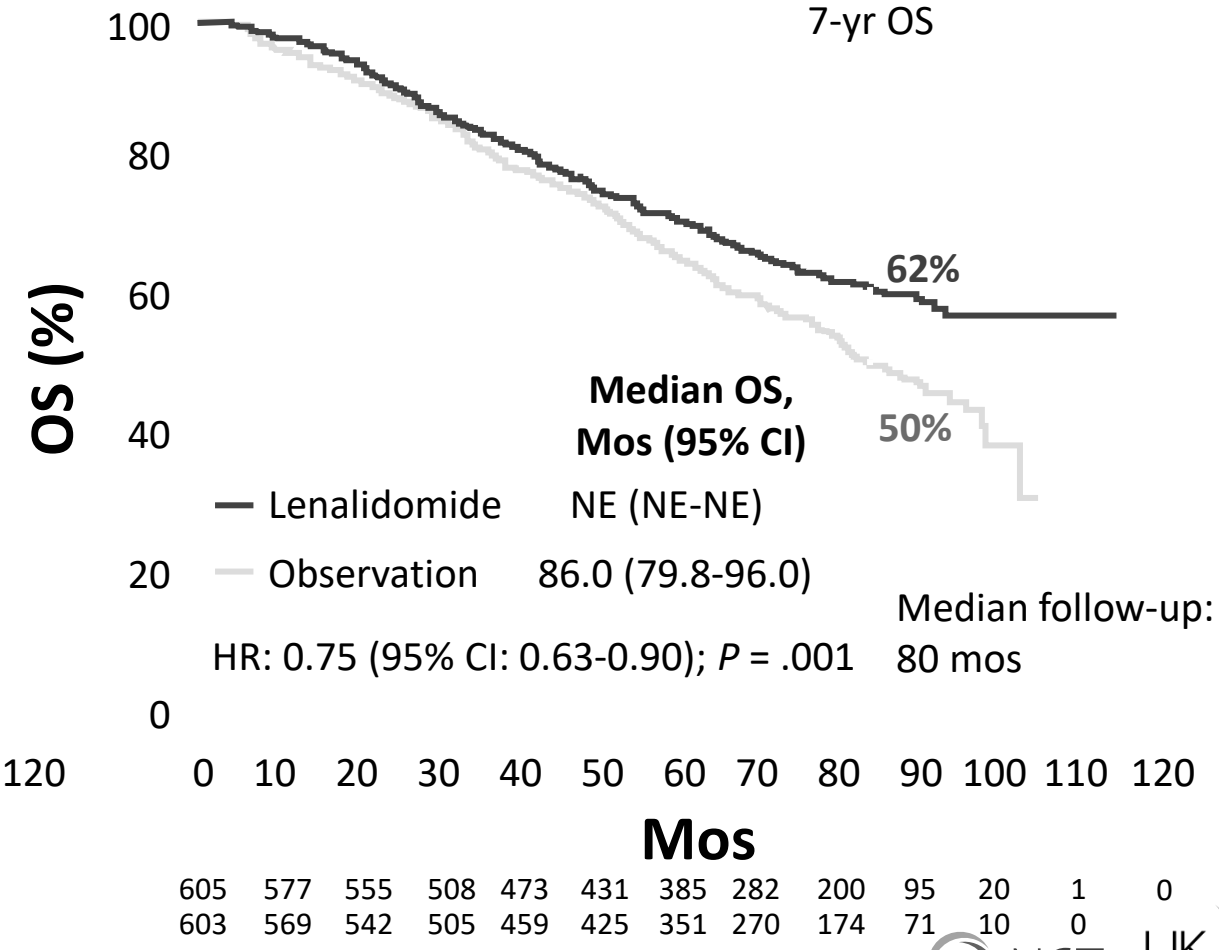
Drugs before and after ABSCT in the Early Days of HDT



Adapted from Einsele, DGHO Slides 2012

PFS and OS With Lenalidomide Maintenance After ASCT in MM: Meta-analysis of 3 Phase III Trials





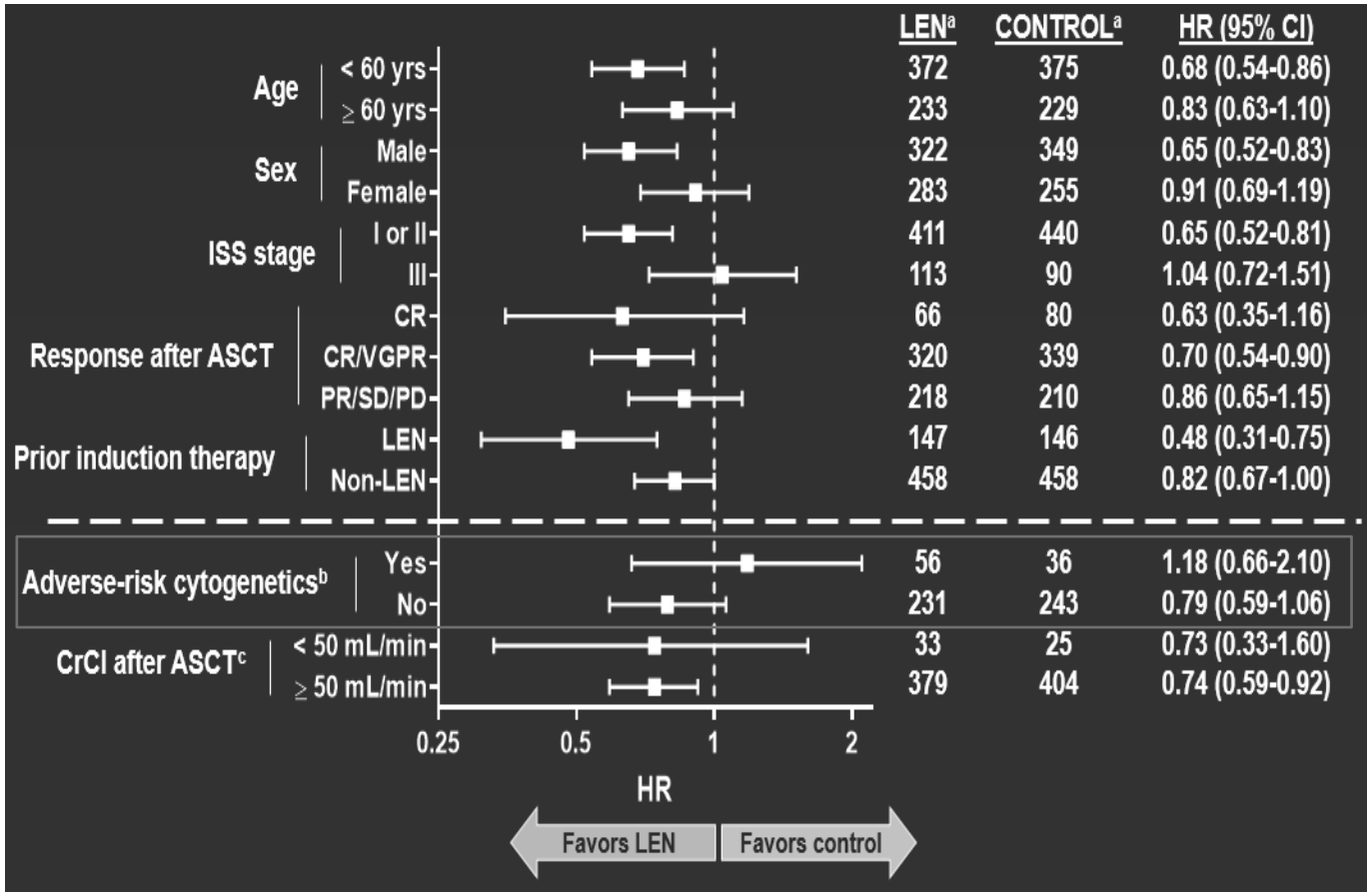
Patients at Risk, n

Len maintenance	605	499	428	353	293	244	191	131	83	28	5	605	577	555	508	473	431	385	282	200	95	20	1	0
Observation	603	419	275	179	125	90	71	52	30	9	0	603	569	542	505	459	425	351	270	174	71	10	0	

McCarthy. JCO. 2017;35:3279.

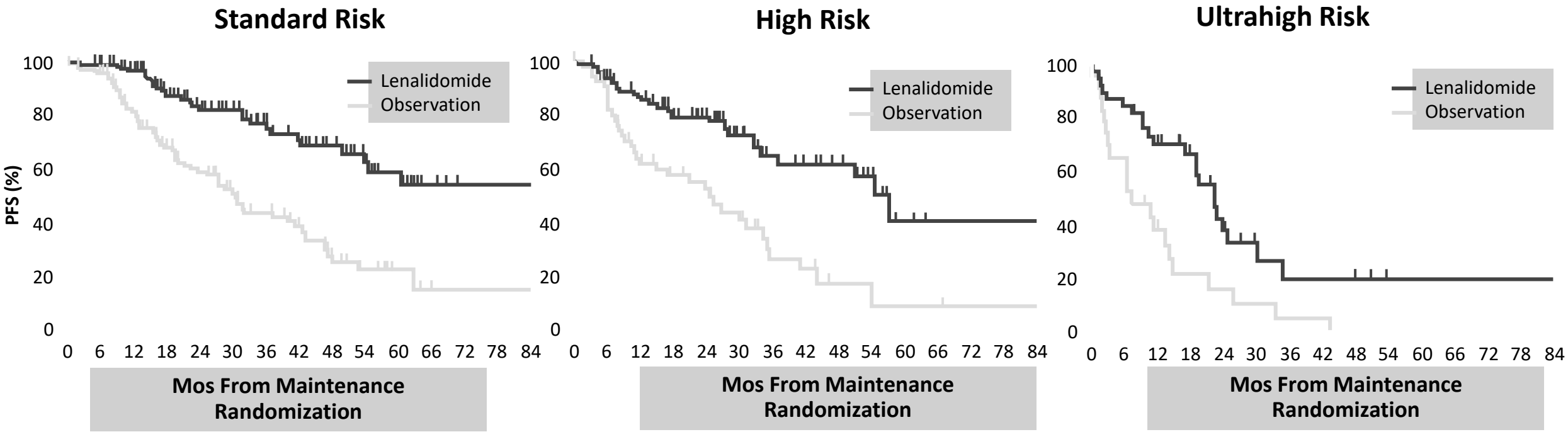
Meta-analysis of Lenalidomide maintenance therapy:
Overall survival – subgroup analysis

- 3 studies included: IFM 2005-02; CALGB 100104 (Alliance); GIMEMA-RVMM-PI-209



McCarthy et al. J Clin Oncol 2017;35:3279-3289

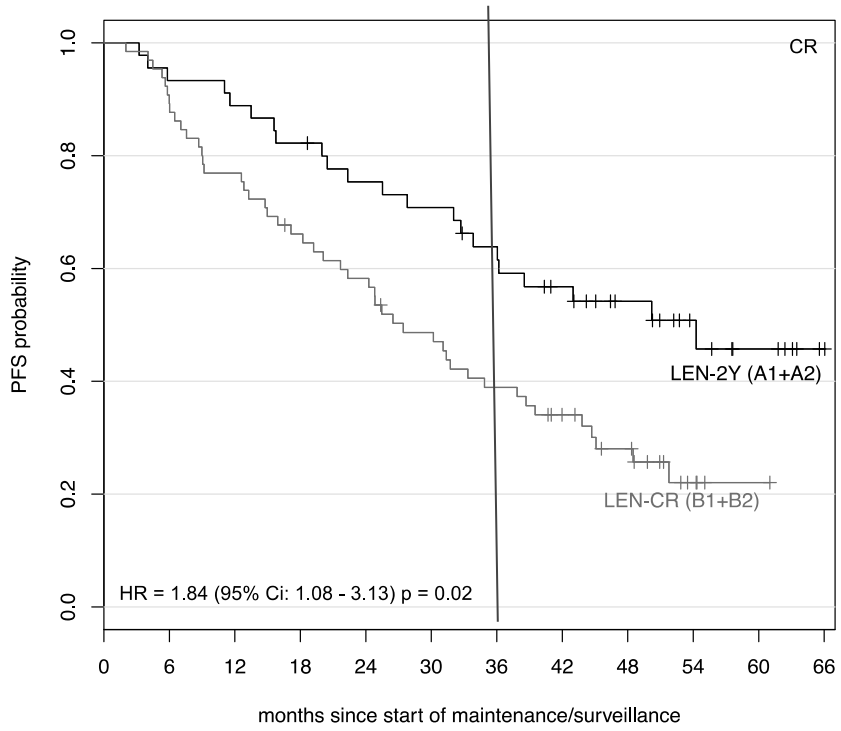
Phase III Myeloma XI Trial: PFS With Len Maintenance in ASCT-Eligible Patients by Cytogenetic Risk

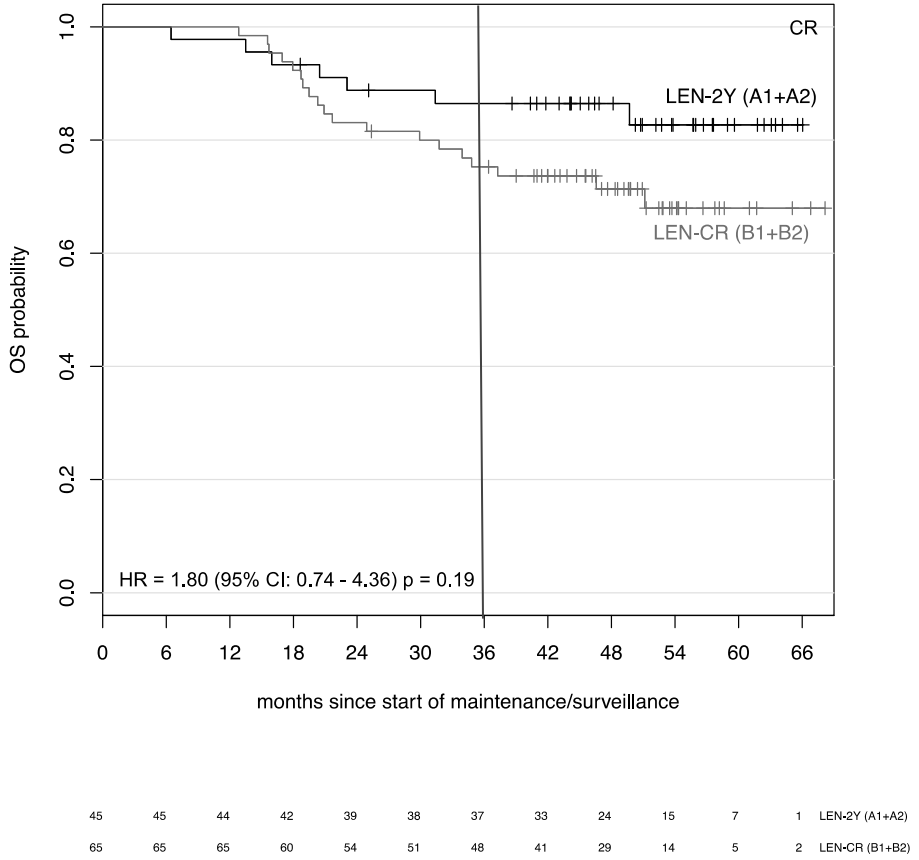


- High risk: presence of either t(4;14), t(14;16), t(14;20), del 17p, or gain 1q
- Ultrahigh risk: presence of more than 1 of these lesions
- Standard risk: absence of these lesions

Jackson. Lancet Oncol. 2019;20:57.

GMMG MM5-Trial CR: Landmark (after cons.) PFS + OS





Multiple Myeloma:
First Line Treatment – EHA/ESMO Guidelines 2021

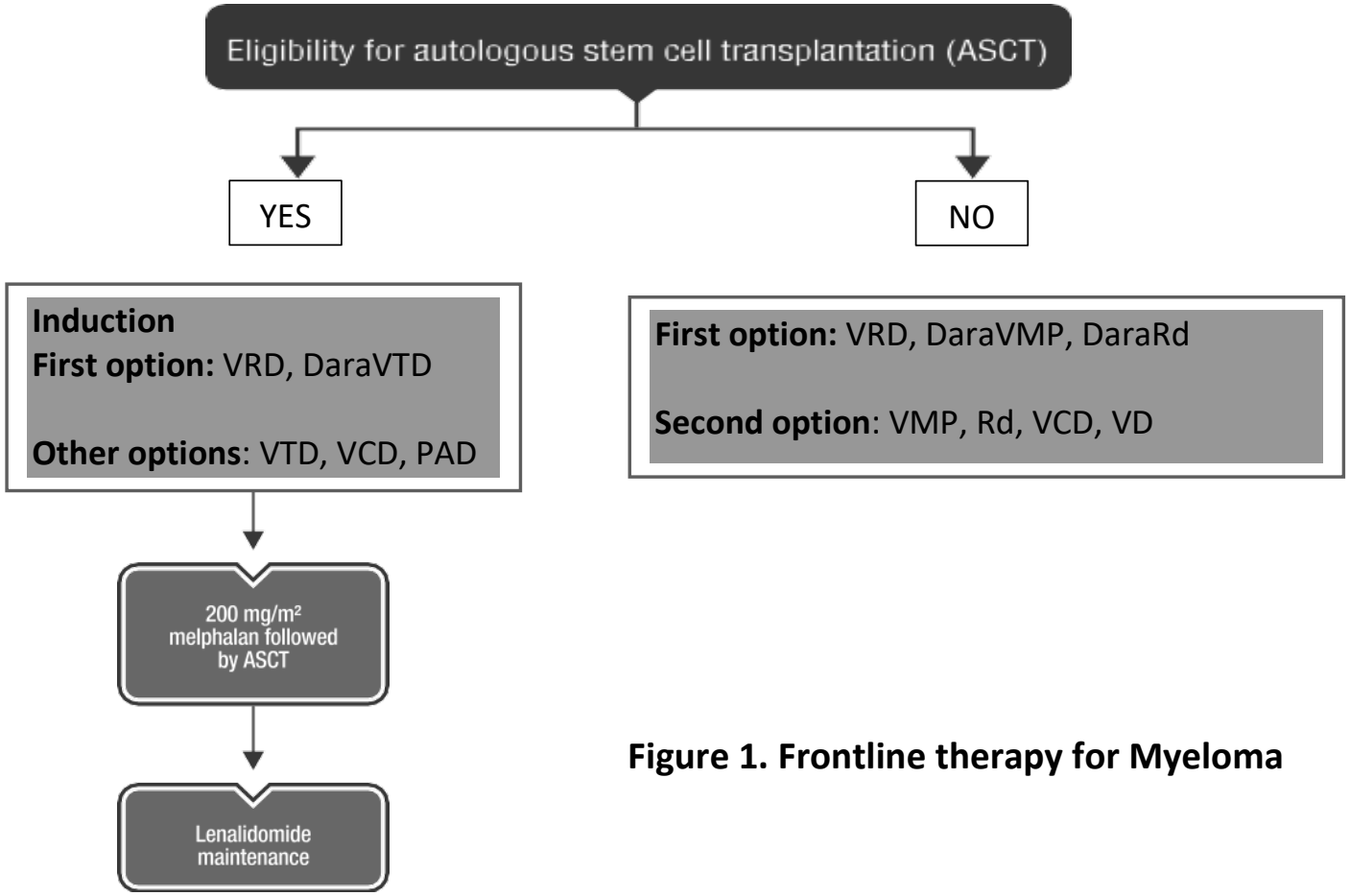


Figure 1. Frontline therapy for Myeloma

Dimopoulos et al. 2021

ORIGINAL ARTICLE

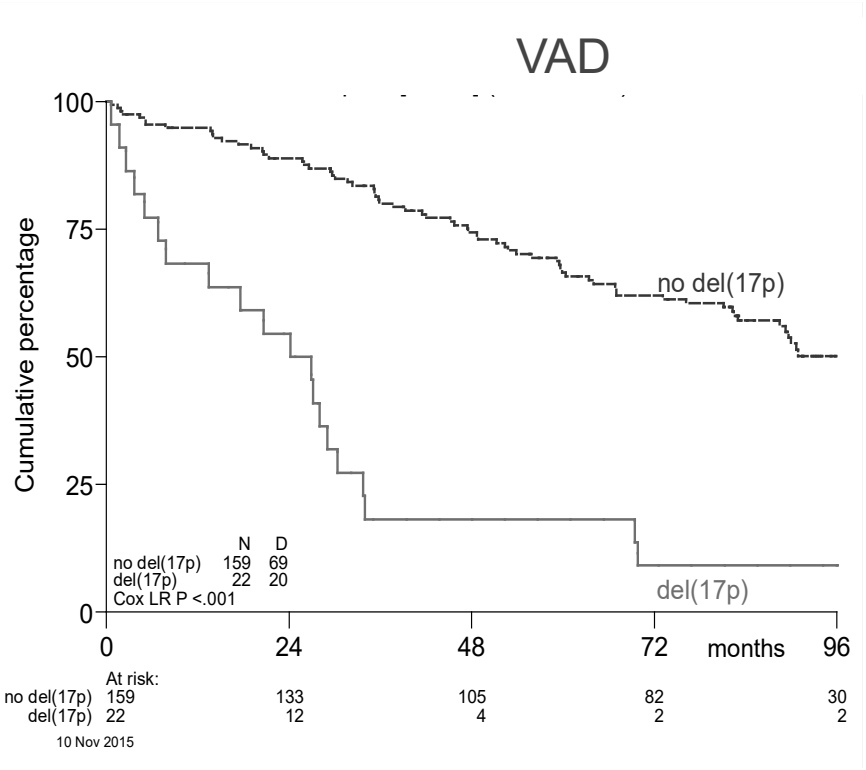
Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial

H Goldschmidt[1,2], HM Lokhorst[3], EK Mai[1], B van der Holt[4], IW Blau[5], S Zweegman[6], KC Weisel[7], E Vellenga[8], M Pfreundschuh[9], MJ Kersten[10], C Scheid[11], S Croockewit[12], R Raymakers[13], D Hose[1], A Potamianou[14], A Jauch[15], J Hillengass[1], M Stevens-Kroef[16], MS Raab[1], A Broijl[17], HW Lindemann[18], GMJ Bos[19], P Brossart[20], M van Marwijk Kooy[21], P Ypma[22], U Duehrsen[23], RM Schaafsma[24], U Bertsch[1], T Hielscher[25], Le Jarari[26], HJ Salwender[27] and P Sonneveld[17]

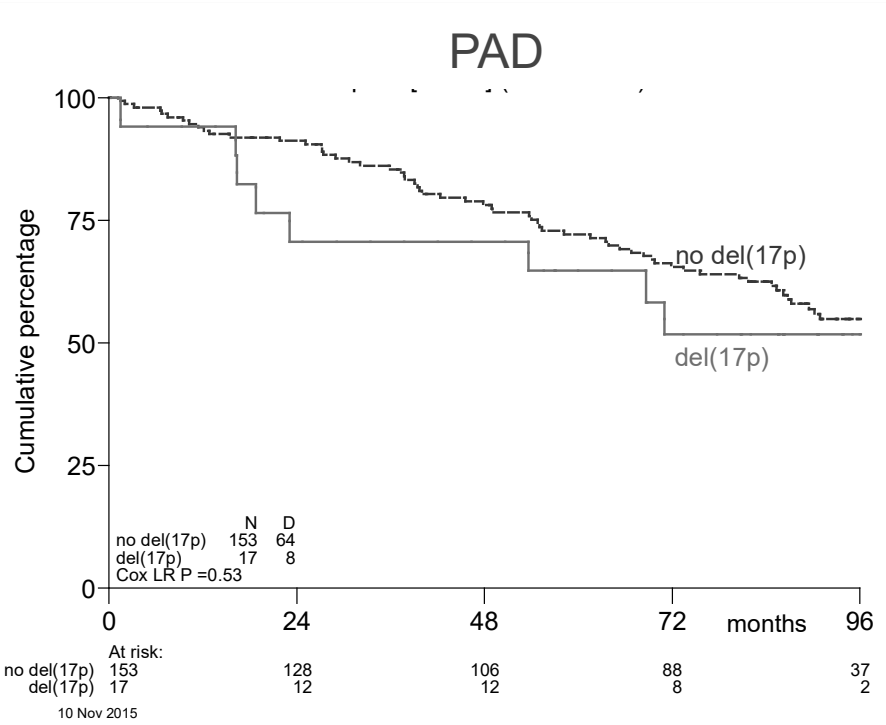
Sonneveld et al., JCO 2013

Goldschmidt et al., Leukemia 2018

HOVON 65/GMMGHD4: OS by Treatment Arm Subgroup with del(17/17p)



p<0.001



p=0.5

Neben et al., Blood 2012

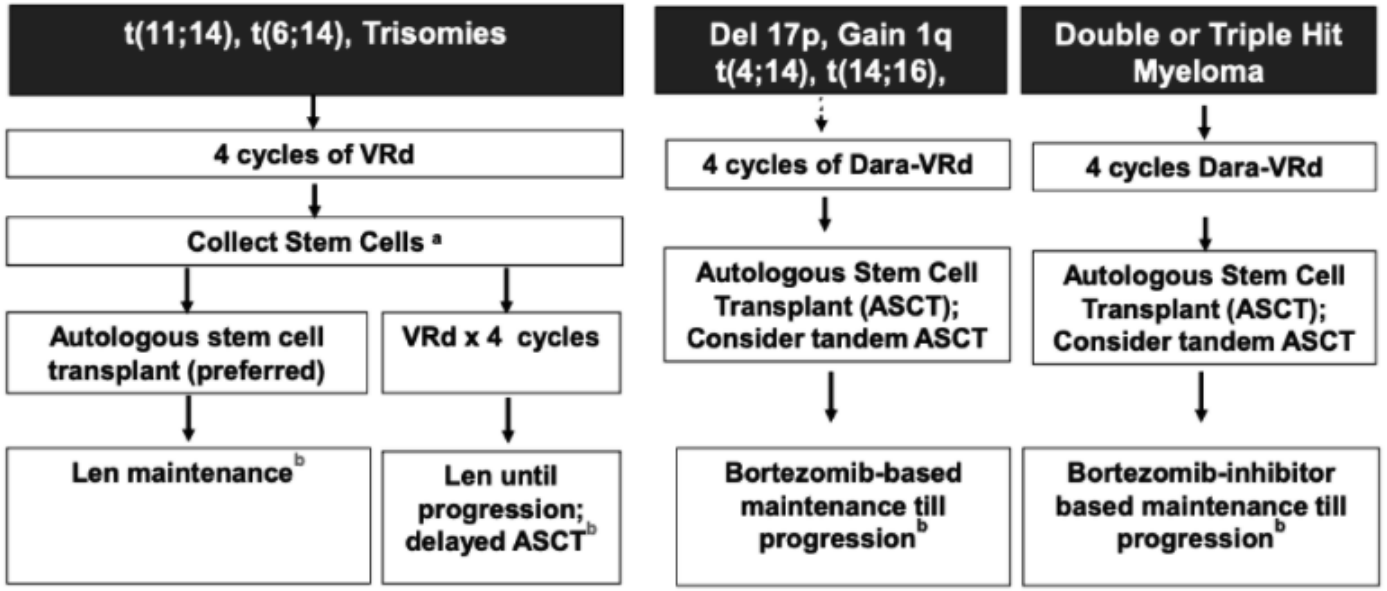
Goldschmidt et al., Leukemia 2017

Mayo Clinic Off-Study Treatment Algorithm for Transplant-Eligible Myeloma Patients

MAYO CLINIC

mSMART – Off-Study

Transplant Eligible



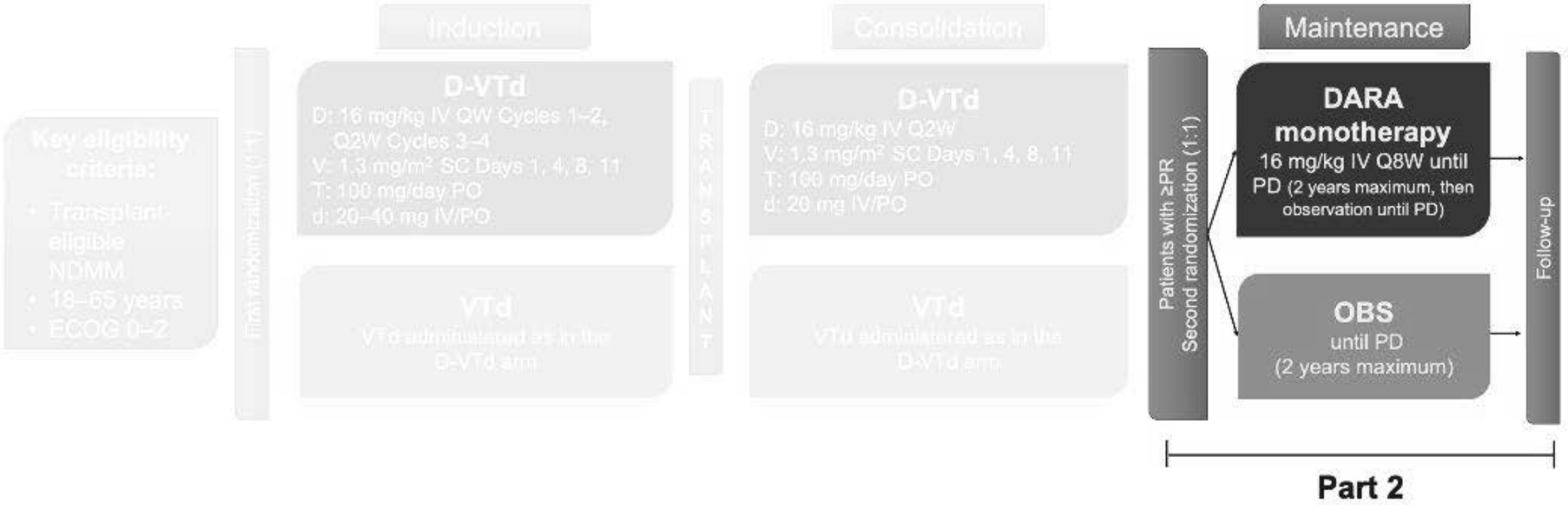
[a] If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor; [b] Duration usually until progression based on tolerance

VRd, Bortezomib, lenalidomide, dexamethasone; Dara, daratumumab

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. v18 //last reviewed June 2020

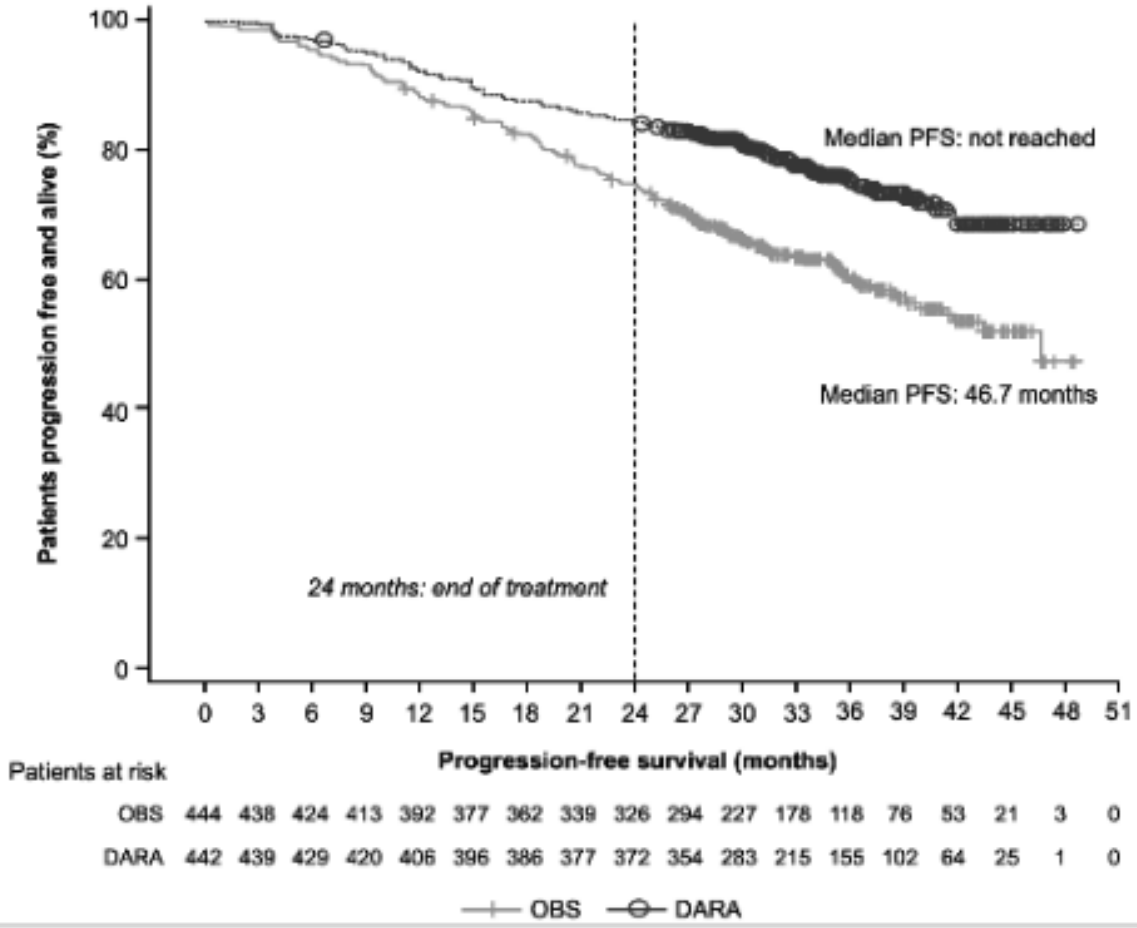
CASSIOPEIA Part 2 Study Design

- Patients who completed consolidation and achieved ≥PR were re-randomized 1:1 to DARA 16 mg/kg IV every 8 weeks or OBS (no maintenance) for 2 years



DARA Significantly Improved PFS From Second Randomization vs OBS

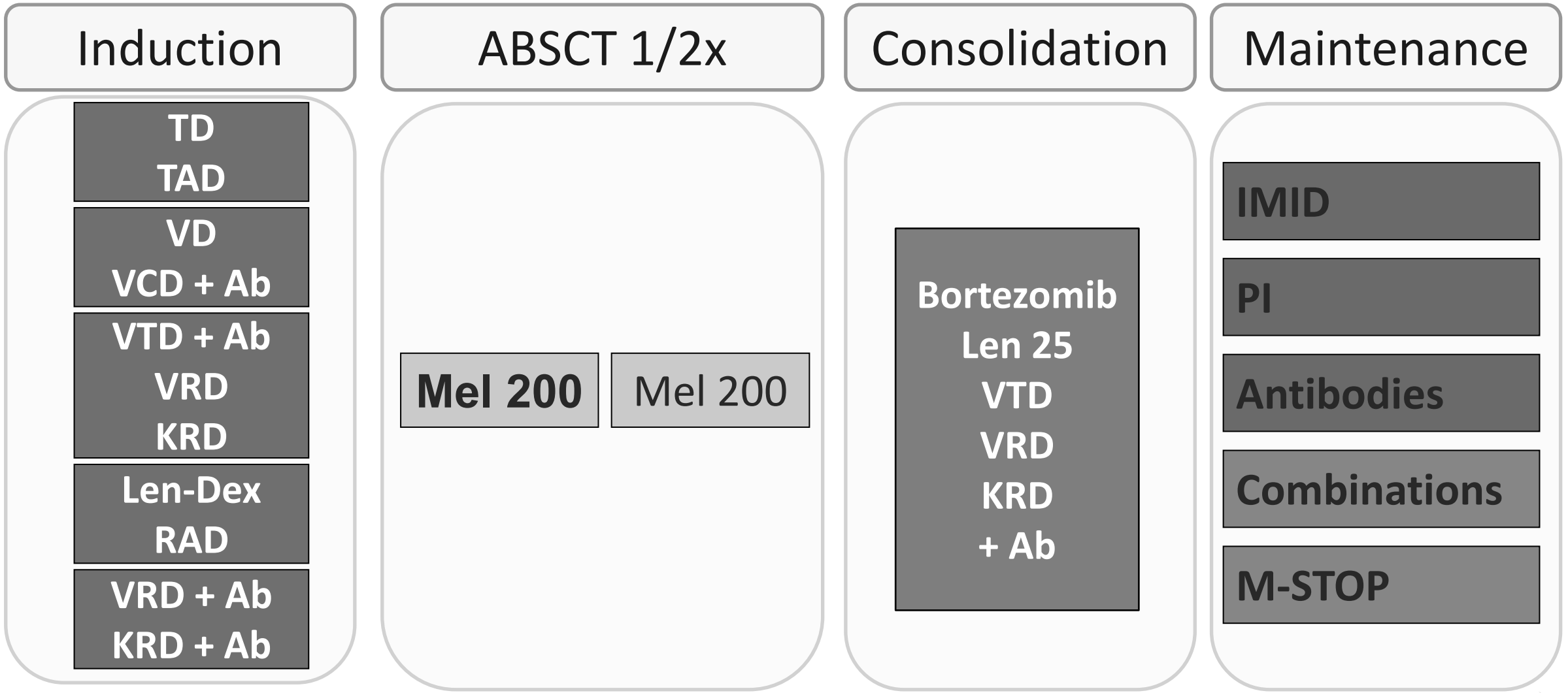
Median follow-up:
35.4 months
from second
randomization



HR 0.53
(95% CI 0.42–0.68)
P<0.0001

CI, confidence interval; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival.

Increasing Number of New Drugs Before and After ABSCT

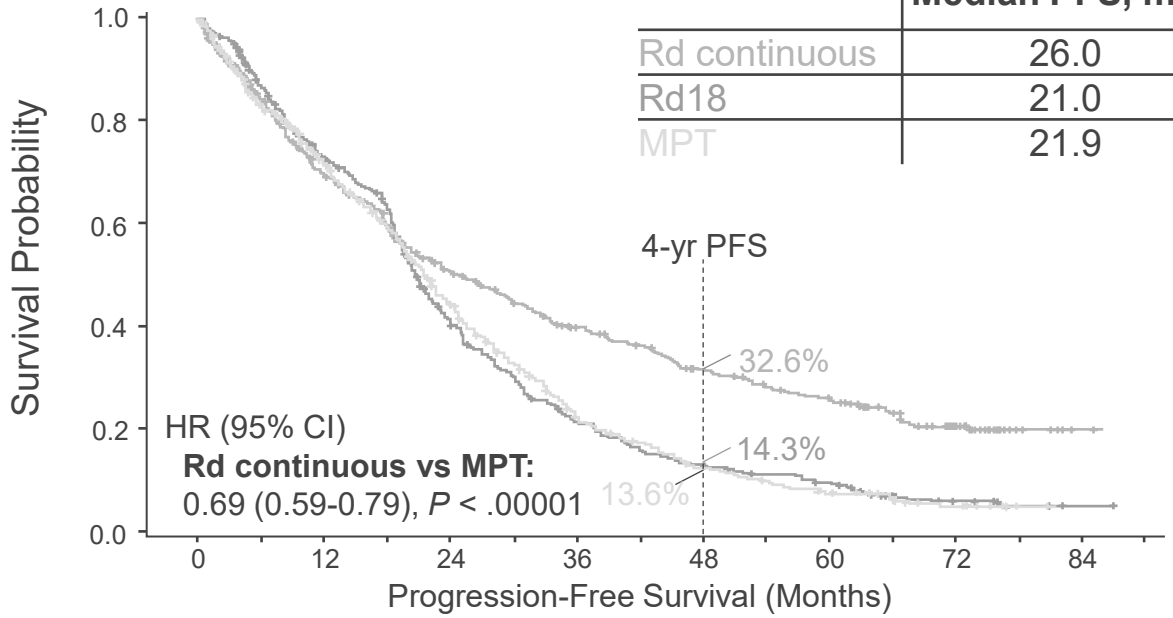


Adapted from Einsele, DGHO Slides 2012

Final analysis of survival outcomes in first trial *PFS*

- Results remain consistent nearly 3 yrs after the original analysis of the primary endpoint, PFS:
  - Rd continuous significantly improved PFS vs MPT ($P < .00001$)

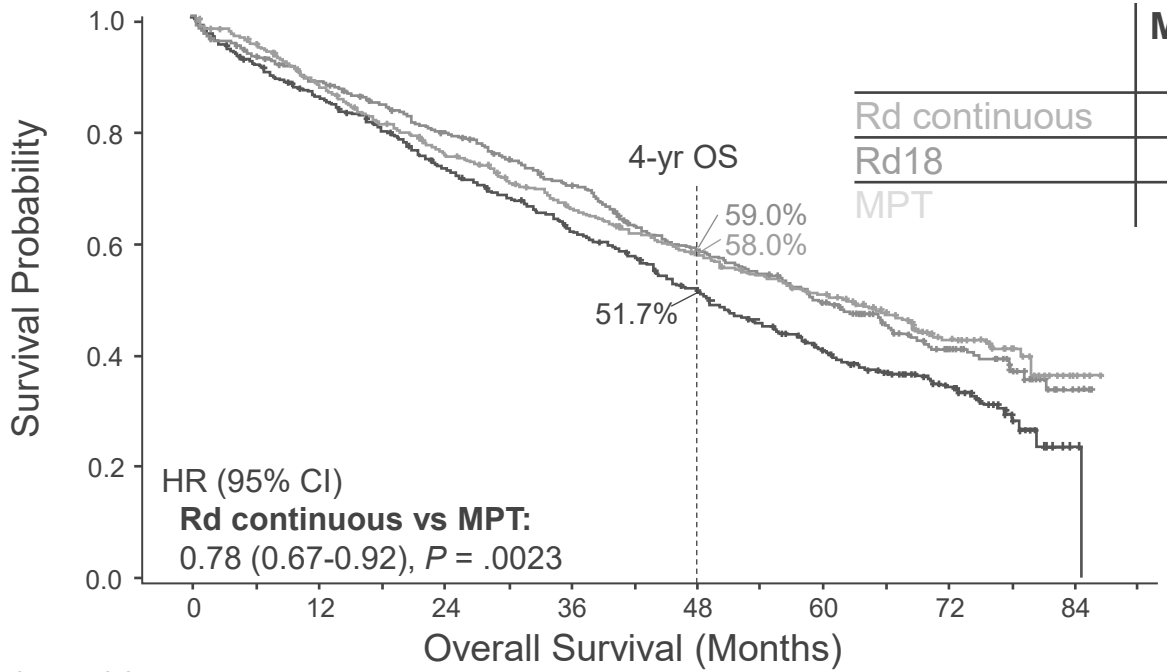
	Median PFS, mos	4-yr PFS, %
Rd continuous	26.0	32.6
Rd18	21.0	14.3
MPT	21.9	13.6



Number at risk								
Rd continuous	535	330	225	160	117	91	37	2
Rd18	541	337	174	90	55	39	10	1
MPT	547	312	180	87	48	28	10	0

HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Final analysis of survival outcomes in first trial *OS*



	Median OS, mos	4-yr OS, %
Rd continuous	59.1	59.0
Rd18	62.3	58.0
MPT	49.1	51.7

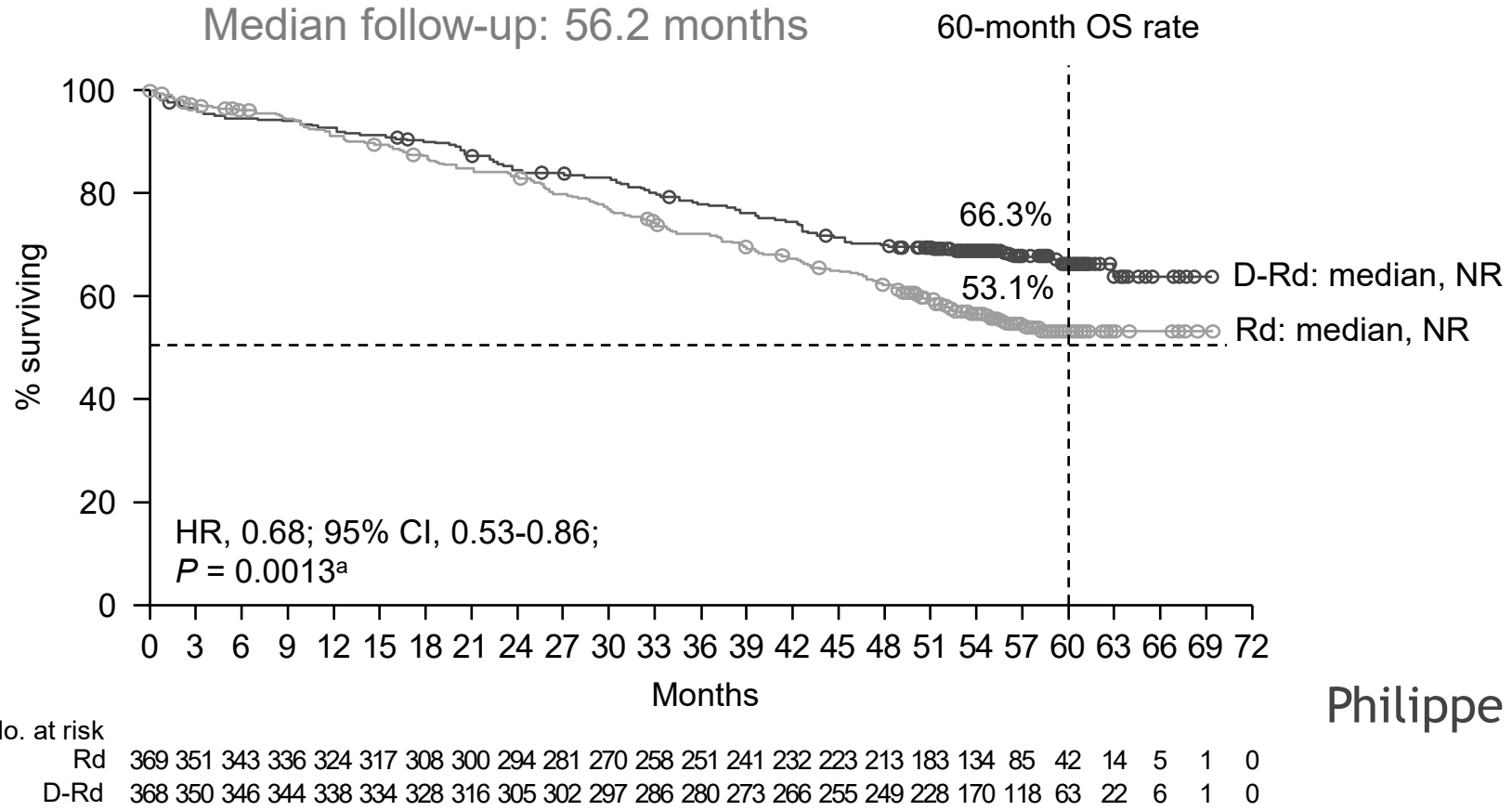
Number at risk

Rd continuous	535	457	403	340	277	226	97	6
Rd18	541	465	394	333	283	239	96	7
MPT	547	448	375	313	254	192	78	2

- Rd continuous significantly extended OS vs MPT (*P* = .0023) and resulted in similar OS vs Rd18
- In patients achieving ≥ VGPR, median OS was 79.5 mos with Rd continuous, 55.7 mos with MPT, and 80.1 mos with Rd18

HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; OS, overall survival; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; VGPR, very good partial response.

MAIA Trial: OS

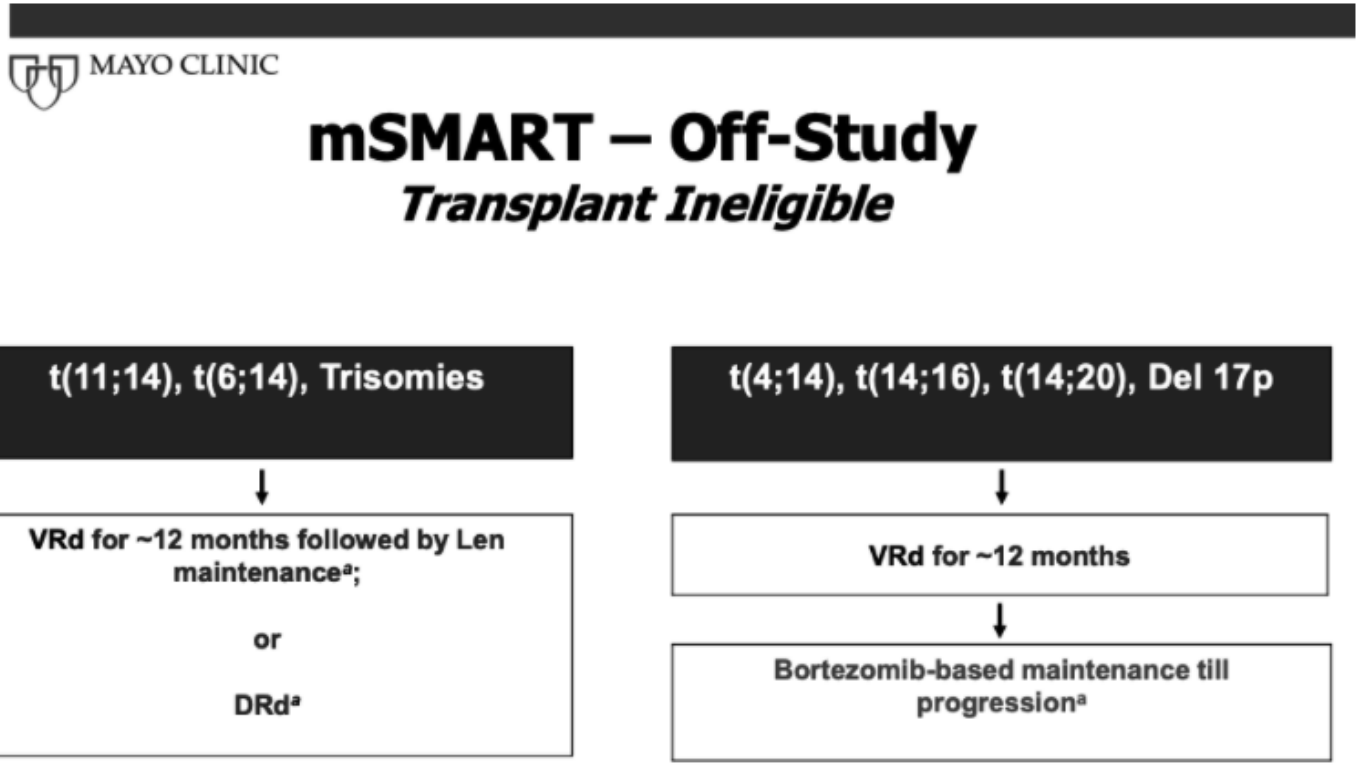


Philippe Moreau IMW 2021

D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

[a]*P* = 0.0013 is statistically significant, crossing the prespecified stopping boundary of *P* = 0.0414.

Mayo Clinic Off-Study Treatment Algorithm for Transplant-Ineligible Myeloma Patients



[a] *Duration is usually until progression, based on tolerance*

VRd, Bortezomib, lenalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone

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. v18 //last reviewed June 2020

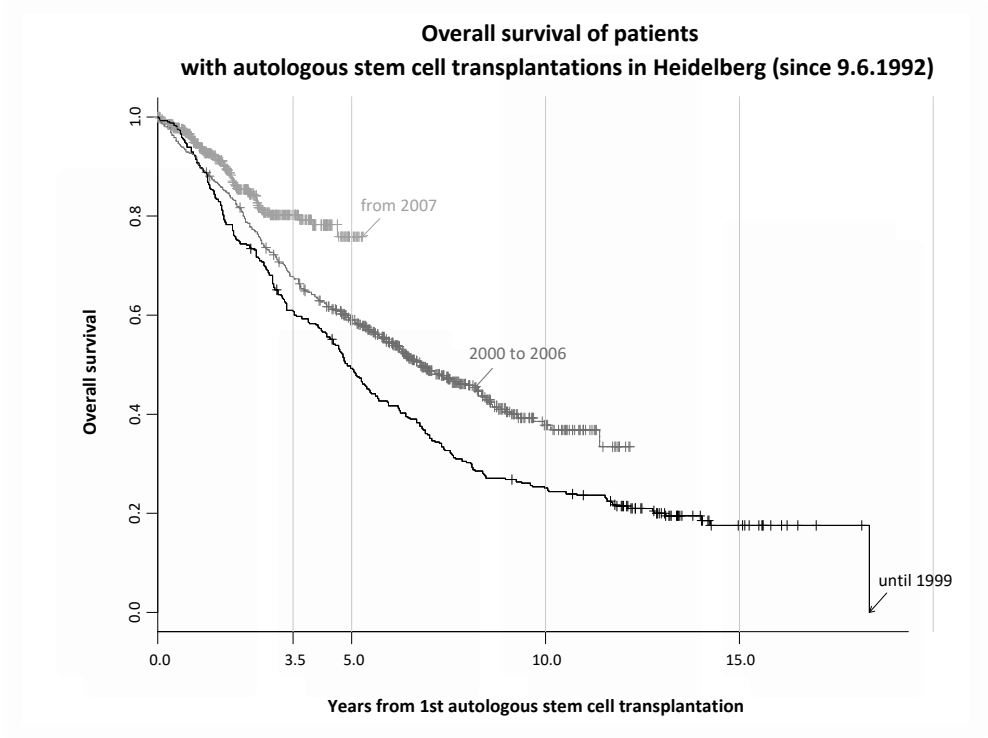
Ongoing Phase 3 and Randomized Phase 2 Trials 2020

Table 4 Ongoing phase 3 and randomized phase 2 comparative studies of continuous therapy and maintenance treatment approaches that have not yet reported data at the time of publication (ClinicalTrials.gov, April 26, 2019).

Study	NCT number	Phase	Maintenance/continuous treatment regimens	*N*	Primary endpoint	Estimated 1° completion date
Post-ASCT maintenance therapy						
GEM2014MAIN	NCT02406144	3	Ixazomib-Rd vs. Rd	316	PFS	Not known
MMRC	NCT02253316	2	Ixazomib vs. R	240	MRD	November 2019
NCI-2015-00138	NCT02389517	2	Ixazomib-Rd vs. R	86	MRD	March 2020
ATLAS	NCT02659293	3	Carfilzomib-Rd vs. R	180	PFS	March 2019
FORTE	NCT02203643	2	Carfilzomib-R vs. R	477	≥VGPR rate post-induction	October 2016[a]
Cassiopeia	NCT02541383	3	Daratumumab vs. observation	1085	PFS	August 2022
EMN18[b]	NCT03896737	2	Daratumumab-ixazomib vs. ixazomib	400	MRD-neg rate; 2-year PFS	February 2022
AURIGA/MMY3021	NCT03901963	3	Daratumumab-R vs. R	214	MRD-neg rate at 12 months	May 2021
GRIFFIN/MMY2004	NCT02874742	2	Daratumumab-R vs. R	222	sCR rate post-consolidation	January 2019
DraMMatic[c]	SWOG1803/BMT CTN 1706	3	Daratumumab-R vs. R	Not known	Not known	Not known
GMMG-HD6	NCT02495922	3	Elotuzumab-R vs. R	564	PFS	June 2020
GMMG-HD7	NCT03617731	3	Isatuximab-R vs. R	662	PFS	May 2025
Continuous frontline therapy, non-ASCT setting						
TOURMALINE-MM2	NCT01850524	3	Ixazomib-Rd vs. placebo-Rd	701	PFS	February 2018
COBRA	NCT03729804	3	Carfilzomib-Rd vs. VRd	250	PFS	December 2021
GEM2017FIT	NCT03742297	3	Daratumumab + carfilzomib-Rd vs. carfilzomib-Rd vs. VMP-Rd	300	CR rate	October 2020
Perseus	NCT03710603	3	Daratumumab-VRd–daratumumab-R vs. VRd–R	690	PFS	May 2029
MMY3019	NCT03652064	3	Daratumumab-VRd–daratumumab-Rd vs. VRd–Rd	360	MRD-neg rate	March 2024
ELOQUENT-1	NCT01335399	3	Elotuzumab-Rd vs. Rd	750	PFS	May 2019
SWOG S1211	NCT01668719	2	Elotuzumab-VRd vs. VRd	122	PFS	May 2019
IMROZ	NCT03319667	3	Isatuximab-VRd–isatuximab-Rd vs. VRd–Rd	440	PFS	December 2022
Post-induction maintenance therapy, non-ASCT setting						
TOURMALINE-MM4 + China continuation	NCT02312258 NCT03748953	3	Ixazomib vs. placebo	706 105	PFS	August 2019 September 2024
Myeloma XIV (FiTNEss)	NCT03720041	3	Ixazomib-R vs. placebo-R (post-ixazomib-Rd)	740	PFS	December 2024
X16108	NCT03733691	2	Ixazomib-R vs. ixazomib	52	PFS, AEs	December 2023
AGMT_MM-2	NCT02891811	2	Carfilzomib vs. observation	146	Post-induction ORR	September 2023

AEs adverse events, *ASCT* autologous stem cell transplant, *CR* complete response, *MRD-neg* negative for minimal residual disease, *ORR* overall response rate, *PFS* progression-free survival, *R* lenalidomide, *Rd* lenalidomide-dexamethasone, *VMP* bortezomib-melphalan-prednisone, *VRd* bortezomib-lenalidomide-dexamethasone.
[a]Data reported from induction/consolidation phase[63]; data not yet reported from the randomized maintenance phase of the study.
[b]Includes information from https://www.myeloma-europe.org/trials/emn-18/.
[c]Information from https://www.swog.org/clinical-trials/s1803.

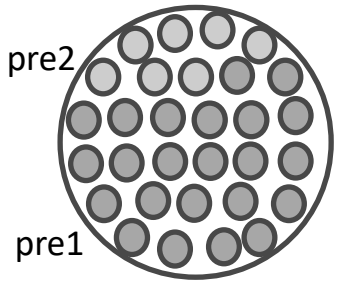
Multiple Myeloma – Heidelberg Center
20 Years ABSCT (n = 1486 pts)



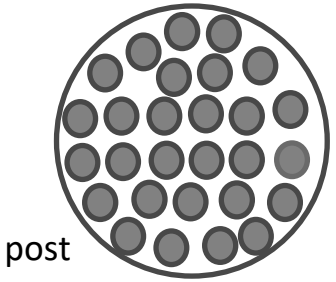
Hillengaß et al., J Cancer Res Clin Oncol. 2013

Regulatory differences and clonal evolution in RRMM

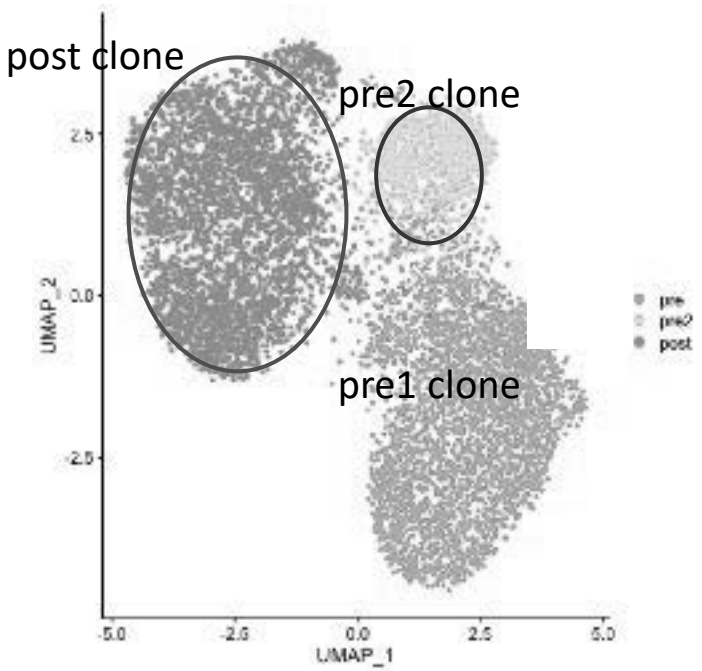
Clonal composition (pre treatment)



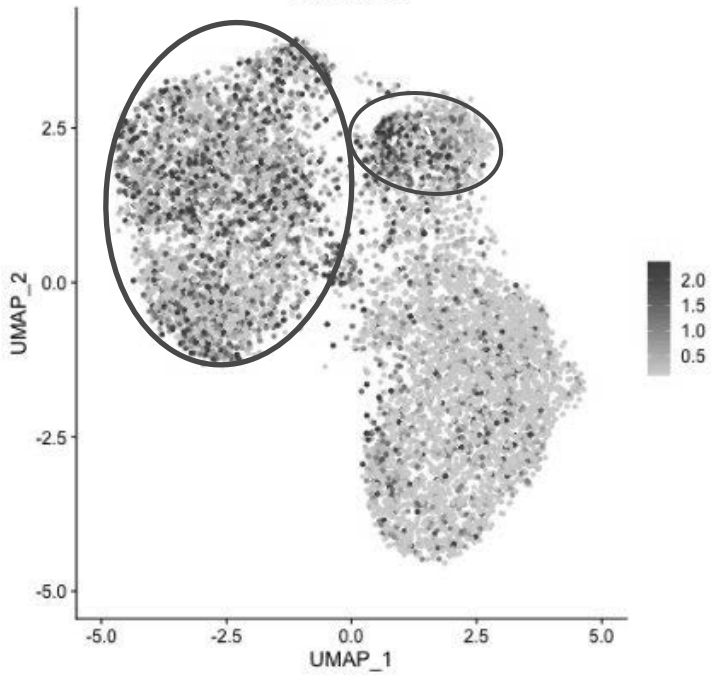
Clonal composition (post treatment)



scATAC-seq clustering



NFKB2 activity



By courtesy of A. Poos, N. Prokoph, M. Raab, K. Rippe, N. Weinhold
Presentation at ASH 2020 and manuscript in preparation

Thank you for your attention!