Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Vittorio Montefusco

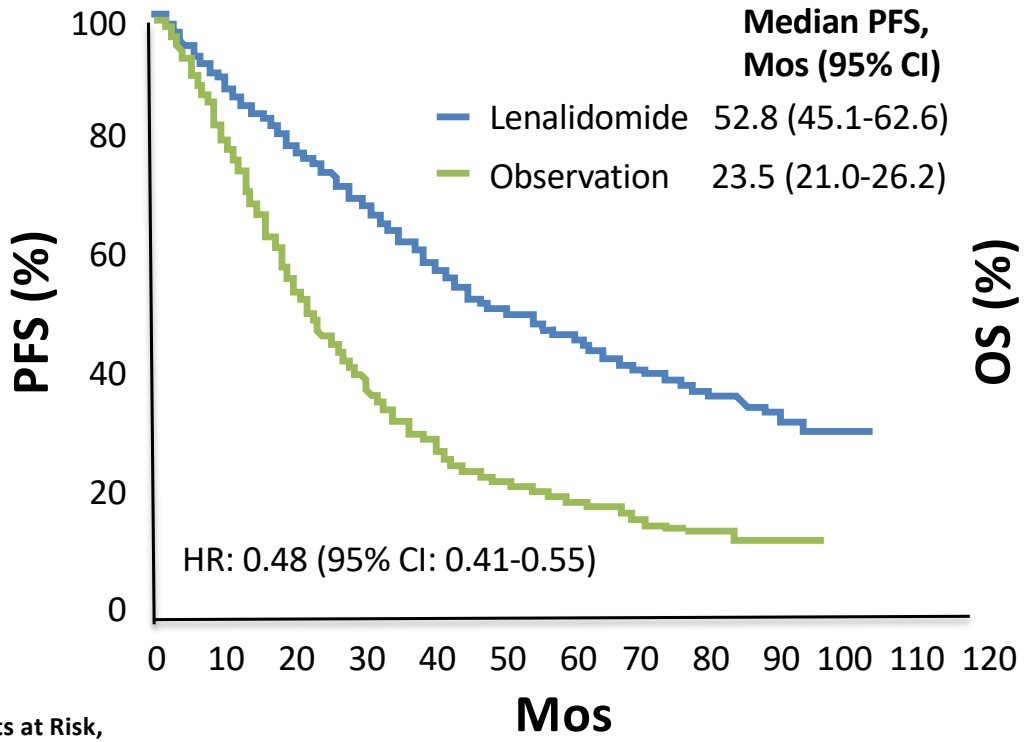
Terapia di prima linea del paziente candidato ad ASCT

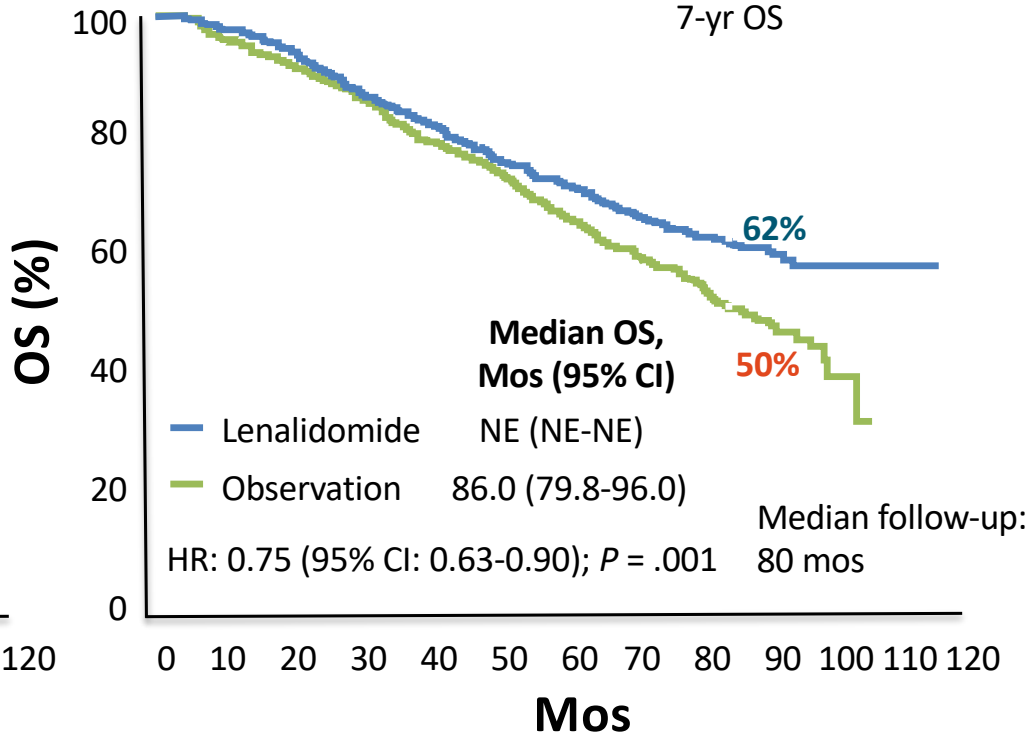
Mantenimento single-agent con IMiD o anti-CD38

Coordinatore Scientifico
Michele CAVO

Comitato Scientifico
Michele CAVO
Maria Teresa PETRUCCI

PFS and OS with Lenalidomide Maintenance after ASCT in MM: Meta-analysis of phase III trials



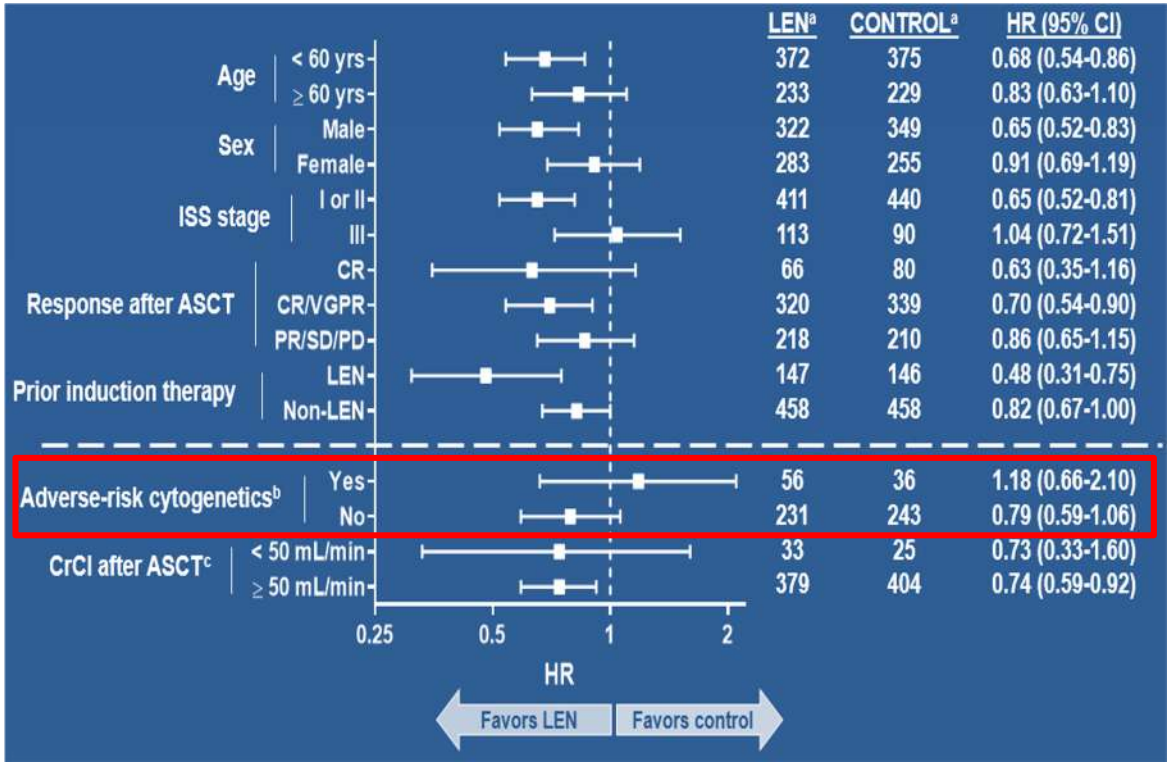


Patients at Risk,																								
n	605	499	428	353	293	244	191	131	83	28	5	605	577	555	508	473	431	385	282	200	95	20	1	0
Len maintenance	603	419	275	179	125	90	71	52	30	9	0	603	569	542	505	459	425	351	270	174	71	10	0	
Observation																								

McCarthy. JCO. 2017;35:3279.

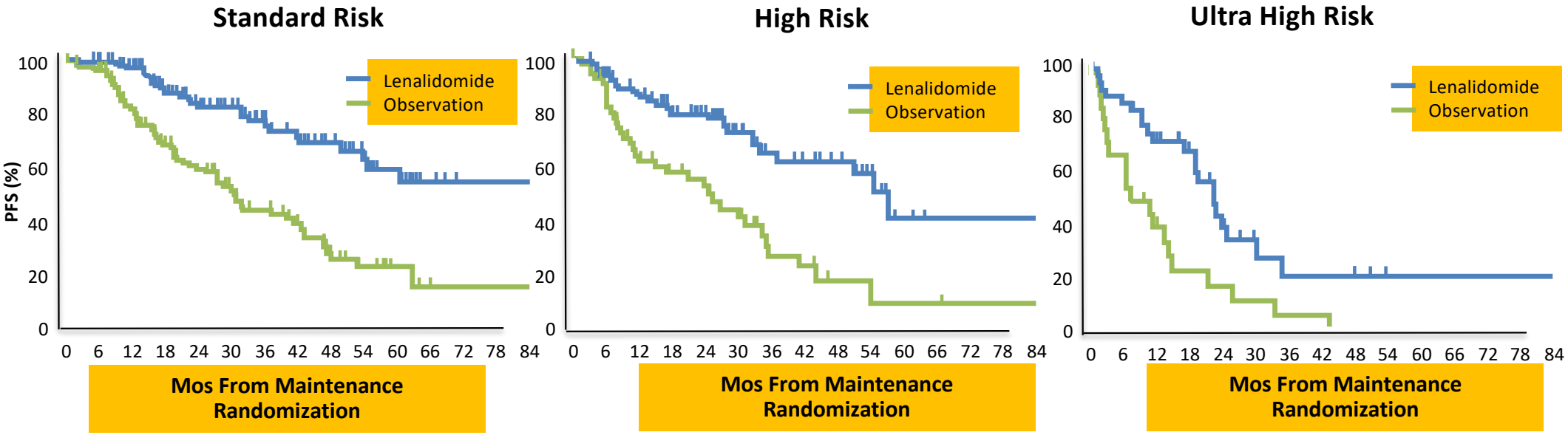
Meta-analysis of Lenalidomide maintenance therapy:
Overall survival – subgroup analysis

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



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

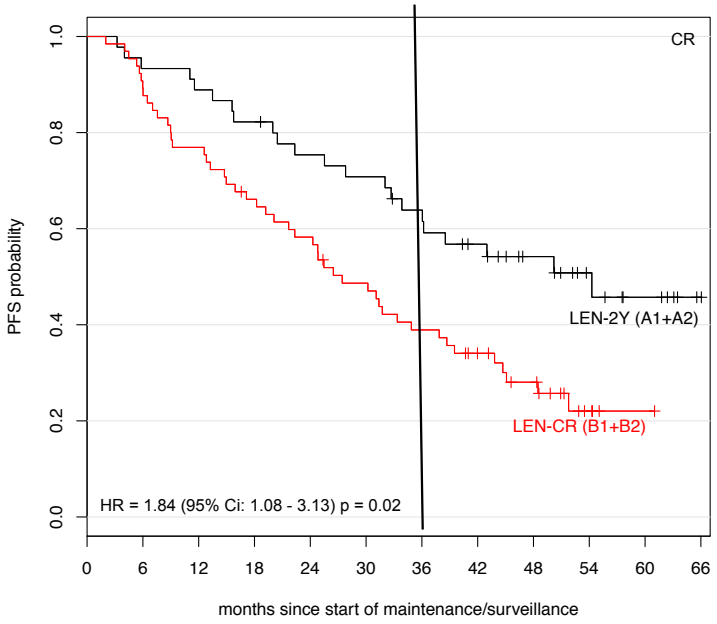
Phase III Myeloma XI trial: Maintenance in ASCT-eligible patients by cytogenetic risk

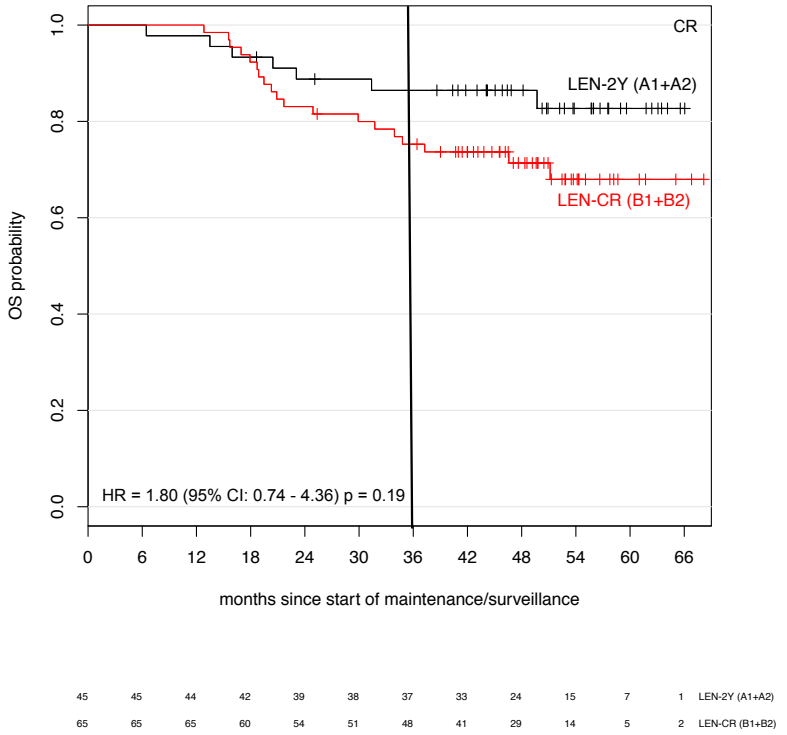


- High risk: presence of either t(4;14), t(14;16), t(14;20), del 17p, or gain 1q
- Ultrahigh risk: presence of more than 1 of these lesions
- Standard risk: absence of these lesions

Jackson. Lancet Oncol. 2019;20:57.

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





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

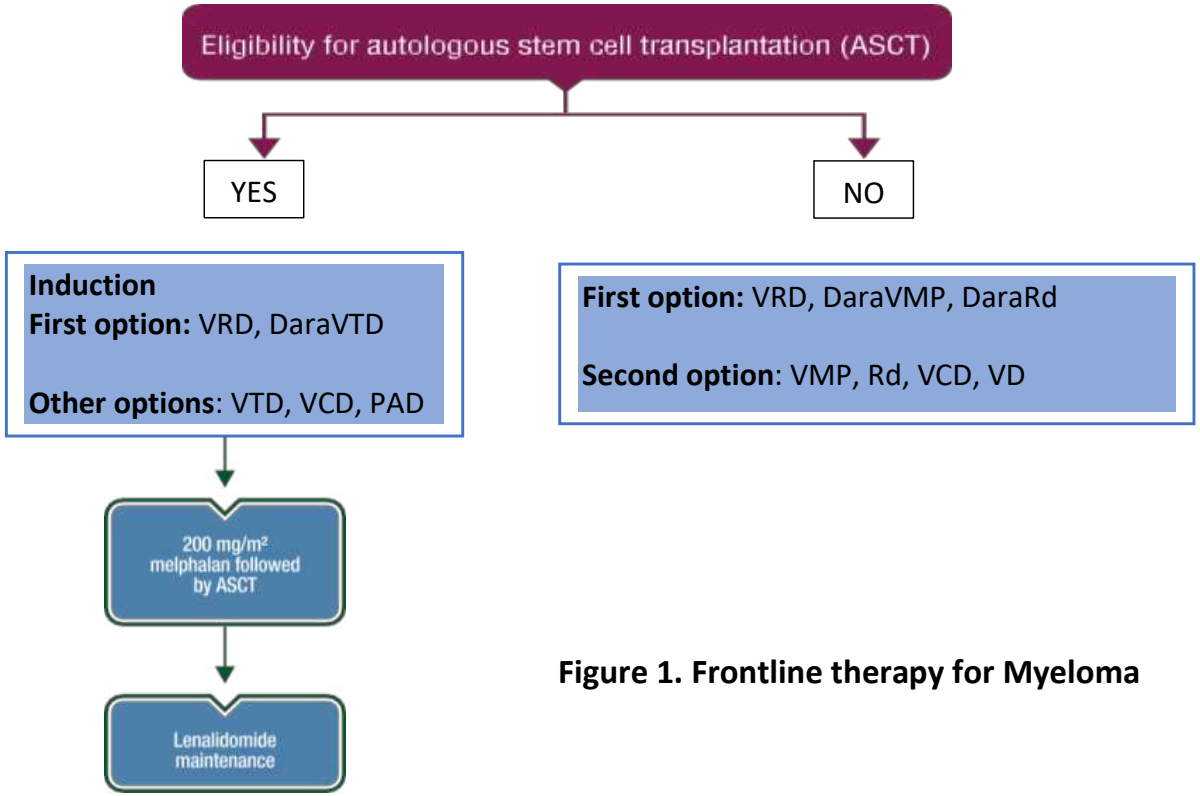


Figure 1. Frontline therapy for Myeloma

Dimopoulos et al. 2021

ORIGINAL ARTICLE

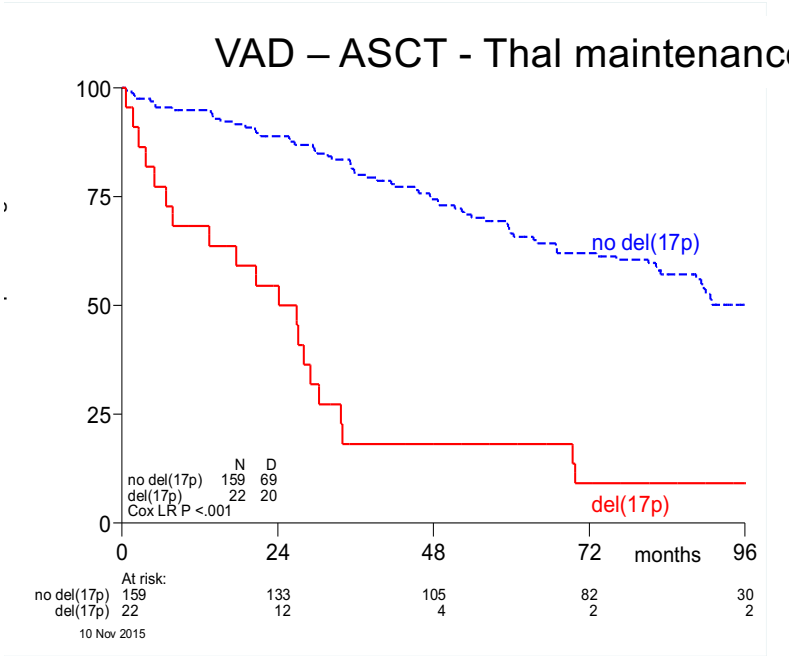
Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial

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]

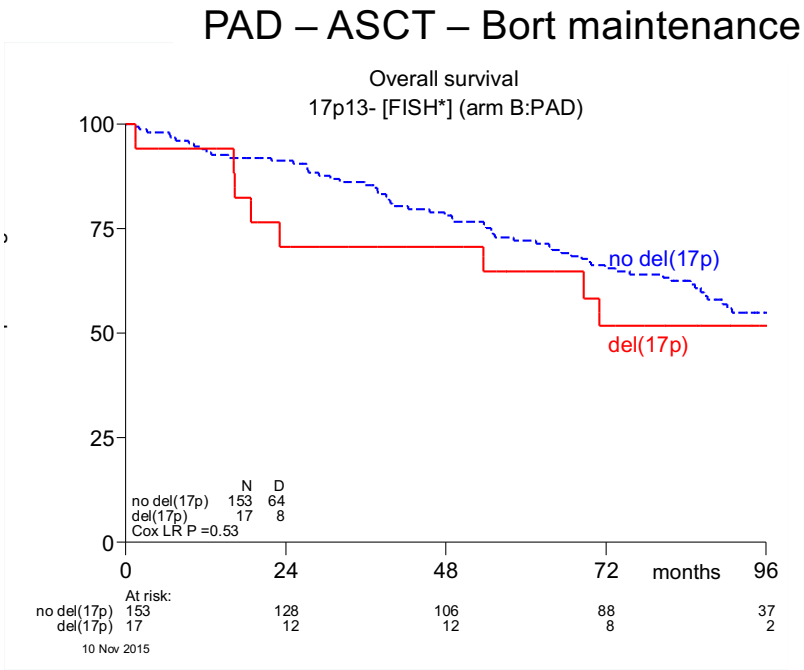
Sonneveld et al., JCO 2013

Goldschmidt et al., Leukemia 2018

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



p<0.001

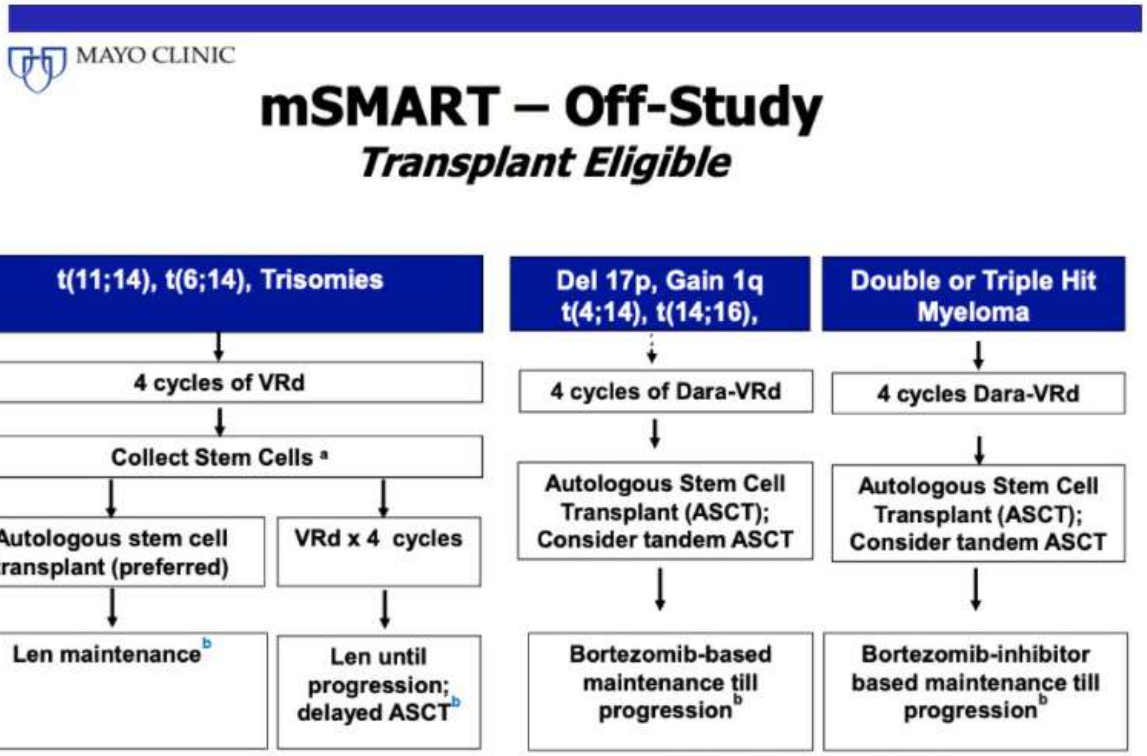


p=0.5

Neben et al., Blood 2012

Goldschmidt et al., Leukemia 2017

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

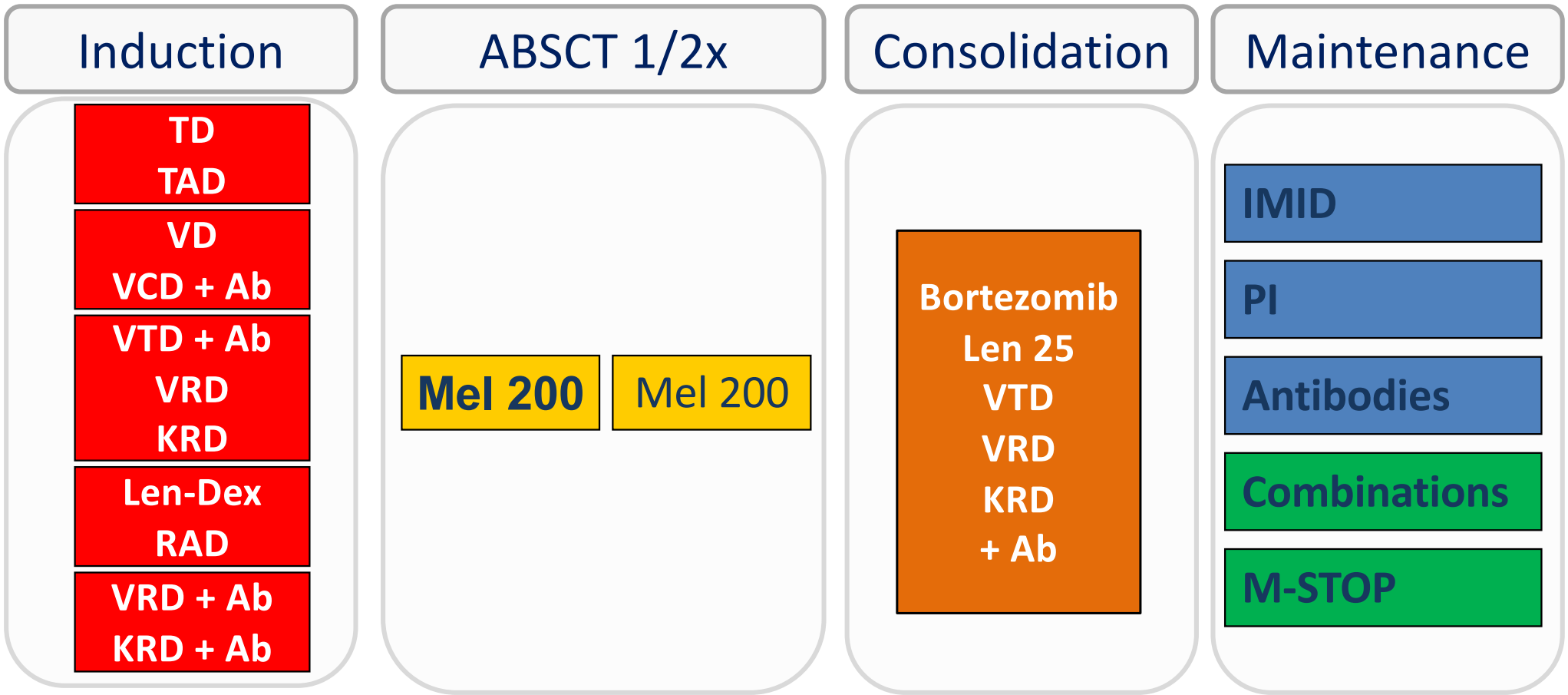


a If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor; b Duration usually until progression based on tolerance

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

Increasing Number of New Drugs Before and After ABSCT

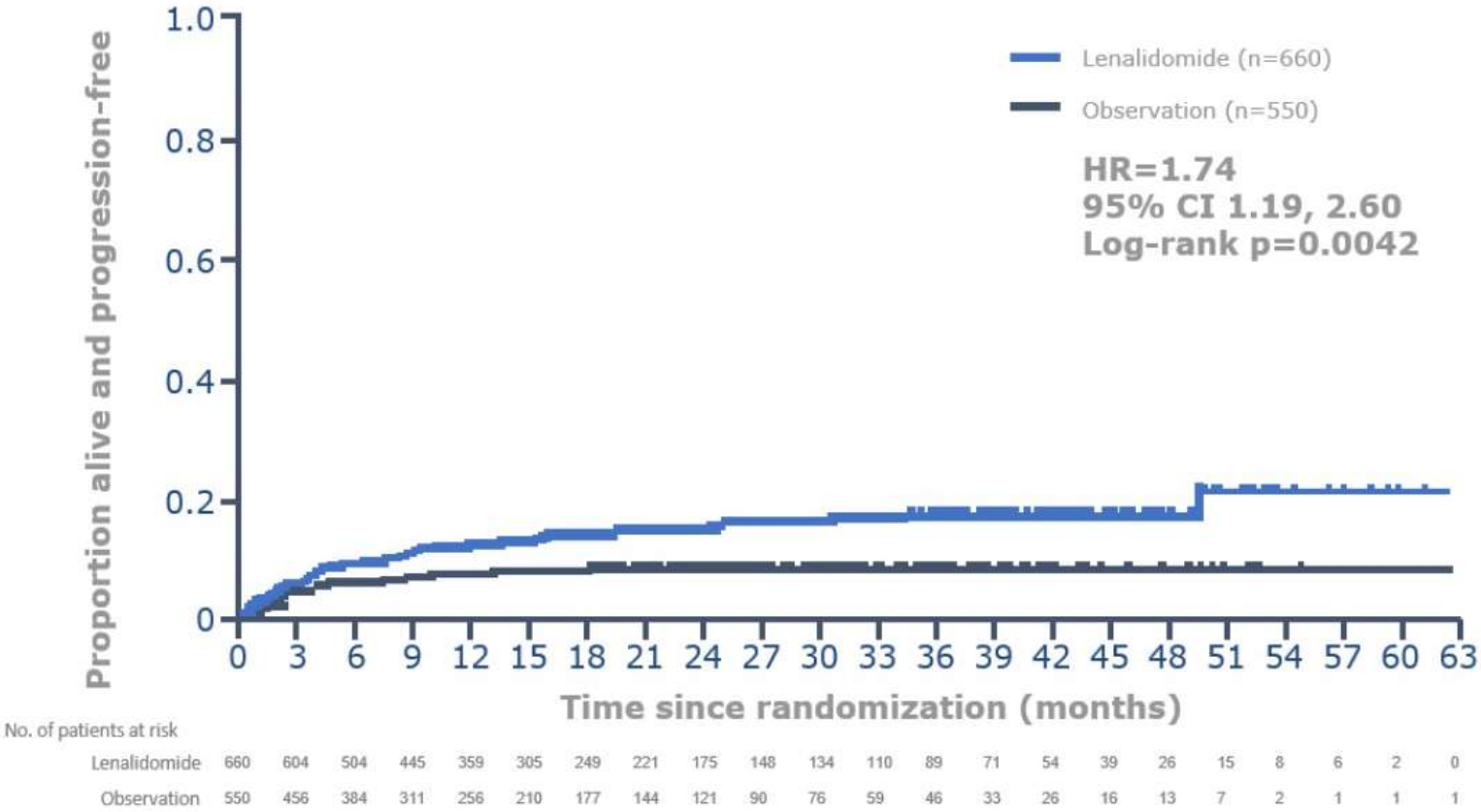


Adapted from Einsele, DGHO Slides 2012

Focus on lenalidomide maintenance

MYELOMA XI: LEN MAINTENANCE IN NDMM

*TIME TO IMPROVED RESPONSE**



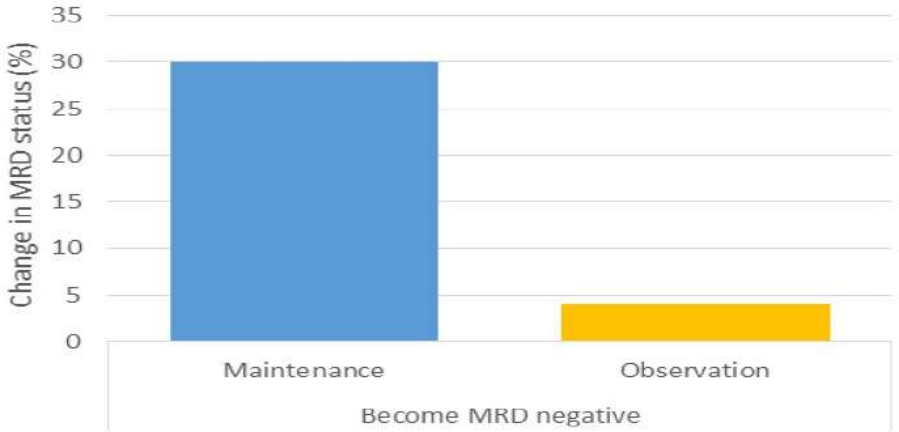
No. of patients at risk

Lenalidomide	660	604	504	445	359	305	249	221	175	148	134	110	89	71	54	39	26	15	8	6	2	0
Observation	550	456	384	311	256	210	177	144	121	90	76	59	46	33	26	16	13	7	2	1	1	1

Relevant grade 3/4 adverse events were: neutropenia 34%, thrombocytopenia 7%, anaemia 4.2%, peripheral neuropathy 1.4%. Venous thromboembolism occurred in 2.3%.
CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma.
Jackson G et al. ASH 2016; Oral Presentation and Abstract 1143

BENEFITS OF MAINTENANCE: MRD NEGATIVITY

- **Conversions to MRD-negativity were seen in 30% of MRD-positive patients on maintenance** compared to 4% of patients randomised to no further therapy (p=0.0045).
- Conversion noted in all induction therapy groups



De Tute, ASH 2017#904 ORAL

MINIMAL RESIDUAL DISEASE IN THE MAINTENANCE SETTING IN MYELOMA XI: PROGNOSTIC SIGNIFICANCE AND IMPACT OF LENALIDOMIDE

- **Significant PFS advantage for MRD$^-$ vs MRD$^+$ (median > 50 vs 20 months; HR, 0.2; 95% CI, 0.11-0.37; p > .0001)**
- **Conversion to MRD$^-$ in 32% of MRD$^+$ pts on maint** vs 4% not receiving maint (p = . 0045)

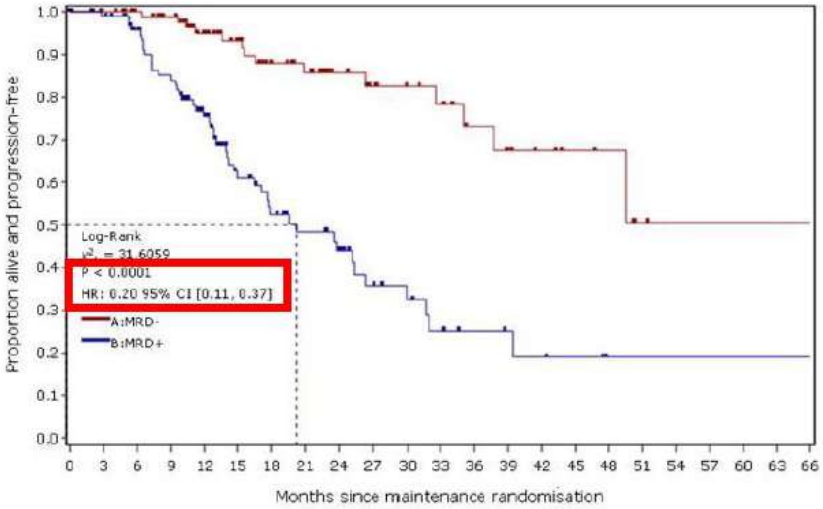


Figure 1 (a). Impact of MRD result for patients with an informative sample at six months post maintenance randomisation. Progression-free survival is greatly superior in the MRD-negative patients (>50 months vs 20 months, p<0.0001, HR 0.2, 95% CI 0.11-0.37).

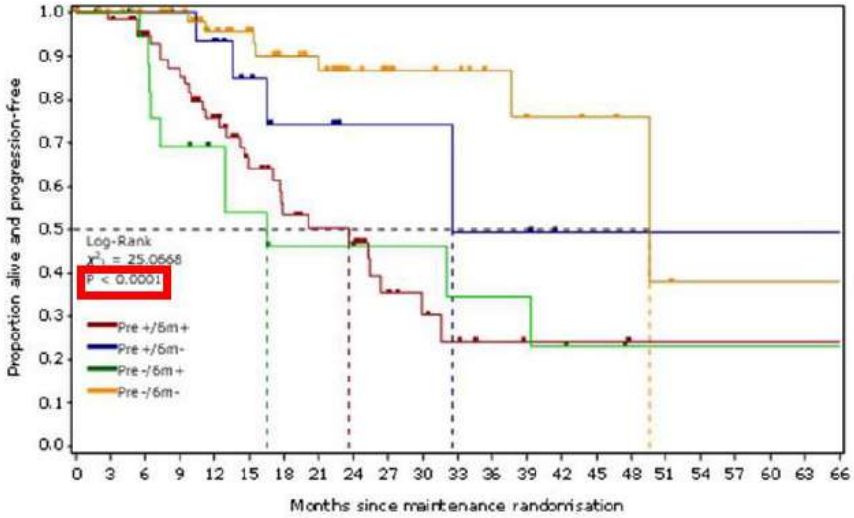


Figure 1 (b). Progression-free survival based on MRD results at both post ASCT/end of treatment and 6 months post maintenance randomisation. Patients with MRD-negativity at both time-points demonstrate the best outcome.

De Tute, #904 ORAL, ASH 2017

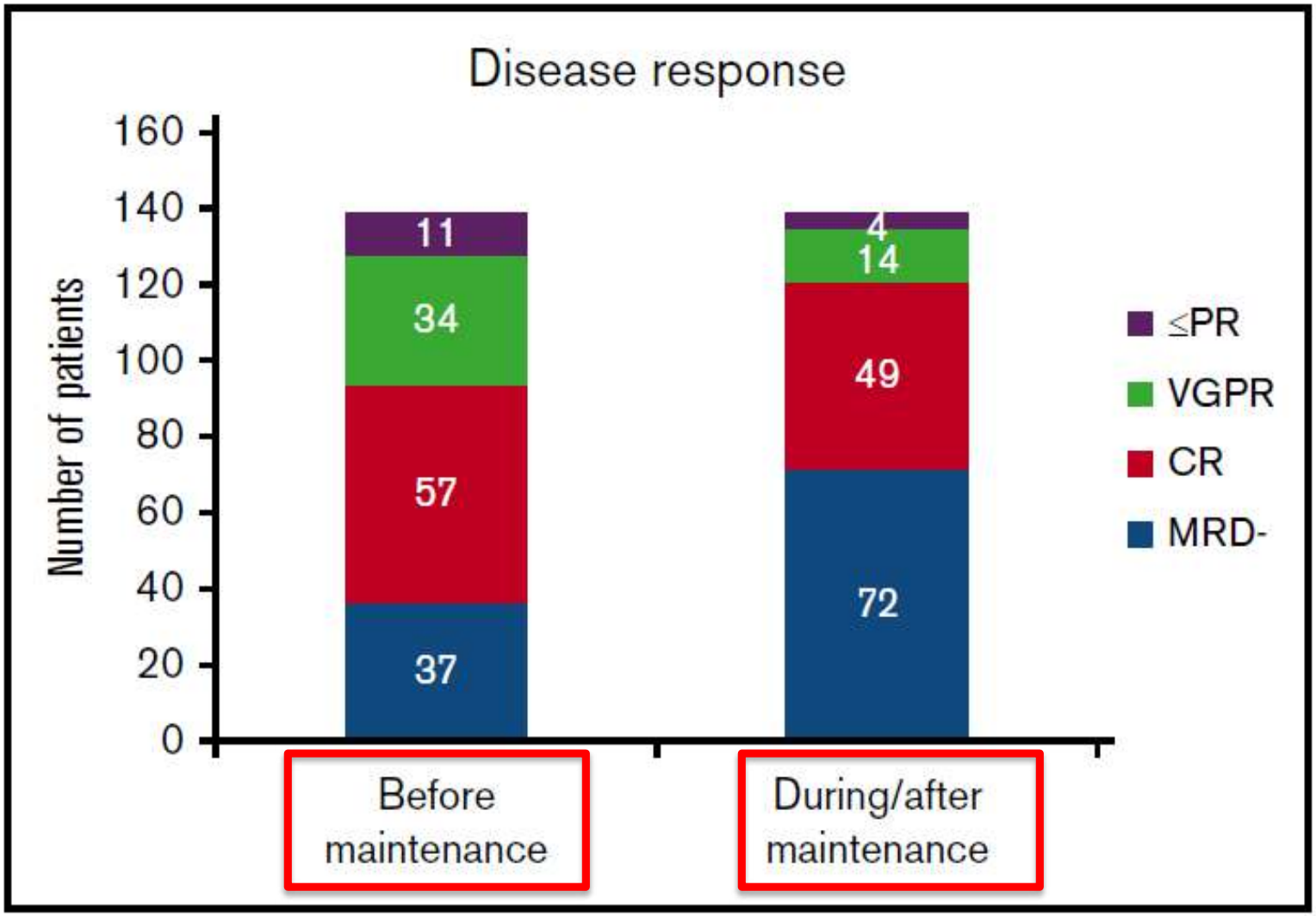
REGULAR ARTICLE

blood advances

Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma

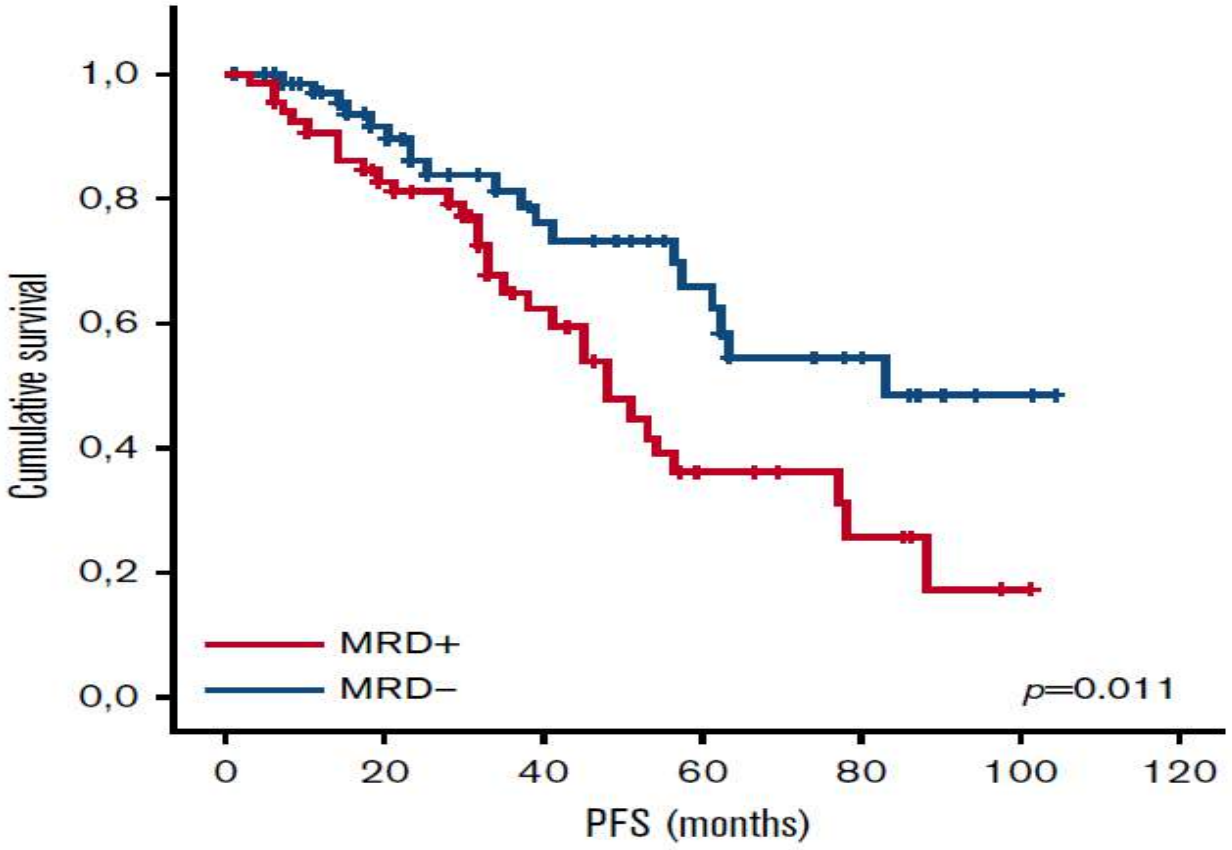
Rafael Alonso,[1,2] María-Teresa Cedena,[1,2] Sandy Wong,[3] Nina Shah,[3] Rafael Ríos-Tamayo,[4] José M. Moraleda,[5] Javier López-Jiménez,[6] Cristina García,[1,2] Natasha Bahri,[3] Antonio Valeri,[1,2] Ricardo Sánchez,[1,2] Luis Collado-Yurrita,[7] Thomas Martin,[3] Jeffrey Wolf,[3] Juan-José Lahuerta,[1,2,*] and Joaquín Martínez-López[1-3,*]

[1]Department of Hematology, Hospital Universitario 12 de Octubre (H12O), Universidad Complutense de Madrid, Madrid, Spain; [2]Clinical Research Hematology Unit, H12O Centro Nacional de Investigaciones Oncológicas (CNIO), Centro de Investigación Biomédica en Red Cáncer (CIBERONC), Madrid, Spain; [3]Division of Hematology/Oncology, Hellen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [4]Department of Hematology, Hospital Univeristario Virgen de las Nieves (HVN), Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Granada, Spain; [5]Department of Hematology, Hospital Clínico Universitario Virgen de la Arrixaca, Insitituto Muriano Investigación Biosanitaria (IMIB)–Arrixaca, Universidad de Murcia, Murcia, Spain; [6]Department of Hematology, Hospital Universitario Ramón y Cajal, Madrid, Spain; and [7]Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain



Alonso et al. Blood Advances 2020

PFS according to MRD status at maximal response



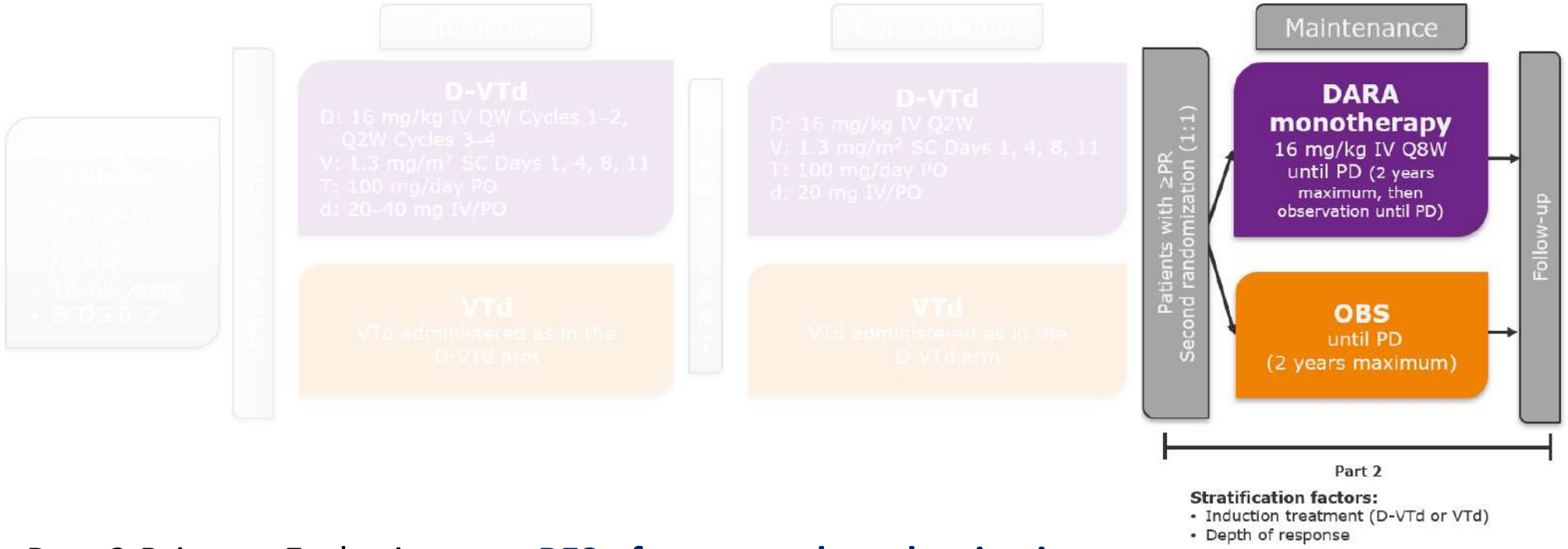
Patients at risk							
MRD+	67	46	23	10	5	1	0
MRD−	72	46	28	18	9	3	0

Alonso et al. Blood Advances 2020

Focus on daratumumab maintenance

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

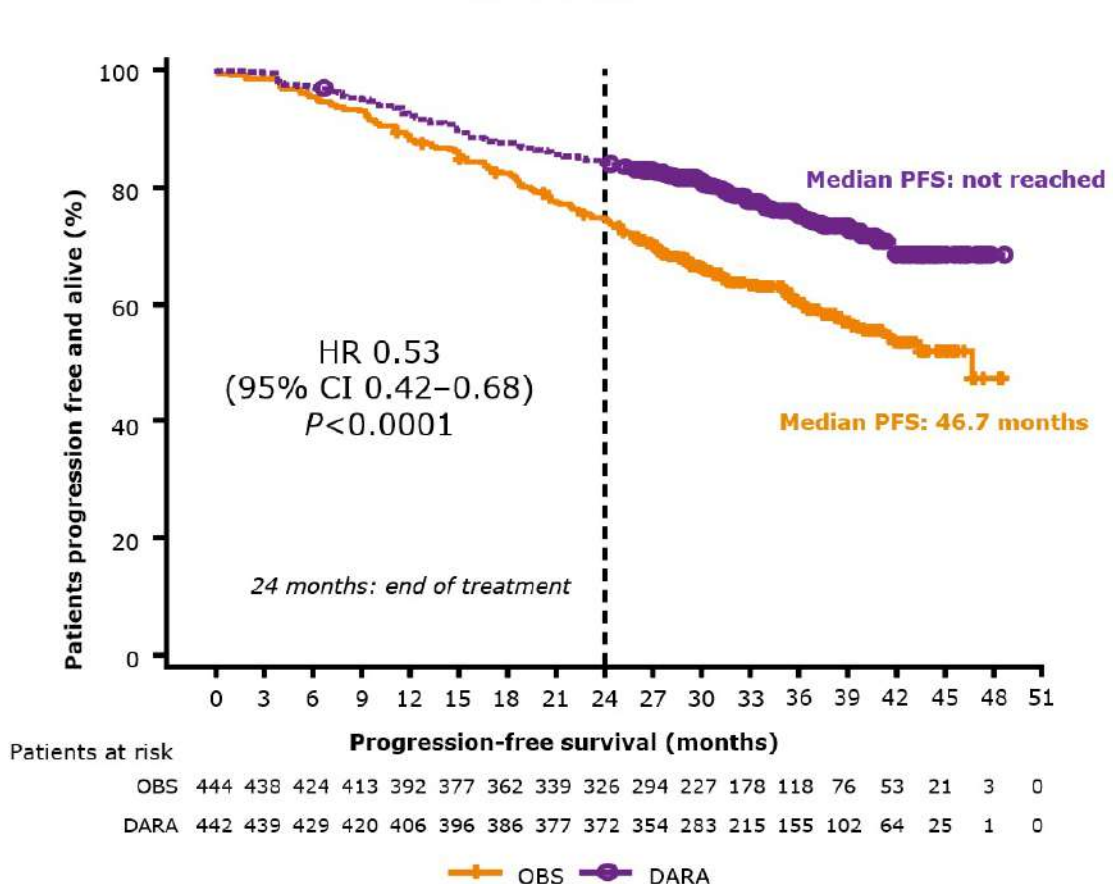


The Part-2 Primary Endpoint was: **PFS after second randomization**

Moreau et al. ASCO 2021

DARA Significantly Improved PFS From Second Randomization vs OBS

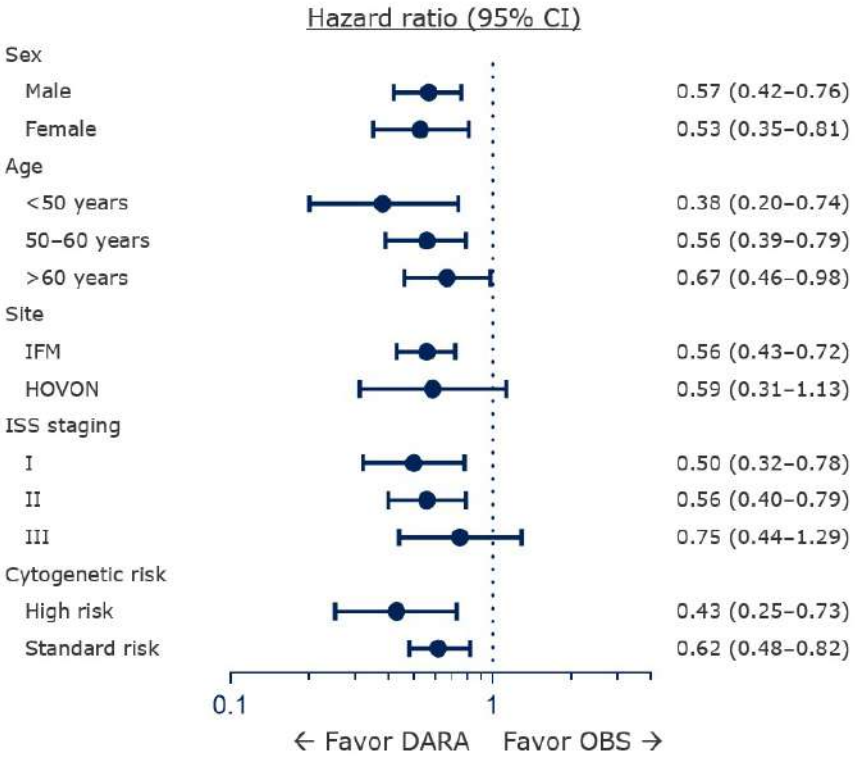
mFUp 35.4 mo from 2° random

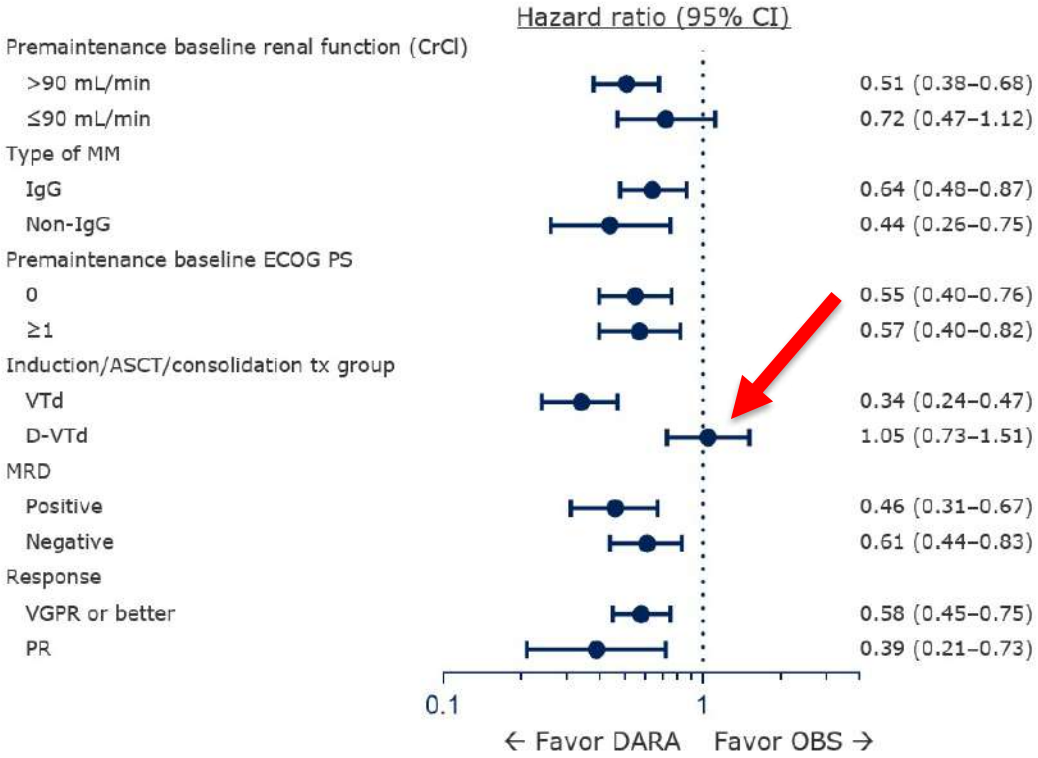


Moreau et al. ASCO 2021

PFS Benefit of DARA Was Consistent Across Most Prespecified Subgroups

mFUp 35.4 mo from 2° random

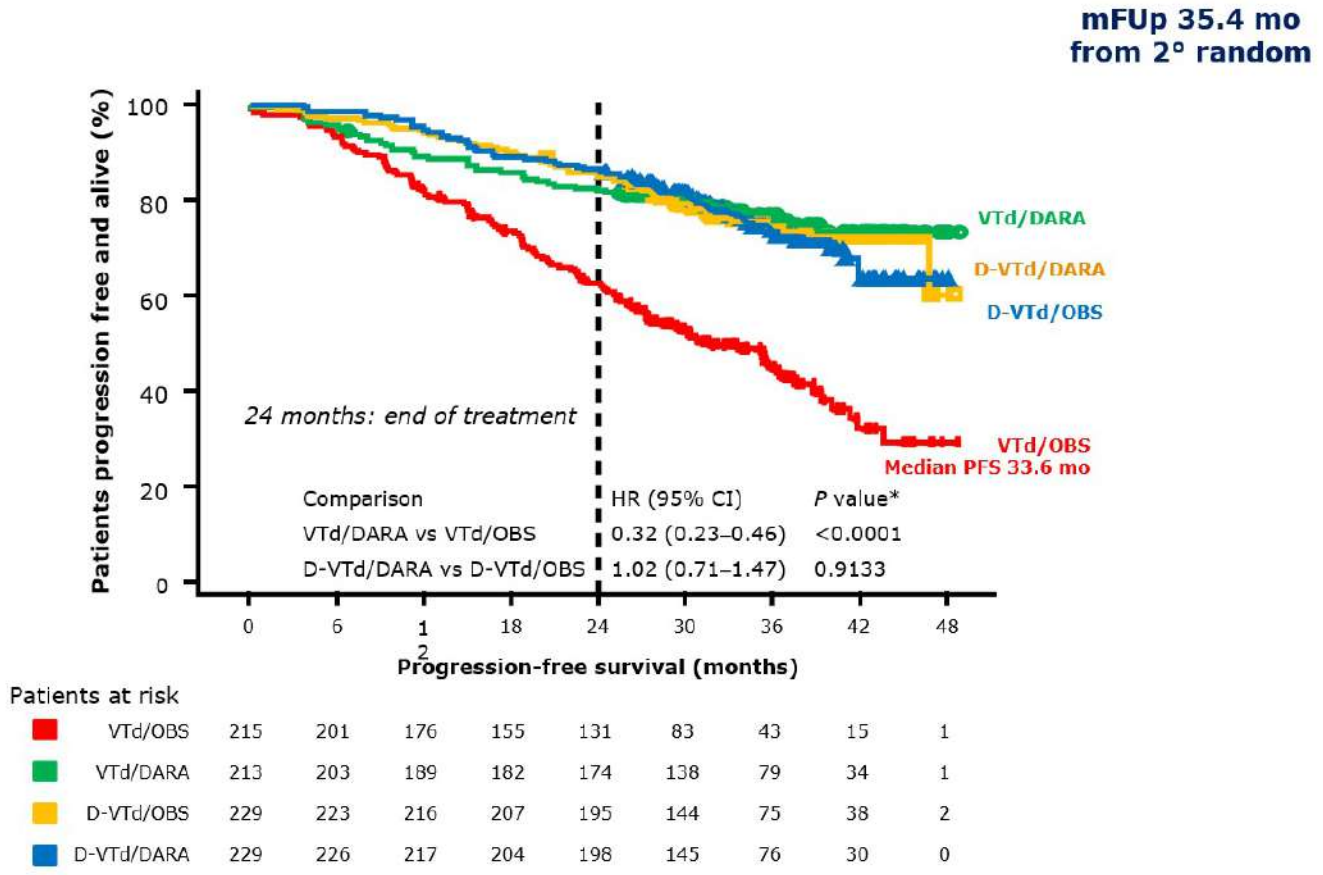




Moreau et al. ASCO 2021

DARA Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

- A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy
- A PFS benefit was observed for VTd/DARA vs VTd/OBS
- PFS was not different for D-VTd/DARA vs D-VTd/OBS



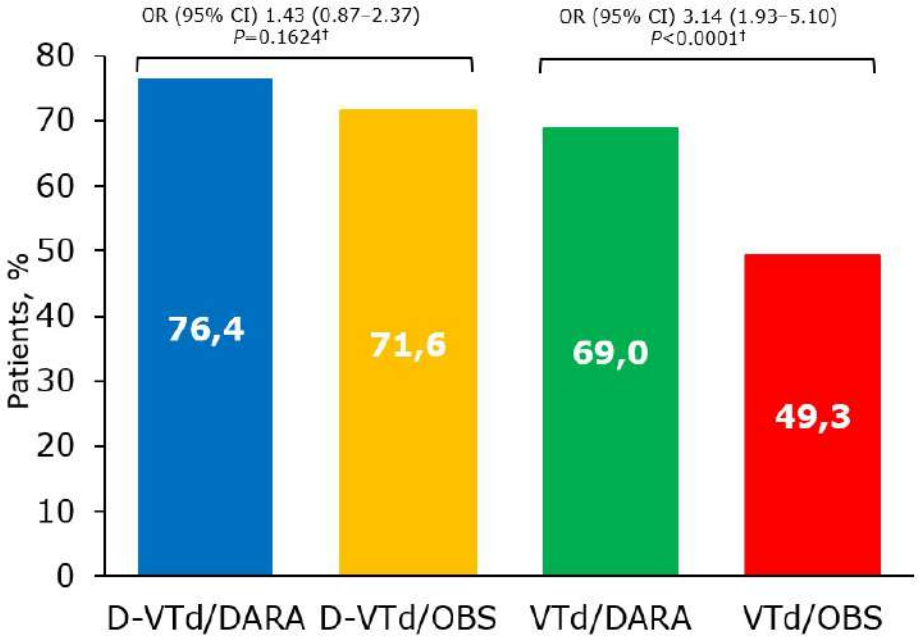
Moreau et al. ASCO 2021

DARA Significantly Improved Depth of Response vs OBS in Patients who Received VTd Induction/Consolidation

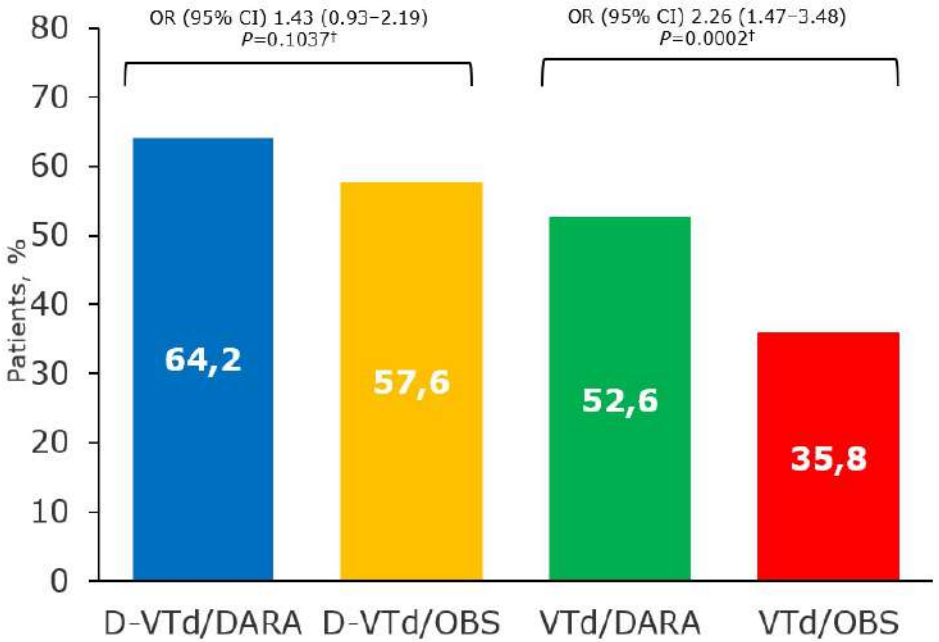
- **Highest rates of ≥CR and MRD negativity were seen with D-VTd/DARA**

mFUp 35.4 mo from 2° random

Rates of ≥CR

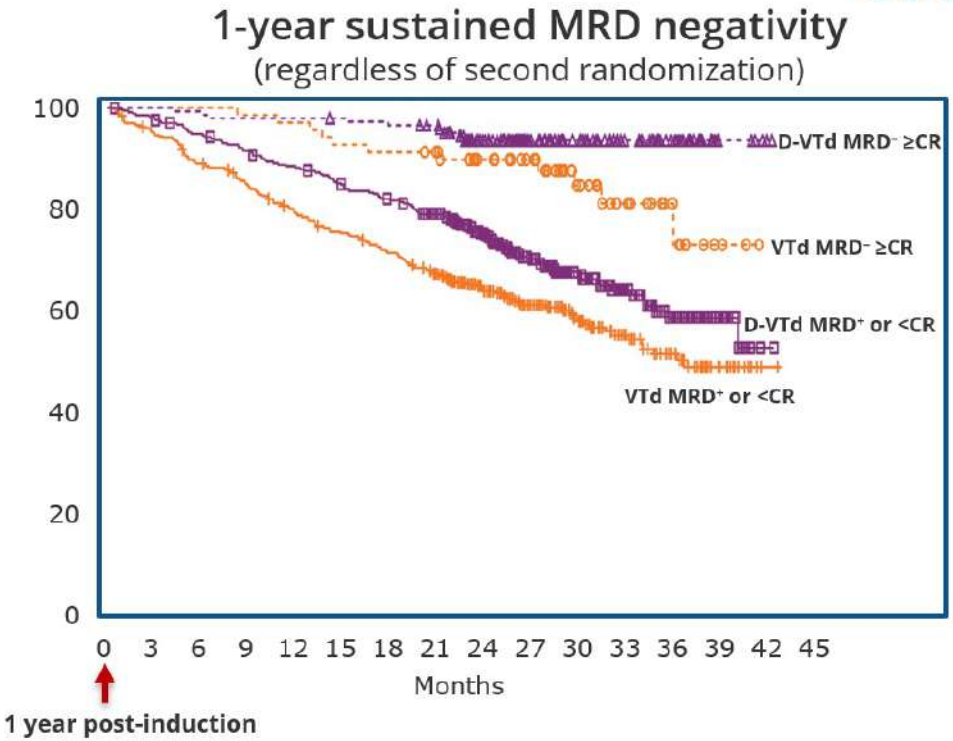


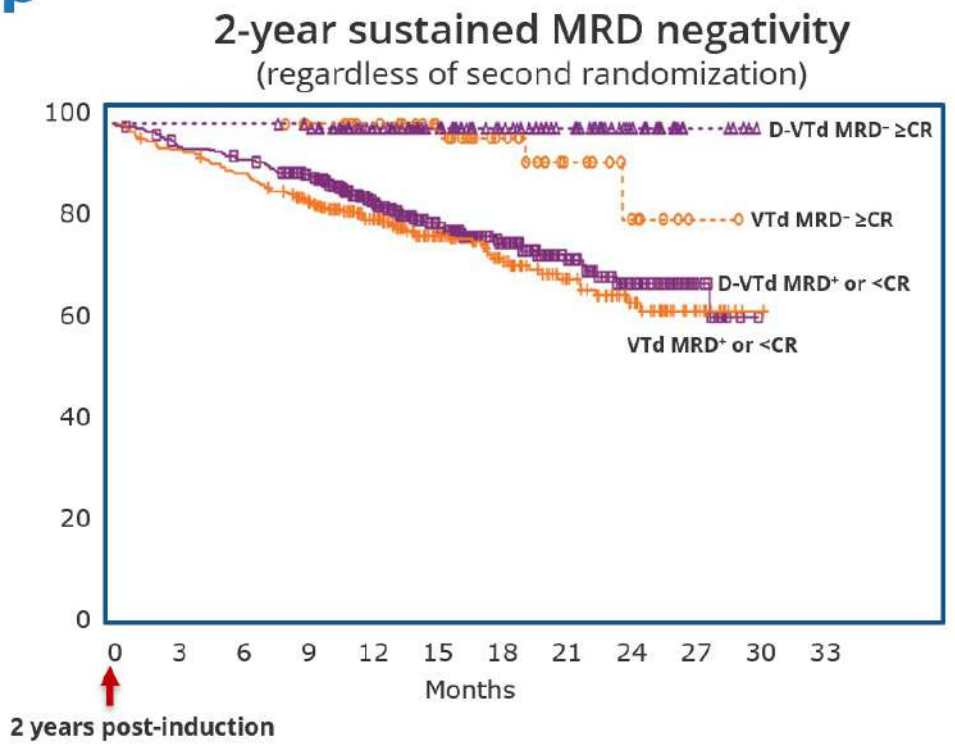
Rates of MRD negativity*



Moreau et al. ASCO 2021

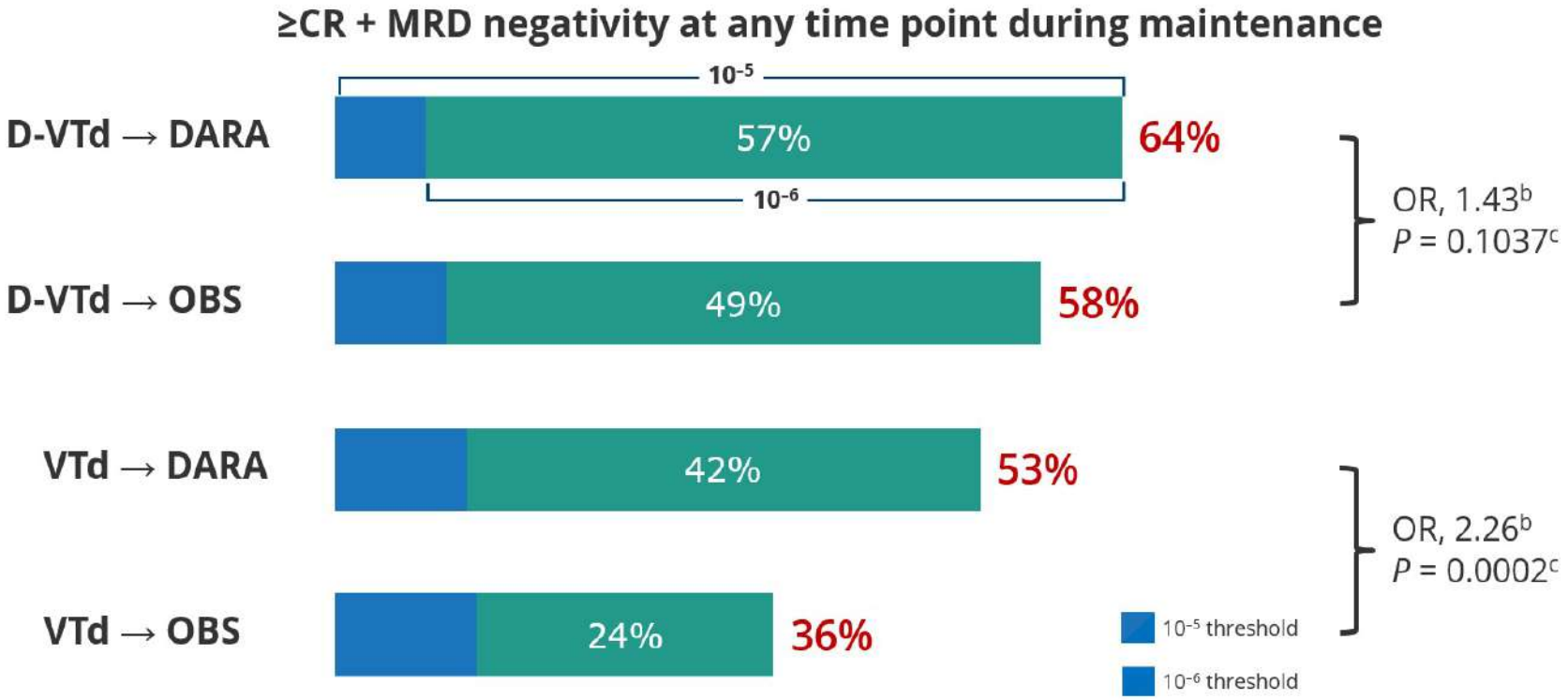
CASSIOPEIA: Landmark PFS Analysis From Post-induction ≥CR + MRD-negativity (MFC; 10^{-5}) Status by Treatment Group





Avet-Loiseau et al. ASH 2021

CASSIOPEIA: Rates of ≥CR + MRD Negativity at 10^{-5} and 10^{-6} (NGS) at Any Time Point During Maintenance[a]

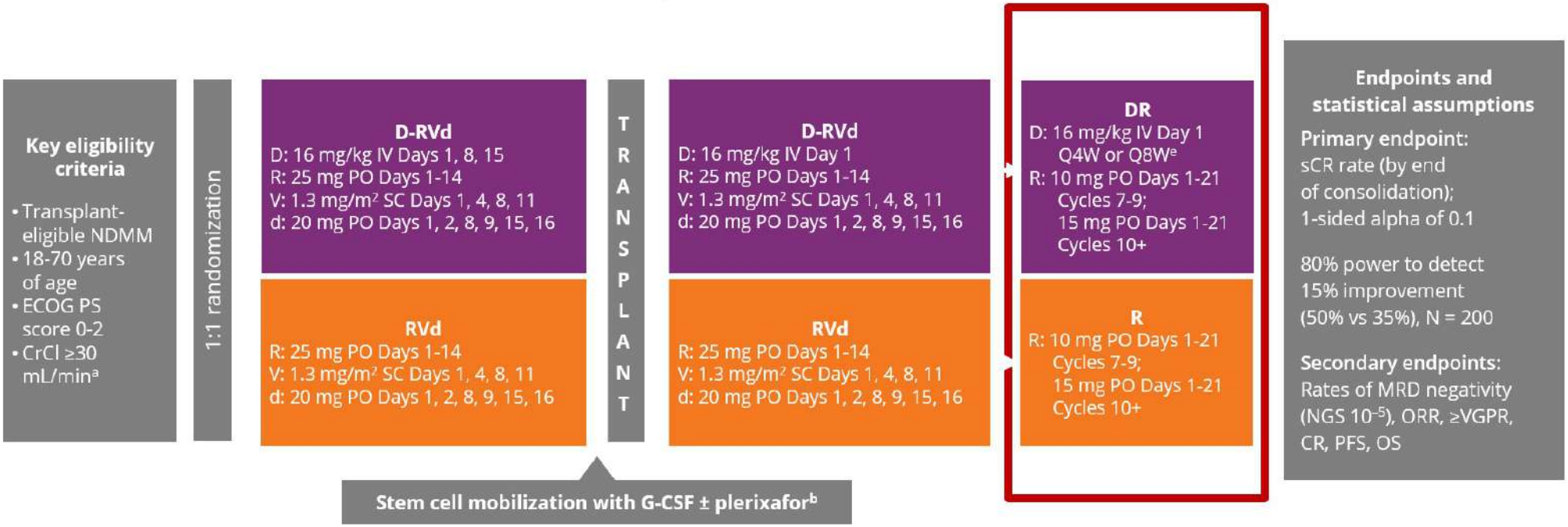


Avet-Loiseau et al. ASH 2021

GRIFFIN: Study Design of the Randomized Phase

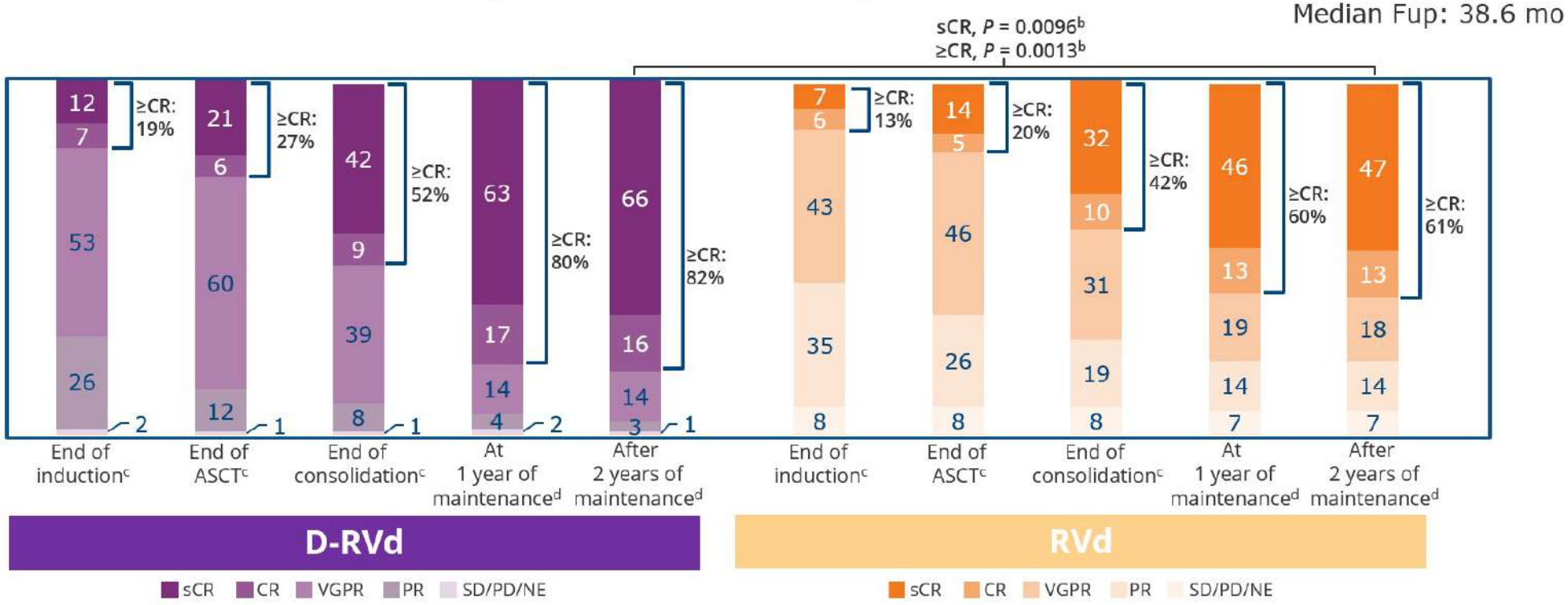
Median Fup: 38.6 mo

- Phase 2 study of D-RVd versus RVd in transplant-eligible NDMM, 35 sites in the United States with enrollment between December 2016 and April 2018



Laubach et al. ASH 2021

GRIFFIN: Responses Deepened Over Time

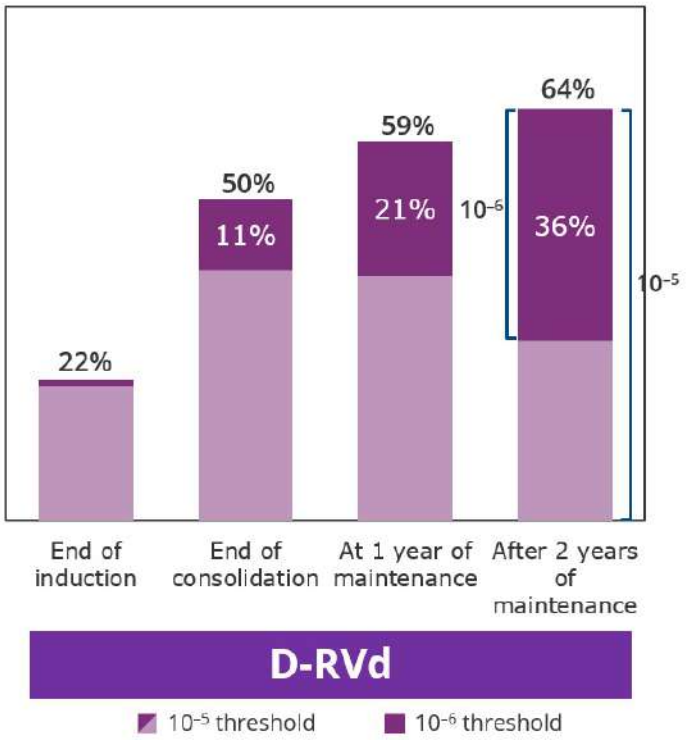


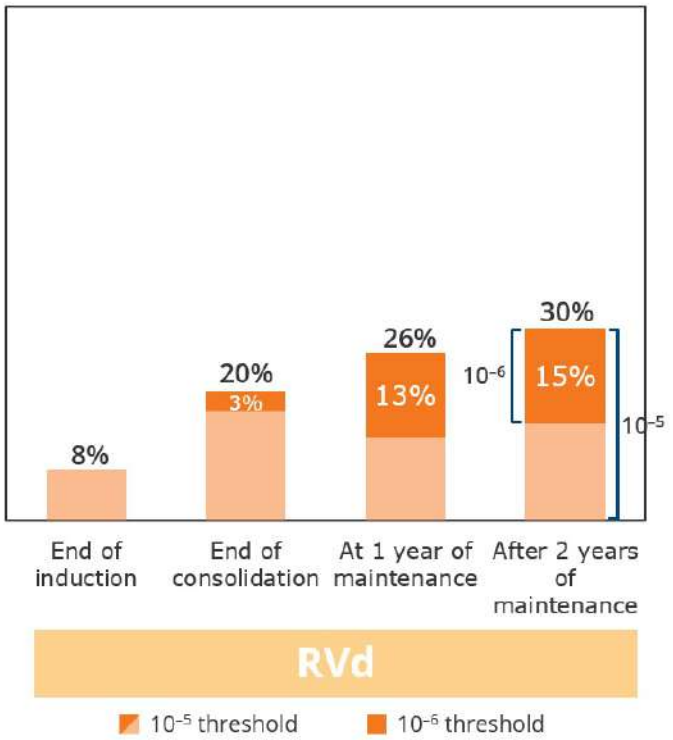
- Response rates for sCR and ≥CR were greater for D-RVd versus RVd at all time points, with the deepest responses occurring after 2 years of maintenance therapy

Laubach et al. ASH 2021

GRIFFIN: MRD-negativity Rates Improved Throughout the DR Maintenance Period

Median Fup: 38.6 mo





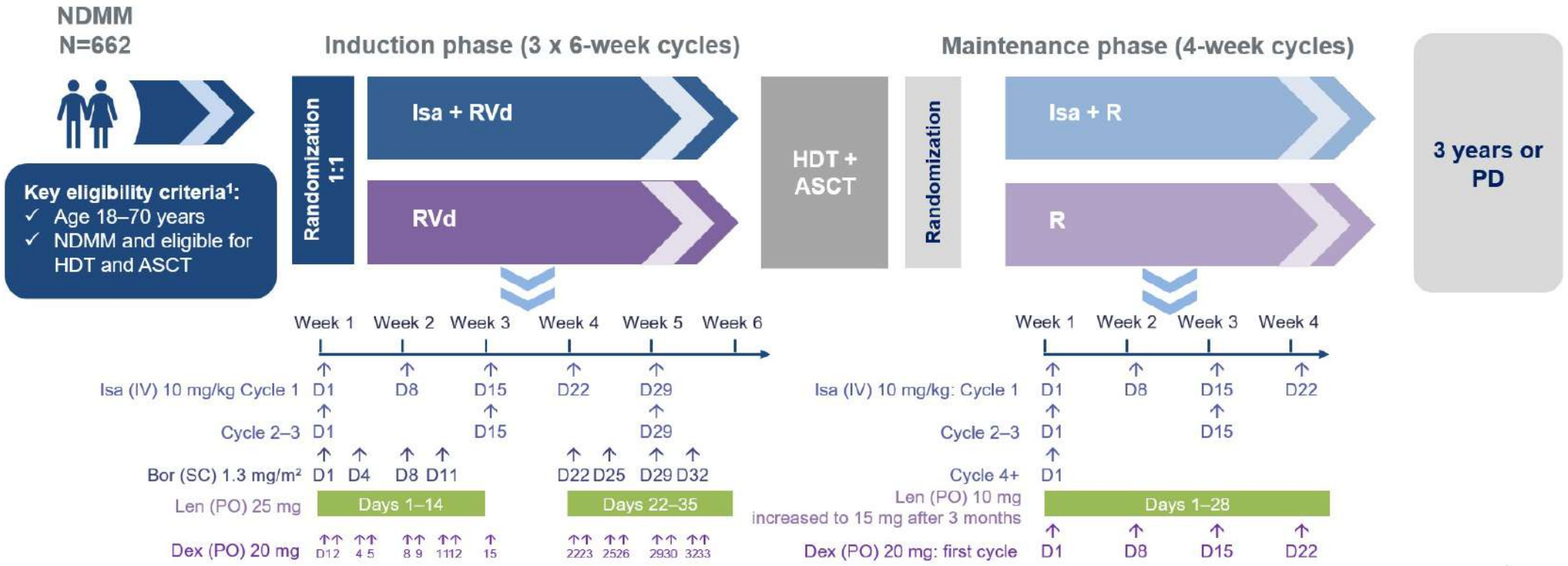
MRD-negative (10^{-5}) conversion rate

- 29% (15/52) of D-RVd patients and 12% (10/82) of RVd patients who were MRD positive at the end of consolidation became MRD negative after 2 years of DR or R maintenance

Laubach et al. ASH 2021

Focus on isatuximab maintenance

The first phase 3 study evaluating Isa + RVd for induction and maintenance in Te NDMM patients



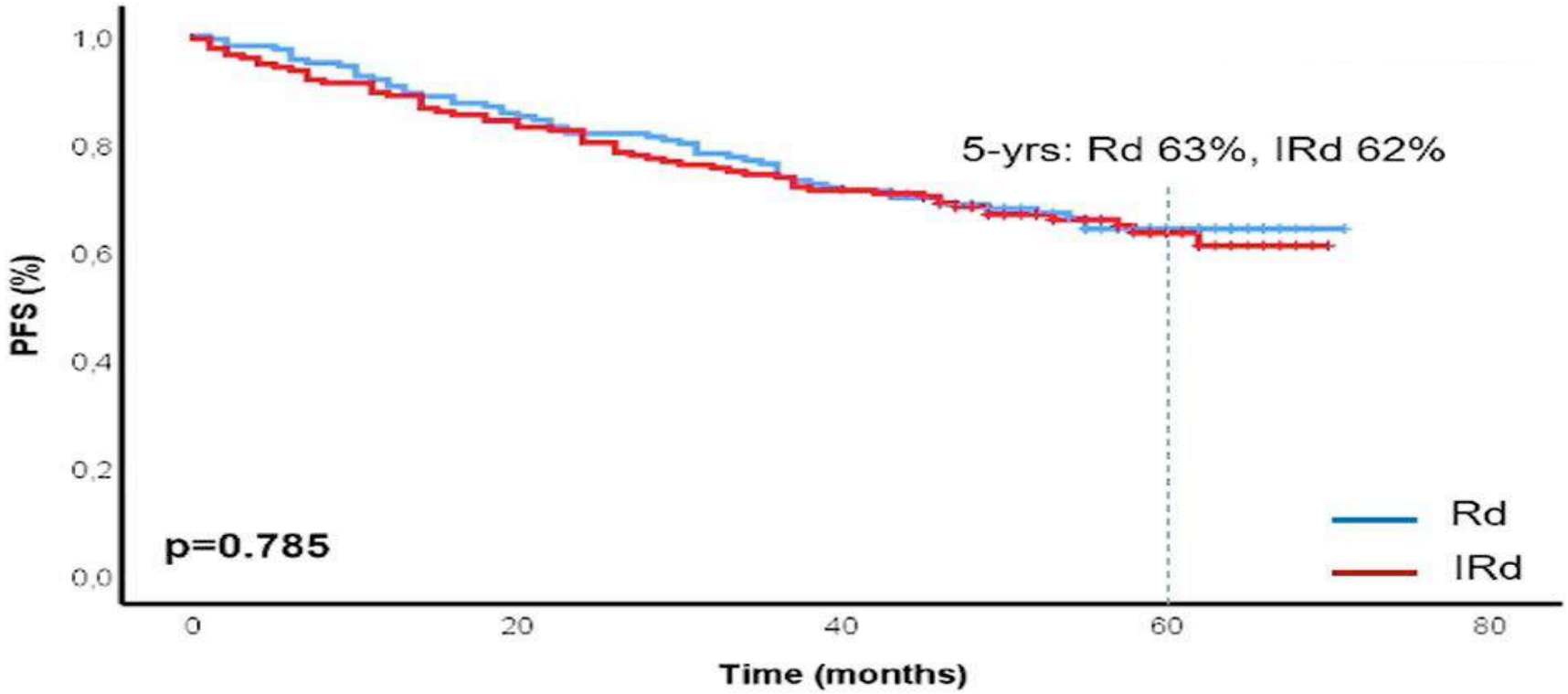
ASCT, autologous stem cell transplant; D, day; d/Dex, dexamethasone; HDT, high-dose therapy; Isa, isatuximab; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PO, oral; R/Len, lenalidomide; SC, subcutaneous; Te, transplant eligible; V/Bor, bortezomib; RVd is off label use in some countries according to the lenalidomide summary of product characteristics.

1. ClinicalTrials.gov: NCT03617731

Focus on ixazomib maintenance

GEM2014 Study
Random IxRd vs Rd

PFS from maintenance start

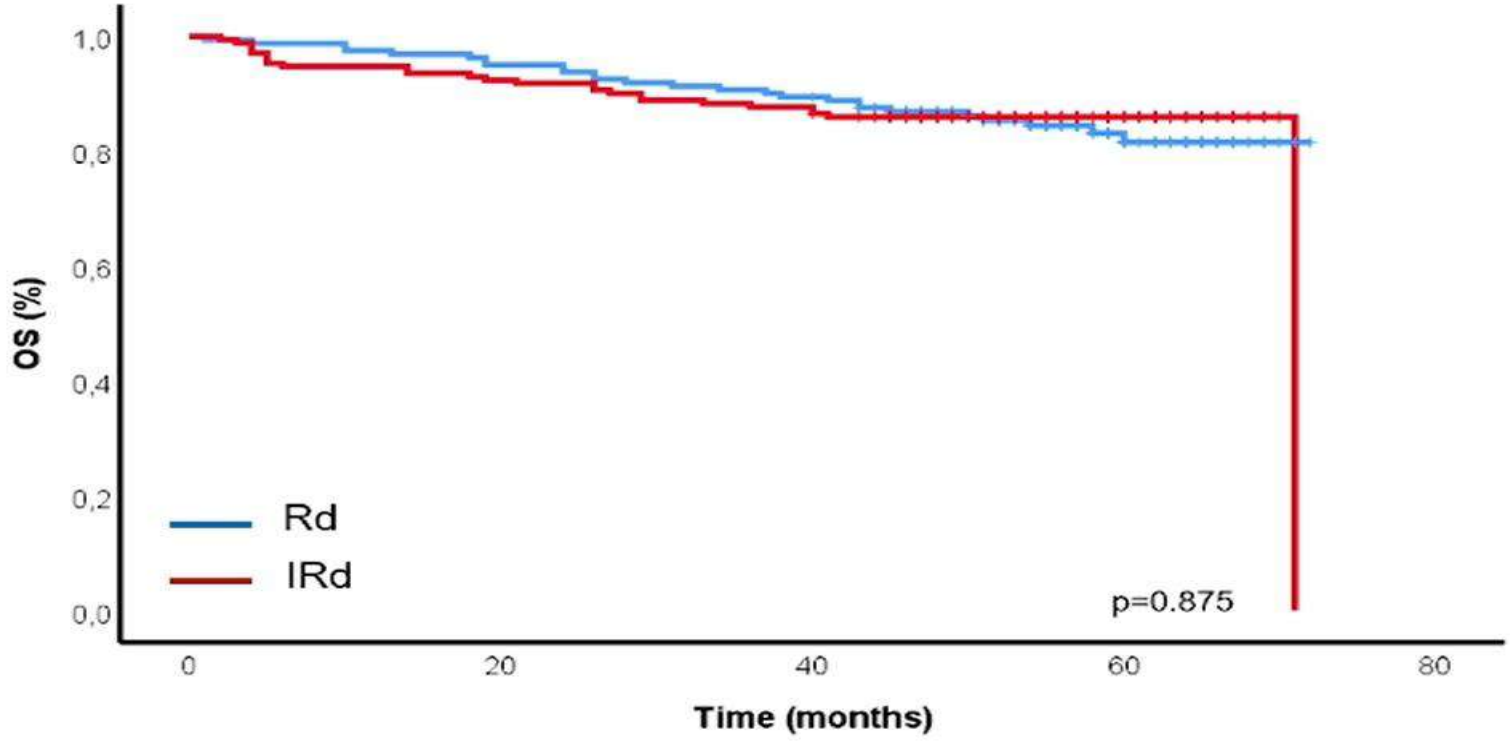


Median follow-up: 56 months

Rosignol et al. ASH 2021

GEM2014 Study
Random IxRd vs Rd

OS from maintenance start



Median follow-up: 56 months

Rosignol et al. ASH 2021

Conclusions

Maintenance is an essential phase of the treatment algorithm.

Maintenance with lenalidomide and/or anti-CD38 MoAbs can deepen the responses and increase MRD negativity rate.

Maintenance duration according to the MRD status has been adressed by ongoing trials.