Nuove prospettive nel

MIELOMA MULTIPLO

NAPOLI Royal Hotel Continental

7-8 MARZO 2022

Innovazioni nella Terapia di Induzione a Trapianto

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Treatment paradigm for transplant-elegible patients

Sequential blocks of therapy

- Induction therapy
- Intensification
- Consolidation
- Maintenance

Continued cytoreduction
Sustained suppression of disease burden

Endpoints

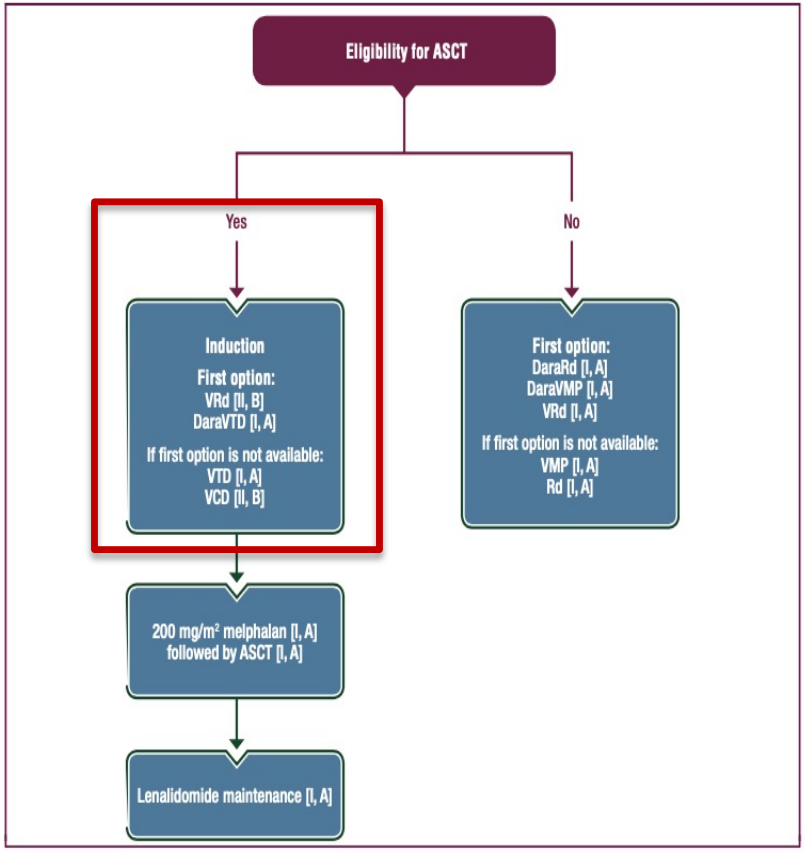
- To maximize the rate of undetectable MRD
- To sustain MRD negativity
- To prolong PFS/OS, offering a chance of cure (to a fraction of patients)
- To inform clinical decisions and tailor treatment

Combination regimens

- Faster and deeper response
- Different mechanisms target multiple clones simultaneously
- Prevention of drug-resistant subclones emergence
- Eradication of all clones

Cavo M et al. Blood 2011;117(23):6063-73;
Cavo et al. Blood 2012;120(1):9-19;
Kumar S, et al. Lancet Oncology 2016;17:e328-46

Linee guida ESMO 2021



QUESTIONS

- *Induction without transplant frontline?*
- *Best induction treatment: will quadruplets substitute triplets?*
- *Therapeutic synergy of induction treatment: the renaissance of consolidation?*

EARLY *VS.* LATE ASCT

		Early	Late	P
Pooled analysis of two trials (n=529)[1,2]	4-year PFS	**44%**	26%	p<0.001 (HR 0.53)
	4-year OS	**84%**	70%	p<0.001 (HR 0.51)
GIMEMA MM-RV-209… Rd-MPR *vs.* Rd-Mel200 (2nd rand: +/- maintenance) EMN MM-RV-441… Rd-CRD *vs.* Rd-Mel200 (2nd rand: R *vs.* RP Maint.)				
IFM-DFCI 2009 trial[3]	4-year PFS	**47%**	35%	p<0.001 (HR 0.69)
	8-year OS	62%	60%	p=NS
RVD x 8 + ASCT at relapse *vs.* RVD x 3 + ASCT (Mel200) + RVD x 2				
EMN02/HO95[4]	3-year PFS	**65%**	57%	p=0,001 (HR 0.73); High Risk 0.53
	3-year OS	86.3%	84.6%	p=NS
Induction VCD x 3-4 => VMP intensive vs ASCT => VRD conso *vs.* no conso => R maint				
FORTE trial [5]	**3-year PFS**	**78%**	**66%**	p=0,02 (HR 0.64);
	3-year OS	**NA**	**NA**	p=NS
KRDx4 + *ASCT vs KRDx4* + 4 KRD consol + Maintennce (Rvs KR). vs KCD+ASCT (FORTE trial)				

1. Rajkumar A, *et al.* N Engl J Med 2014;371:895–905; 2. Gay F, *et al.* Lancet Oncol 2015;16(16):1617–29; 3. Attal M, *et al.* Blood 2015;126: Abstract 391. Presented at ASH 2015;
4. Cavo M, *et al.* Blood 2016;128: Abstract 673. Presented at ASH 2016, Oliva S ASH 2020 .

Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial

Francesca Gay, Pellegrino Musto*, Delia Rota-Scalabrini, Luca Bertamini, Angelo Belotti, Monica Galli, Massimo Offidani, Elena Zamagni, Antonio Ledda, Mariella Grasso, Stelvio Ballanti, Antonio Spadano, Michele Cea, Francesca Patriarca, Mattia D'Agostino, Andrea Capra, Nicola Giuliani, Paolo de Fabritiis, Sara Aquino, Angelo Palmas, Barbara Gamberi, Renato Zambello, Maria Teresa Petrucci, Paolo Corradini, Michele Cavo, Mario Boccadoro*

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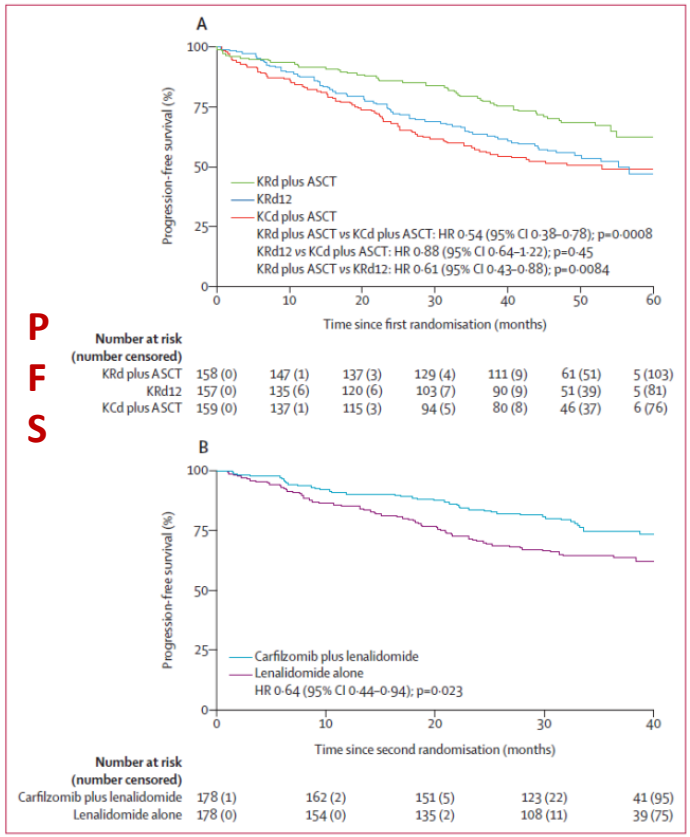
https://doi.org/10.1016/S1470-2045(21)00535-0

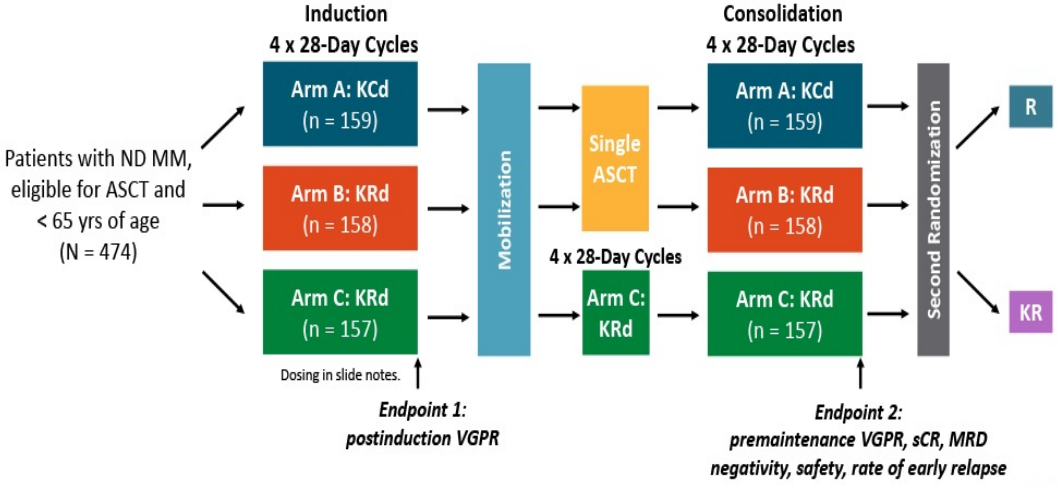
KRD vs KCD +/- ASCT



PFS

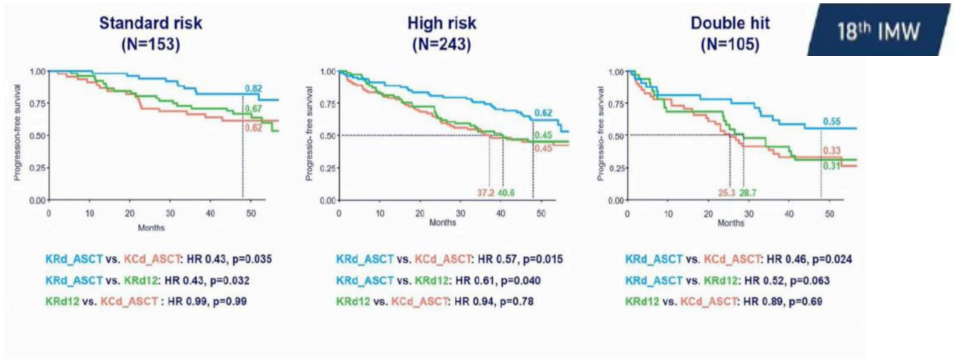
FORTE Efficacy by Cytogenetic Risk: Study Design

- Multicenter, randomized, open-label phase II study



Gay. ASCO 2021. Abstr 8002.

Slide credit: clinicaloptions.com



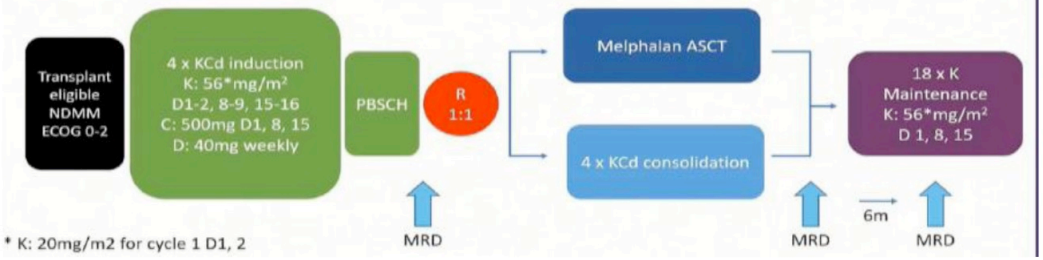
CARDAMON

CARDAMON STUDY DESIGN

18th IMW

Primary Endpoints:
- ≥VGPR pre-randomisation
- PFS at 2 years

KCD x 8 vs KCD x 4 + ASCT



* K: 20mg/m2 for cycle 1 D1, 2

CARDAMON

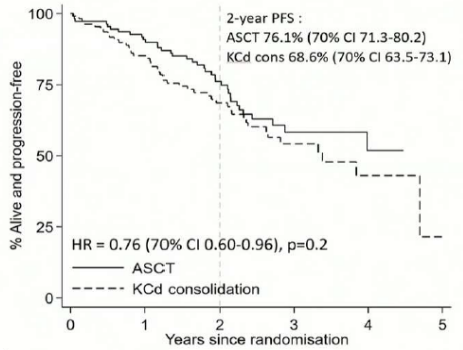
UPDATED PROGRESSION FREE SURVIVAL BY RANDOMISATION ARM

Median follow-up from randomisation
32.1 months

2-year PFS for KCd is not non-inferior to ASCT

The difference in 2-year PFS rate (KCd cons vs ASCT) using the rate in the experimental arm and the HR is

-6.5% (70% CI -11.1% to -1.0%)

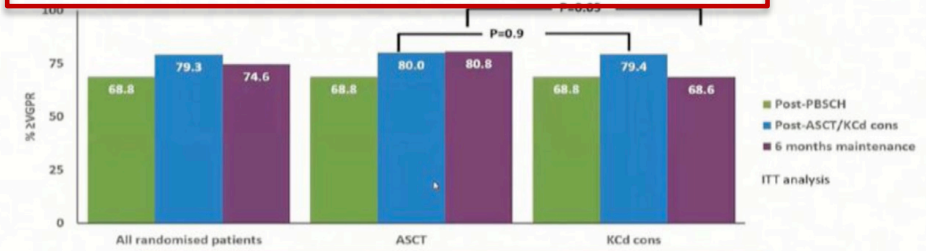


In follow-up

ASCT	109	98	62	23	8	0
KCd consolidation	109	90	54	20	6	0

CARDAMON

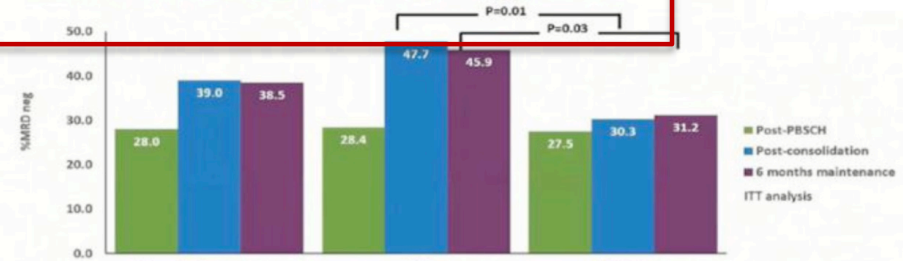
RESPONSES FOLLOWING ASCT/ CONS AND MAINTENANCE



MAINTENANCE VS POST-ASCT/KCD CONS	ASCT N=89	KCD CONS N=91	P VALUE
Response improved	31 (34.8)	11 (12.1)	<0.001
Response remained the same	45 (50.6)	58 (63.7)	0.07
Response worsened	13 (14.6)	22 (24.2)	0.1

CARDAMON

MRD NEGATIVE RATES BY ARM



MAINTENANCE VS POST-ASCT/KCD CONS	ASCT N=75	KCD CONS N=67	P VALUE
MRD neg improved	11 (14.7)	8 (11.9)	0.6
MRD neg remained the same	59 (78.7)	52 (77.6)	0.9
MRD neg worsened	5 (6.7)	7 (10.4)	0.4

JAMA Oncology | Original Investigation

Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma

The MANHATTAN Nonrandomized Clinical Trial

Ola Landgren, MD, PhD; Malin Hultcrantz, MD, PhD; Benjamin Diamond, MD; Alexander M. Lesokhin, MD; Sham Mailankody, MBBS; Hani Hassoun, MD; Carlyn Tan, MD; Urvi A Shah, MD; Sydney X. Lu, MD, PhD; Meghan Salcedo, RN; Kelly Werner, RN; Jenna Rispoli, RN; Julia Caple, RN; Allison Sams, NP; Dennis Verducci, NP; Katie Jones, NP; Isabel Concepcion, NP; Amanda Ciardello, MS; Aisara Chansakul, BS; Julia Schlossman, BA; Elizabet Tavitian, BS; Tala Shekarkhand, BS; Angela Harrison, MS; Casey Piacentini, BS; Even H. Rustad, MD, PhD; Venkata Yellapantula, PhD; Kylee Maclaughlan, MD, PhD; Francesco Maura, MD; Heather J. Landau, MD; Michael Scordo, MD; David J. Chung, MD, PhD; Gunjan Shah, MD; Oscar B. Lahoud, MD; Katie Thoren, PhD; Kazunori Murata, PhD; Lakshmi Ramanathan, PhD; Maria E. Arcila, MD; Caleb Ho, MD; Mikhail Roshal, MD, PhD; Ahmet Dogan, MD, PhD; Andriy Derkach, PhD; Sergio A. Giralt, MD; Neha Korde, MD

JAMA Oncol. doi:10.1001/jamaoncol.2021.0611
Published online April 15, 2021.

D-KRD x 8 without ASCT (41 patients)

Figure 1. Response to Therapy, by Number of Cycles and Follow-up

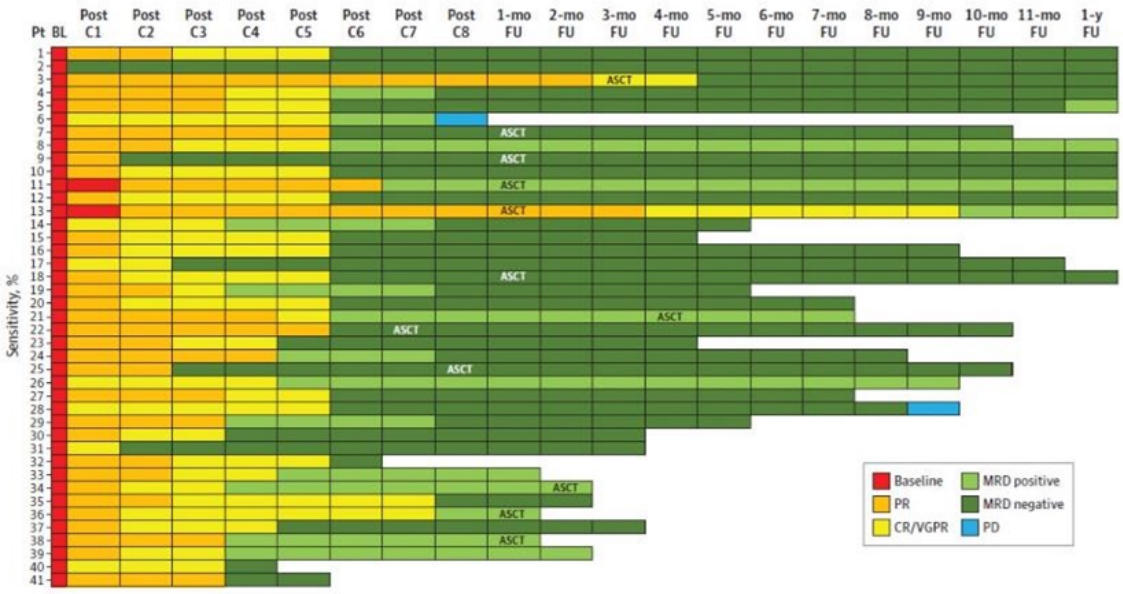
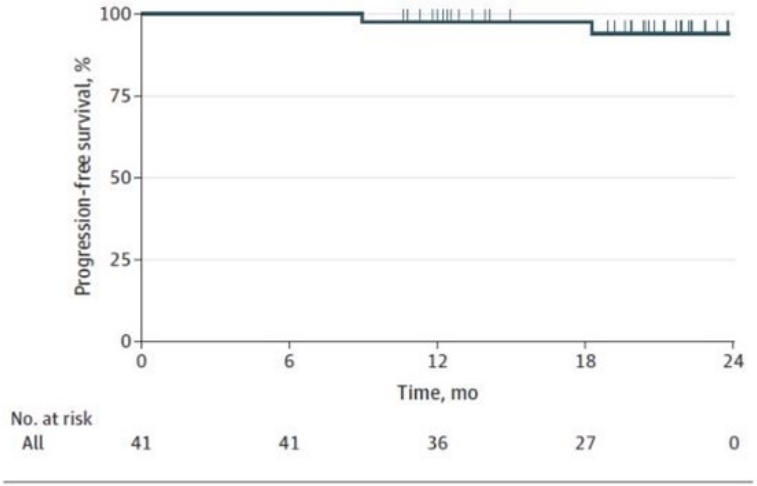


Figure 2. Progression-free Survival



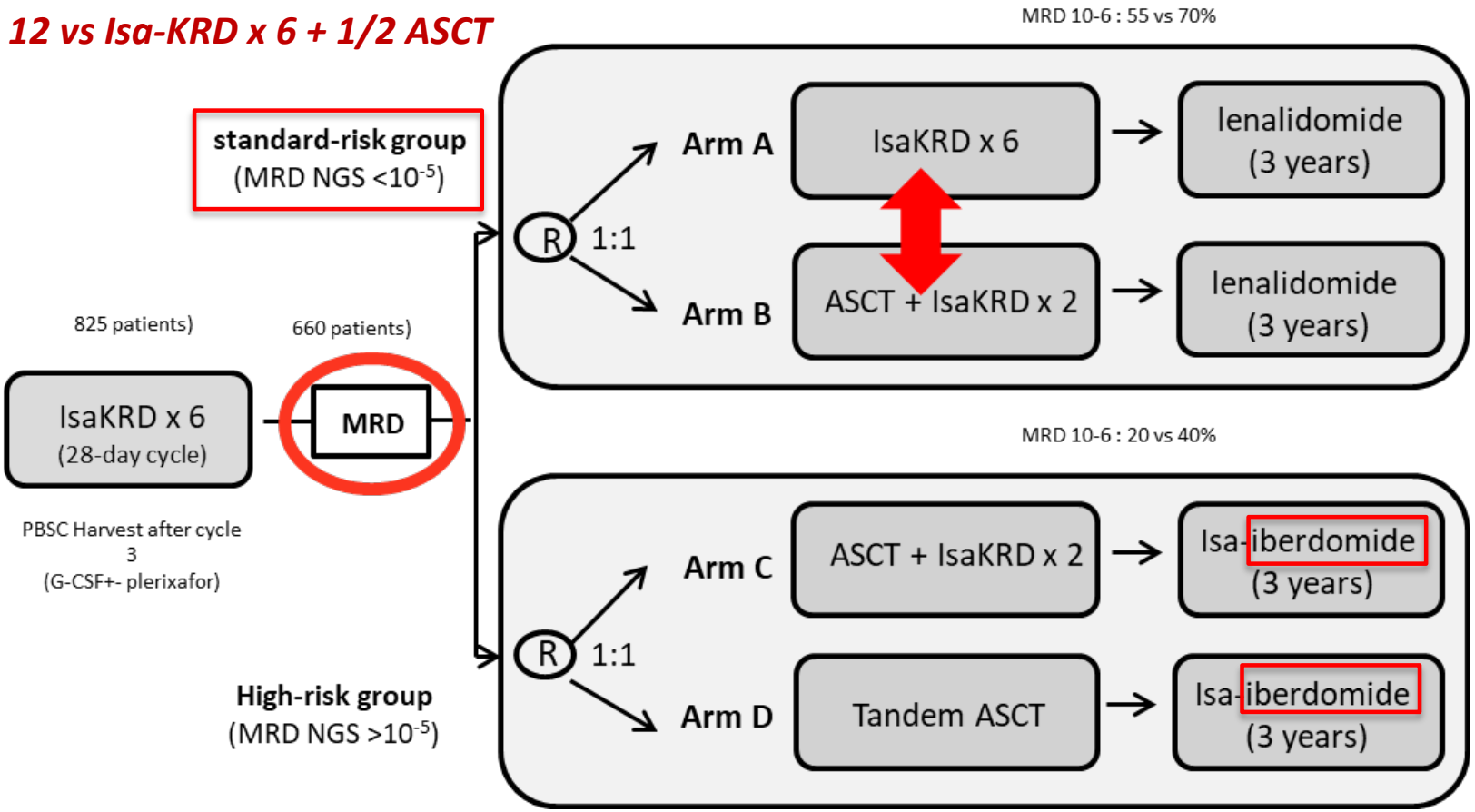
CR: 95%; MRD-: 71%

MIDAS study : MInimal res Disease Adapted Strategy

Induction and PBSC harvest

Risk-adapted consolidation and maintenance

Isa-KRD x 12 vs Isa-KRD x 6 + 1/2 ASCT



Which is the best induction therapy? VRd *vs* VTD

Figure 4. ≥ VGPR and MRD-Negative Rates After Induction and ASCT in the GEM Studies[a]

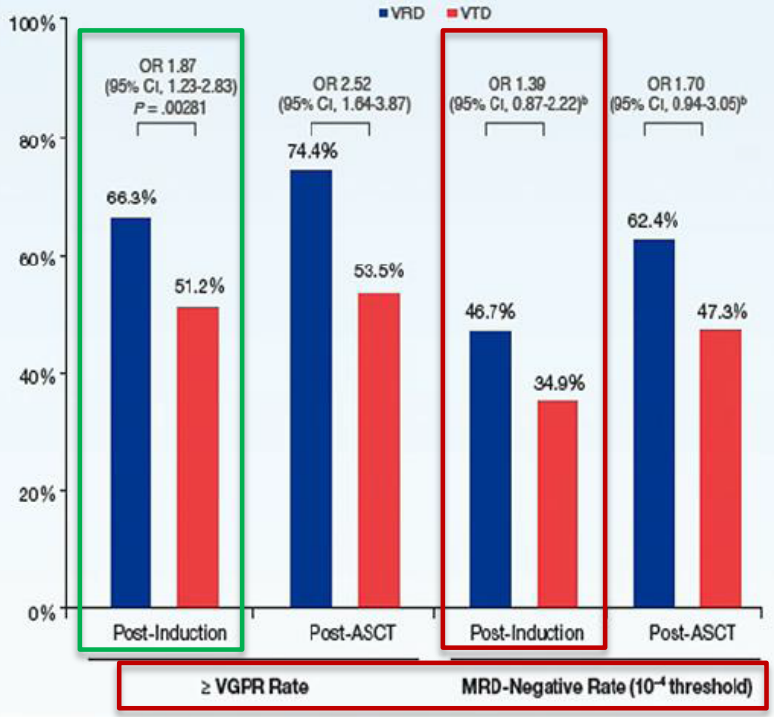
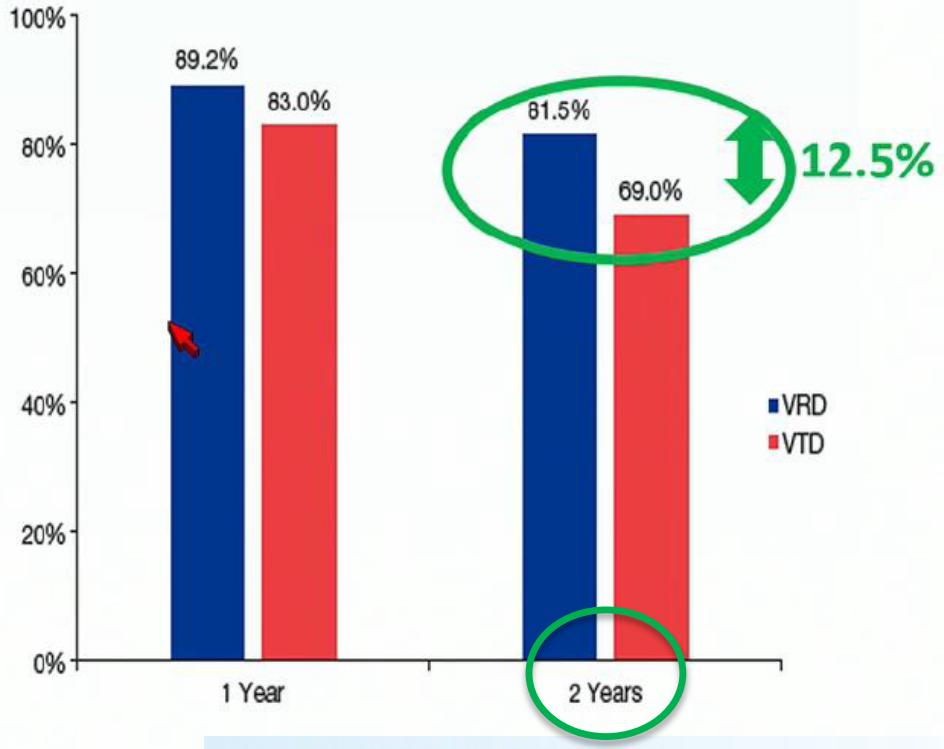


Figure 5. Event-Free PFS in the GEM Studies



Rosinol L et al. Blood. 2019 Oct 17; 134(16): 1337–1345.
Rosinol et al. EHA 2019

Table 3. Peripheral Neuropathy[a]

	VRD GEM2012 (n = 458)	VTD GEM2005 (n = 130)
Grade ≥ 2	95 (20.7)	58 (44.6)
Grade 3/4	25 (5.5)	20 (15.4)

Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial

Francesca Gay, Pellegrino Musto*, Delia Rota-Scalabrini, Luca Bertamini, Angelo Belotti, Monica Galli, Massimo Offidani, Elena Zamagni, Antonio Ledda, Mariella Grasso, Stelvio Ballanti, Antonio Spadano, Michele Cea, Francesca Patriarca, Mattia D'Agostino, Andrea Capra, Nicola Giuliani, Paolo de Fabritiis, Sara Aquino, Angelo Palmas, Barbara Gamberi, Renato Zambello, Maria Teresa Petrucci, Paolo Corradini, Michele Cavo, Mario Boccadoro*

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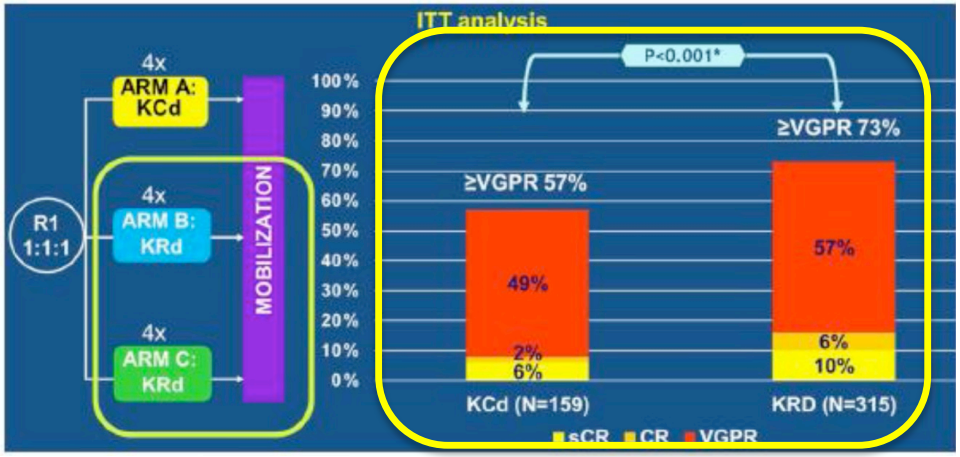
KRD vs KCD (+/- ASCT)

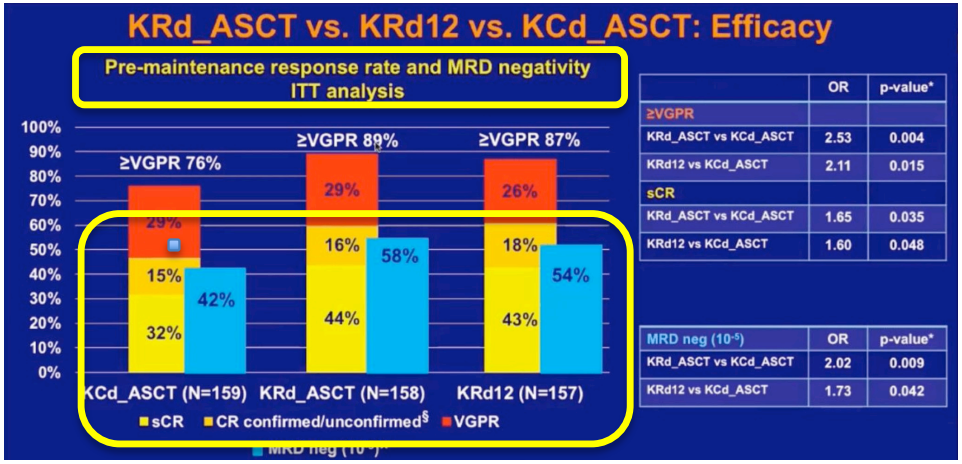


	Induction, intensification, and consolidation			Maintenance	
	KRd-ASCT (n=158)	KRd12 (n=157)	KCd plus ASCT (n=159)	Carfilzomib plus lenalidomide (n=178)	Lenalidomide (n=178)
Overall response	153 (97%)	148 (94%)	144 (91%)	178 (100%)	178 (100%)
Stringent complete response*	72 (46%)*	69 (44%)*	51 (32%)*	121 (68%)	115 (65%)
Complete response	13 (8%)	20 (13%)	15 (9%)	17 (10%)	18 (10%)
At least a complete response†	85 (54%)†	89 (57%)†	66 (42%)†	138 (78%)	133 (75%)
Very good partial response	55 (35%)	47 (30%)	55 (35%)	38 (21%)	38 (21%)
At least a very good partial response‡	140 (89%)‡	136 (87%)‡	121 (76%)‡	176 (99%)	171 (96%)
Partial response	13 (8%)	12 (8%)	23 (14%)	2 (1%)	7 (4%)
Stable disease	2 (1%)	1 (1%)	6 (4%)	..	..
Progressive disease	1 (1%)	..	5 (3%)	..	..
Not evaluable	2 (1%)	8 (5%)	4 (3%)	..	..
Minimal residual disease by multiparameter flow cytometry (sensitivity 10^{-5})§	98 (62%)§	88 (56%)§	69 (43%)§	145 (81%)	140 (79%)
Complete response: evaluable population	56	58	41	100	99
Minimal residual disease by next-generation sequencing (sensitivity 10^{-5})¶	45 (80%)	40 (69%)	30 (73%)	88 (88%)	82 (83%)

Data are n, n (%), or n (%; 95% CI). KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd-ASCT=four KRd induction cycles, MEL200-ASCT, four KRd consolidation cycles. KRd12=12 KRd cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, four KCd consolidation cycles. *p=0·027 for the overall comparison. †p=0·016 for the overall comparison. ‡p=0·0070 for the overall comparison. §p=0·0032 for the overall comparison. ¶In patients evaluable for complete response.

Table 2: Best response in the intention-to-treat population

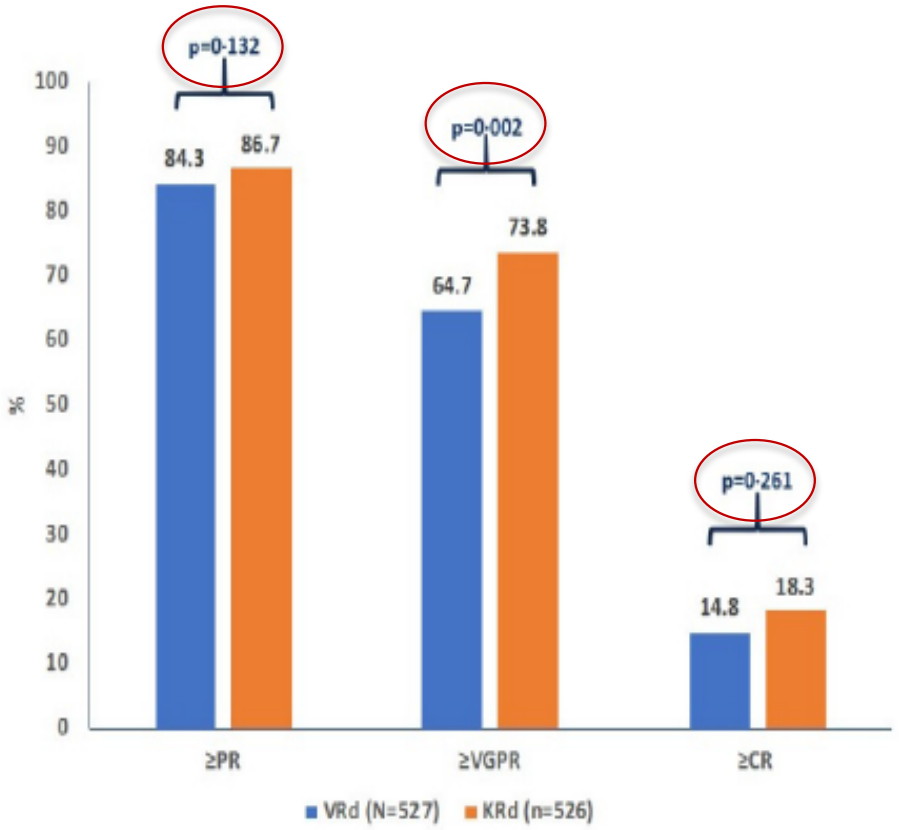
Gay F, et al. J Clin Oncol. 2019;37 Suppl:8002. Presented at ASCO 2019.



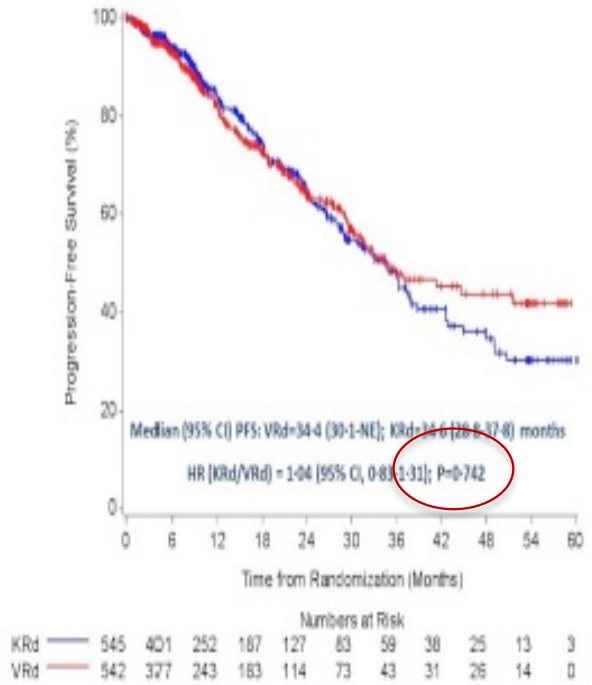
	OR	p-value*
≥VGPR		
KRd_ASCT vs KCd_ASCT	2.53	0.004
KRd12 vs KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT vs KCd_ASCT	1.65	0.035
KRd12 vs KCd_ASCT	1.60	0.048

MRD neg (10^{-5})	OR	p-value*
KRd_ASCT vs KCd_ASCT	2.02	0.009
KRd12 vs KCd_ASCT	1.73	0.042

VRD or KRD? The ENDURANCE phase III trial



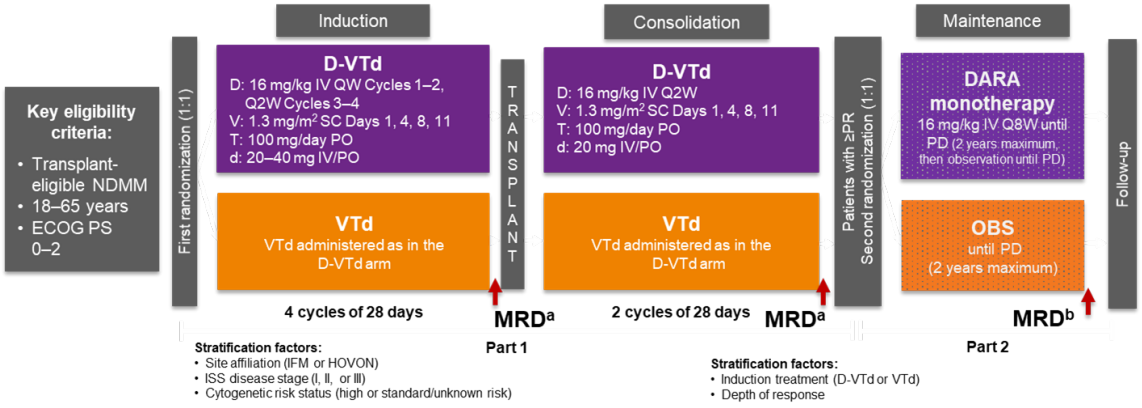
Progression Free Survival from Induction Randomization



- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31·7 (28·5-44·6) and KRd = 32·8 (27·2-37·5) months

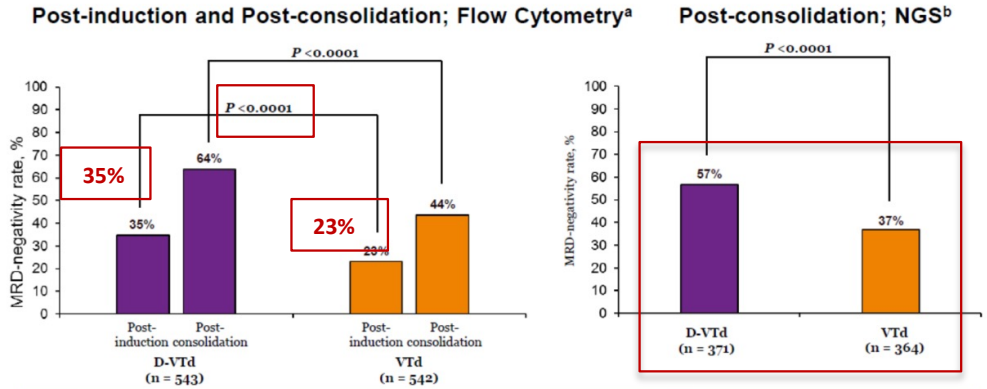
Low risk-patients without immediate intention to ASCT, VRD 12 cycles, KRD 9 cycles

D-VTD vs VTD



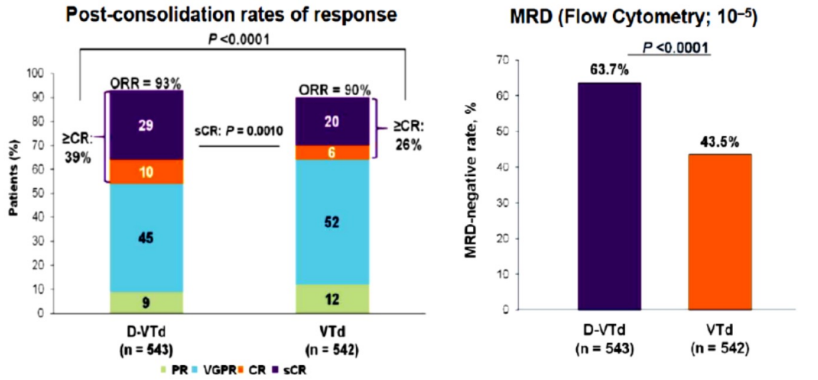
ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; QW, every week; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; PD, progressive disease; OBS, observation; IFM, Intergroupe Francophone du Myélome; HOVON, the Dutch-Belgian Cooperative Group for Hematology-Oncology.
[a]MRD analyses were performed at predefined time points for all patients, regardless of response. [b]MRD analyses were performed in patients with ≥VGPR at Weeks 25, 52, and 105.

MRD-negativity Rates (10^{-5})



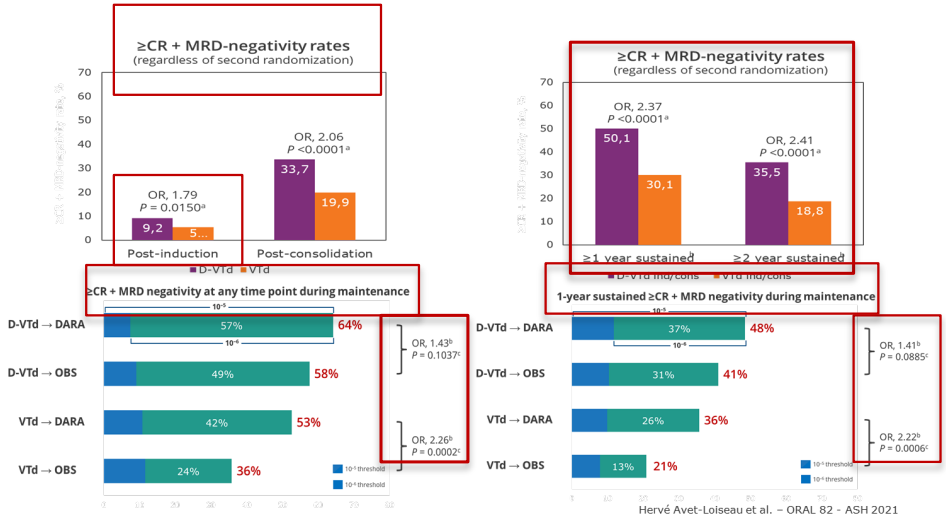
- Early (post-induction) significant difference in MRD-negativity rates for D-VTd versus VTd
- Post-consolidation MRD-negativity rates were significantly higher for D-VTd versus VTd, confirming post-induction MRD-negativity rates

CASSIOPEIA study: depth of response



D-VTd improved the rate of sCR (primary study endpoint), ≥CR and MRD negativity

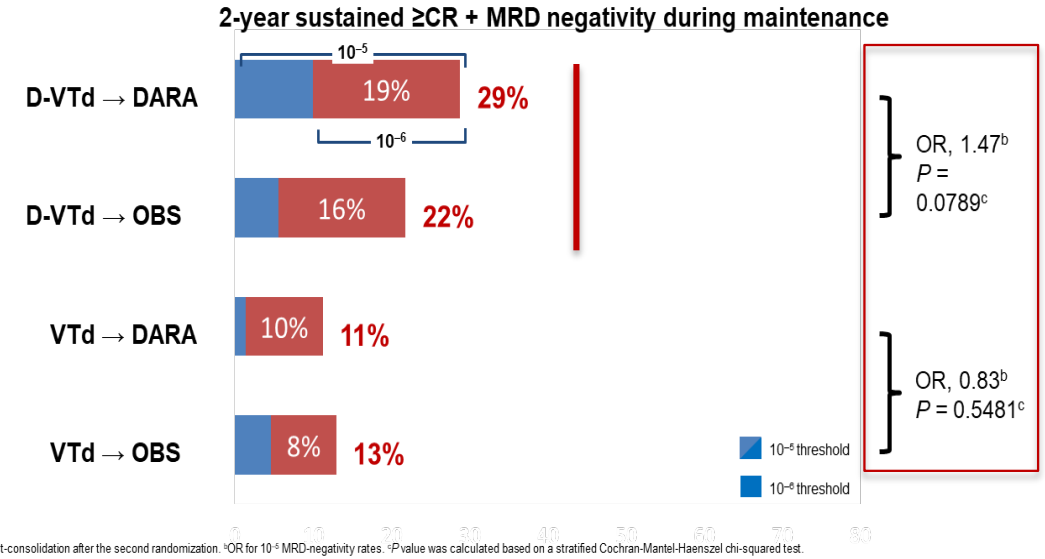
Moreau P et al. Lancet 2019



Hervé Avet-Loiseau et al. – ORAL 82 - ASH 2021

Hervé Avet-Loiseau et al. – ORAL 82 - ASH 2021

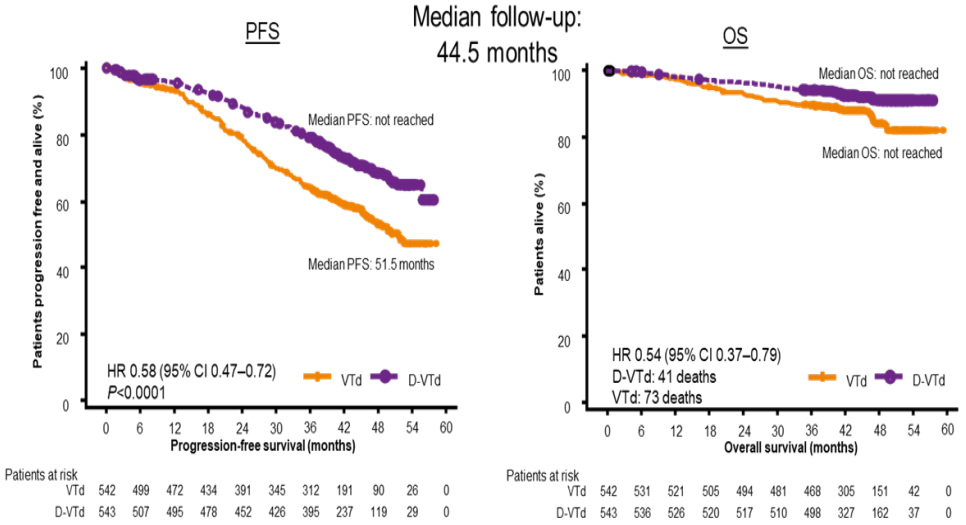
CASSIOPEIA: Rates of 2-year Sustained ≥CR + MRD Negativity at 10^{-5} and 10^{-6} (NGS) at Any Time Point During Maintenance[a]



[a]Post-consolidation after the second randomization. [b]OR for 10^{-5} MRD-negativity rates. [c]*P* value was calculated based on a stratified Cochran-Mantel-Haenszel chi-squared test.

Hervé Avet-Loiseau et al. – ORAL 82 - ASH 2021

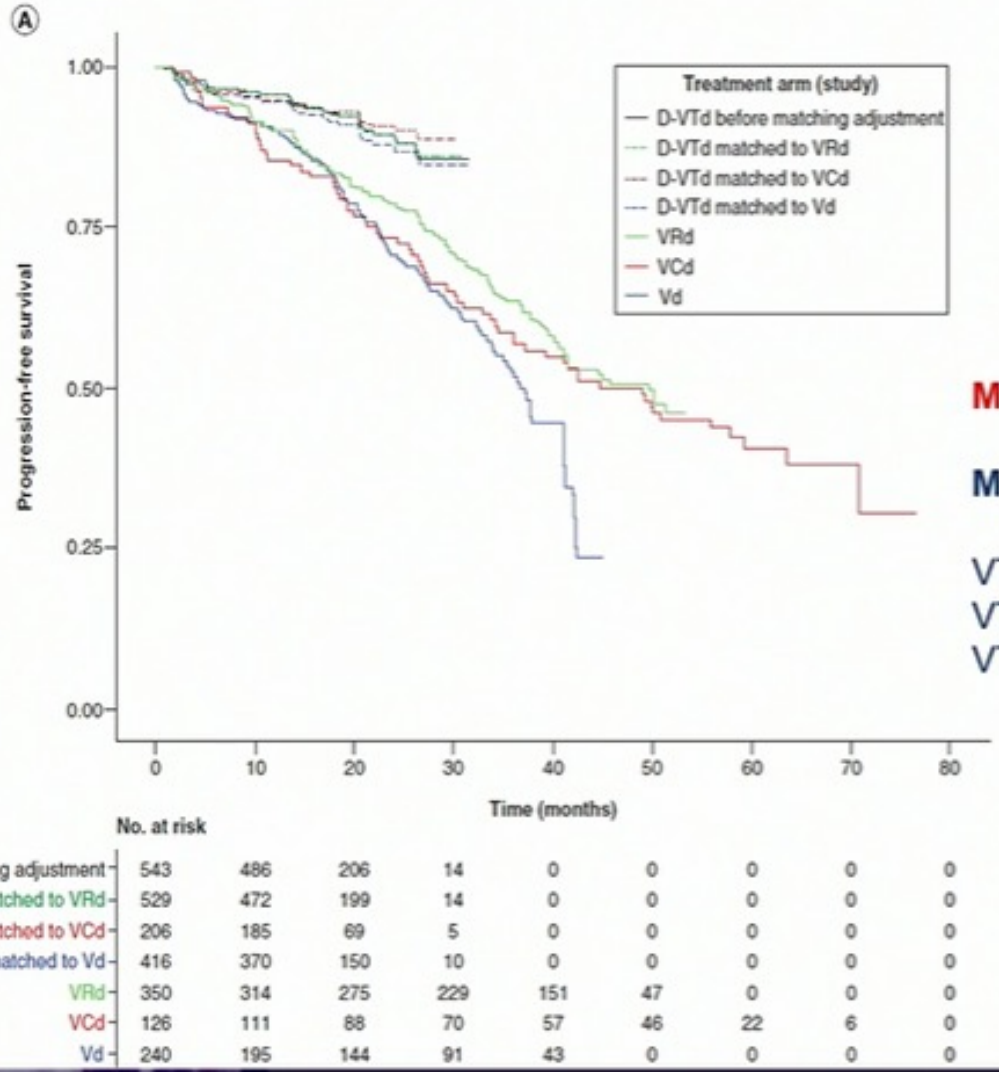
Updated Analyses From First Randomization Confirm Benefits of D-VTd vs VTd Induction/Consolidation



CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

Philippe Moreau et al., Lancet Oncol 2021, https://doi.org/10.1016/ S1470-2045(21)00428-9

Matchting adjusted indirect analysis (MAIC)



No. at risk

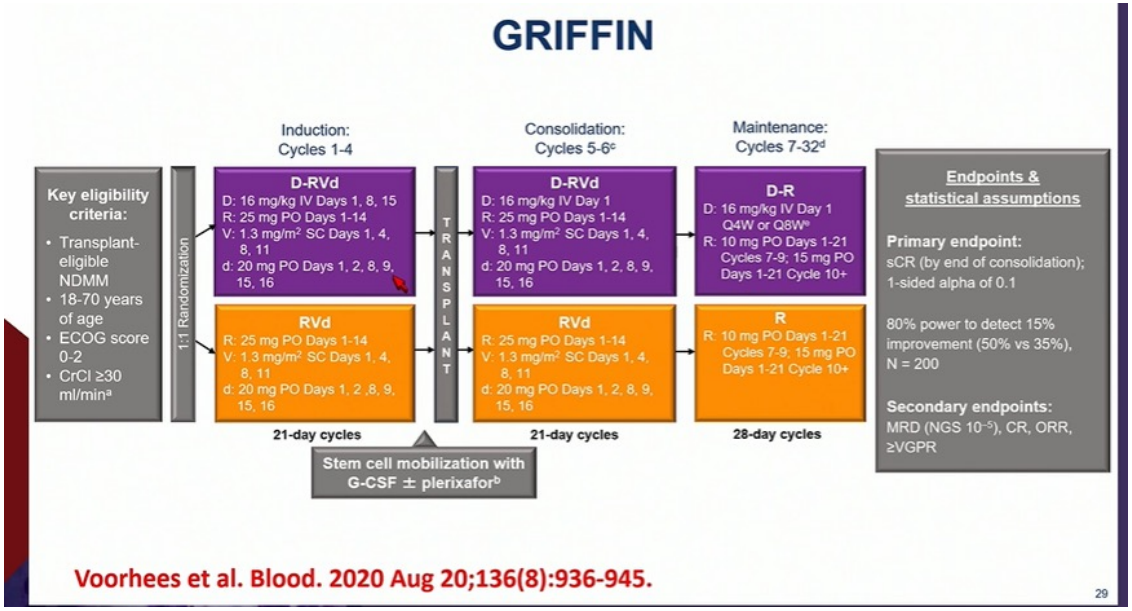
Treatment arm									
D-VTd before matching adjustment	543	486	206	14	0	0	0	0	0
D-VTd matched to VRd	529	472	199	14	0	0	0	0	0
D-VTd matched to VCd	206	185	69	5	0	0	0	0	0
D-VTd matched to Vd	416	370	150	10	0	0	0	0	0
VRd	350	314	275	229	151	47	0	0	0
VCd	126	111	88	70	57	46	22	6	0
Vd	240	195	144	91	43	0	0	0	0

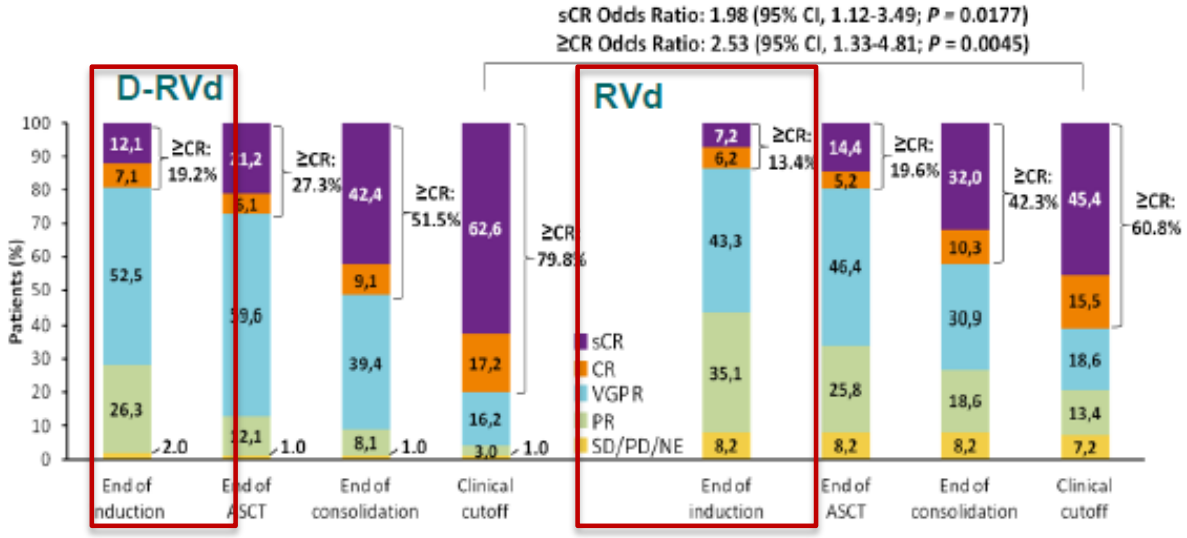
Moreau et al. Immunotherapy 2021

MAIC for PFS

VTD-dara vs VRD, HR 0.47
VTD-dara vs VCD, HR 0.35
VTD-dara vs VD, HR 0.42

D-VRD vs VRD

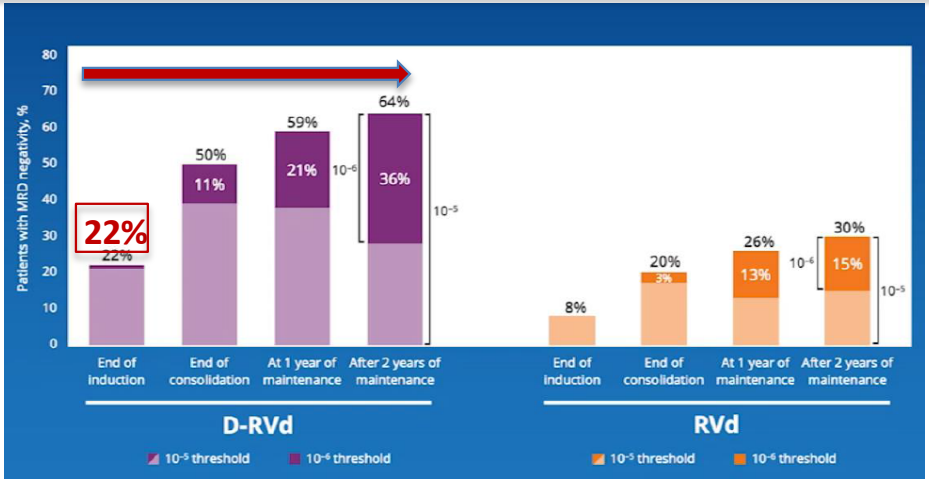




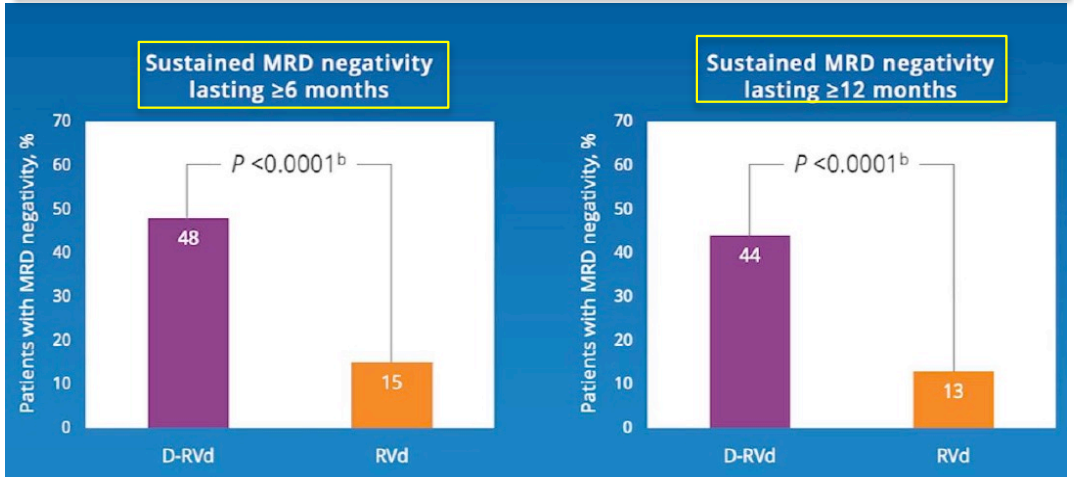
MRD-negativity (10^{-5}) post-induction:

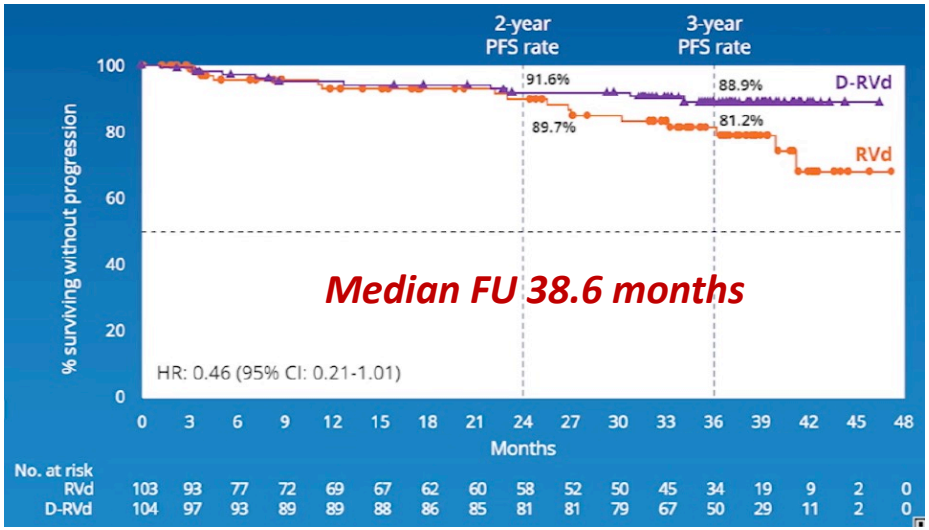
21.2% vs 5.8%

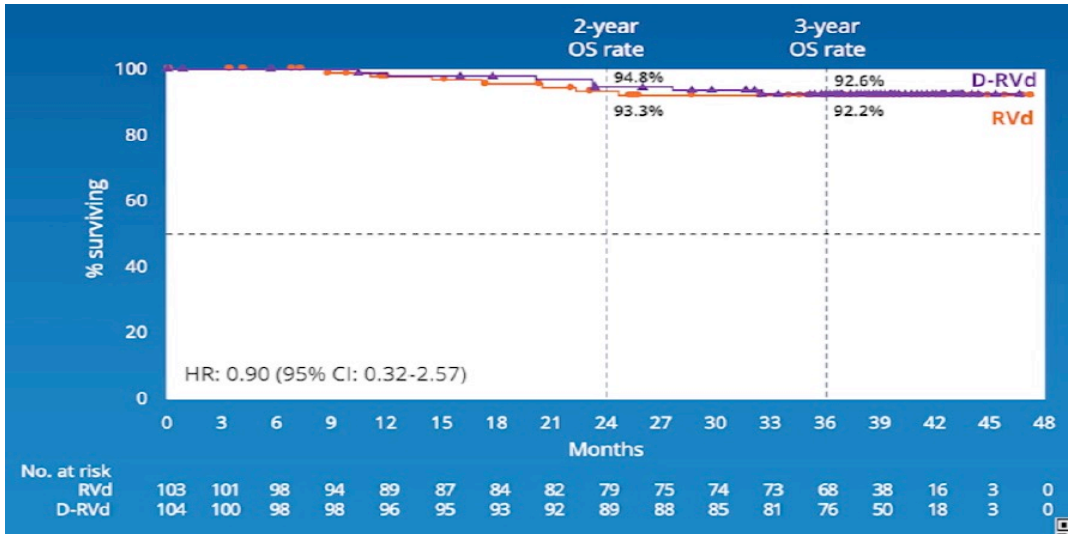
GRIFFIN: MRD-negativity[a] Rates Improved Throughout the DR Maintenance Period



GRIFFIN: D-RVd Improved Rates of Durable MRD Negativity[a] (10^{-5}) Lasting ≥6 Months or ≥12 Months Versus RVd

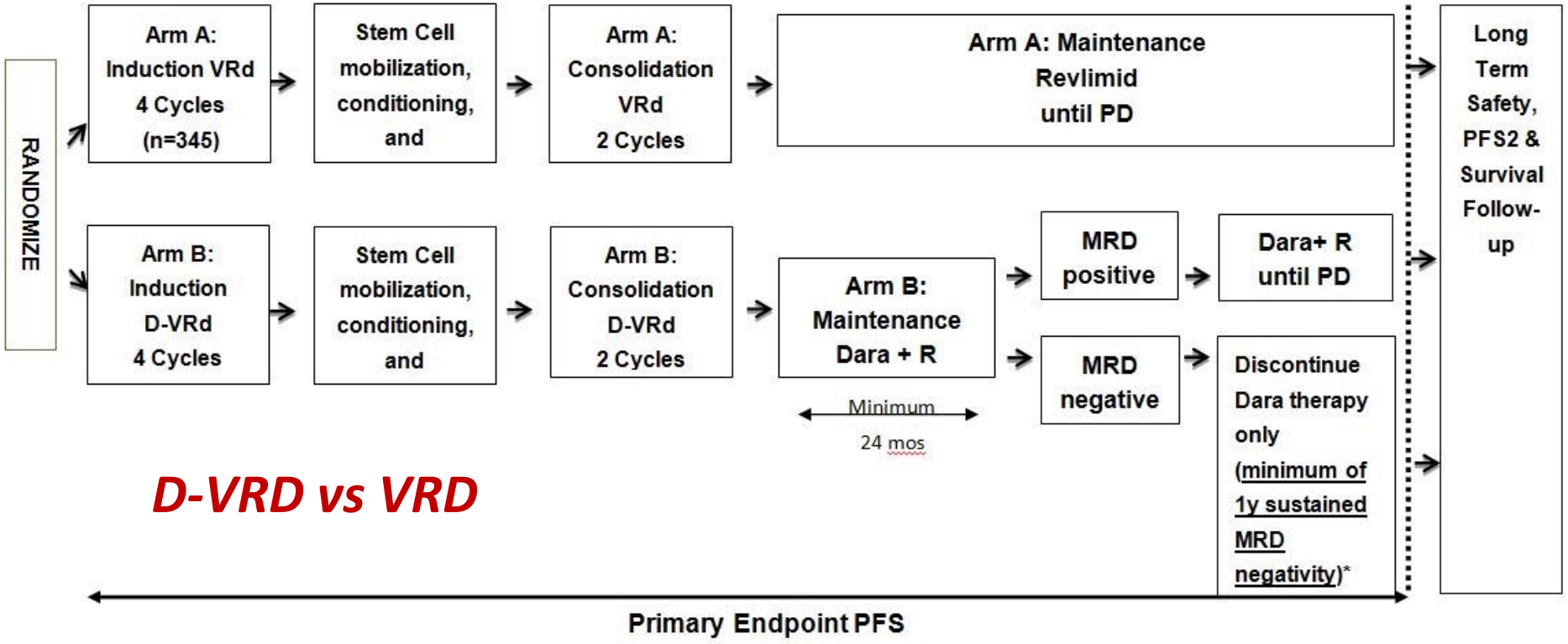






Laubach J et al, ASH 2021

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma who are Eligible for High-Dose Therapy. **The Perseus Study (EMN17)**



D-VRD vs VRD

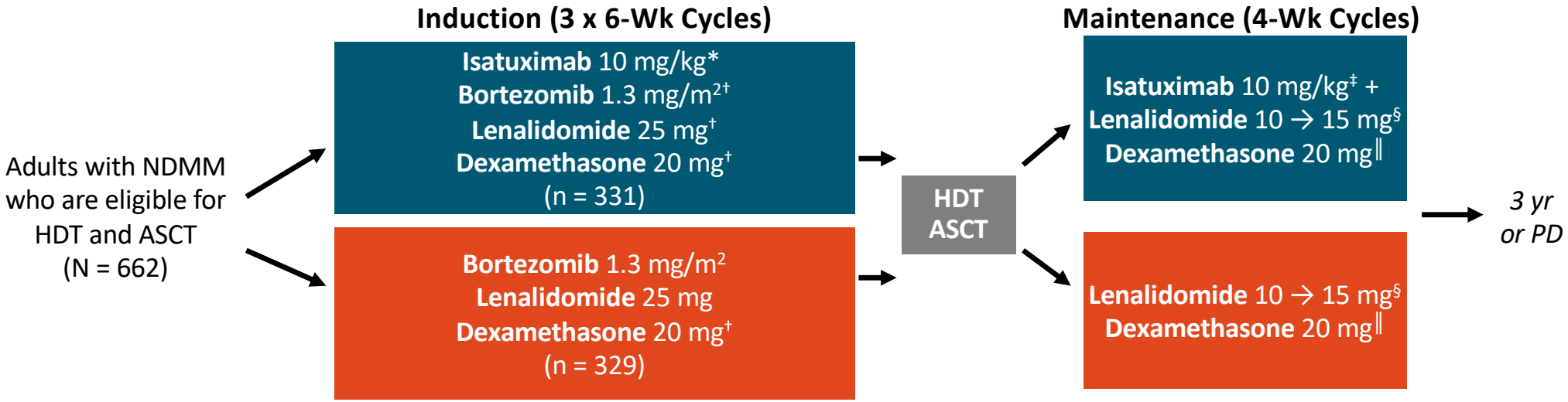
*opportunity to restart therapy upon relapse from CR or loss of MRD status

Key: CR=complete response; Dara=daratumumab; D-VRd=daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; MRD=minimum residual disease; PD=progressive disease; PFS2= progression-free survival on next line of therapy; R=lenalidomide; SPM=second primary malignancy; VRd=bortezomib, lenalidomide, and dexamethasone.

GMMG-HD7: Study Design

Isa-VRD (3 cycles) vs VRD (4 cycles)

- Open-label, randomized, multicenter phase III trial



*Cycle 1: D1, 8, 15, 22, 29; cycles 2-3: D1, 15, 29.
†Bortezomib D1, 4, 8, 11, 22, 25, 29, 32; lenalidomide Days 1-14 and 22-35; dexamethasone D1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33.
Data cutoff: April 2021.

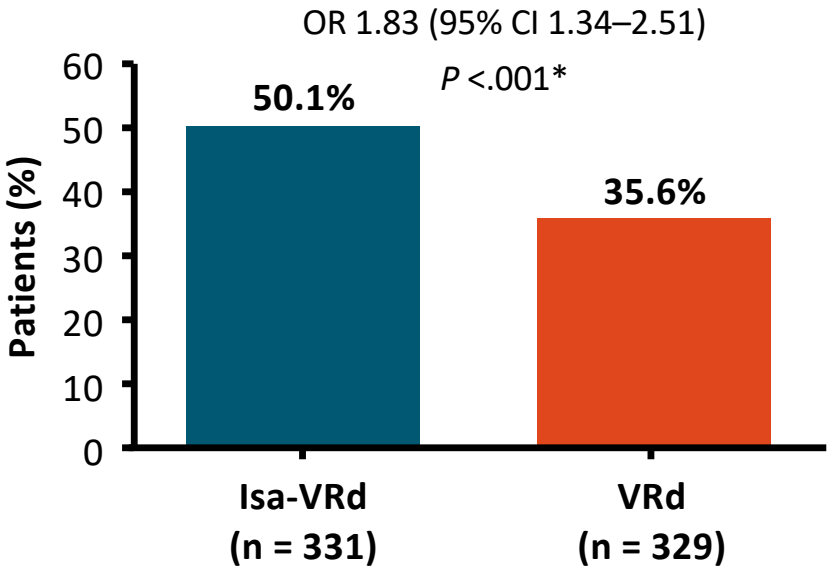
‡Cycle 1: D1, 8, 15, 22; Cycles 2-3: D1, 15; Cycle 4+: D1.
§Days 1-28. Increase dose to 15 mg after 3 mos
‖Dexamethasone D1, 8, 15, 22 in C1.

- Primary endpoint: MRD negativity at end of induction (NGF, sensitivity 10^{-5}) stratified according to R-ISS
- Secondary endpoints: CR after induction, safety
- MRD negativity assessed after cycle 3, HDT, 12 mos, and 24 mos as well as at end of study

Goldschmidt. ASH 2021. Abstr 463.

GMMG-HD7: MRD Negativity (Primary Endpoint) and Response Rates at End of Induction

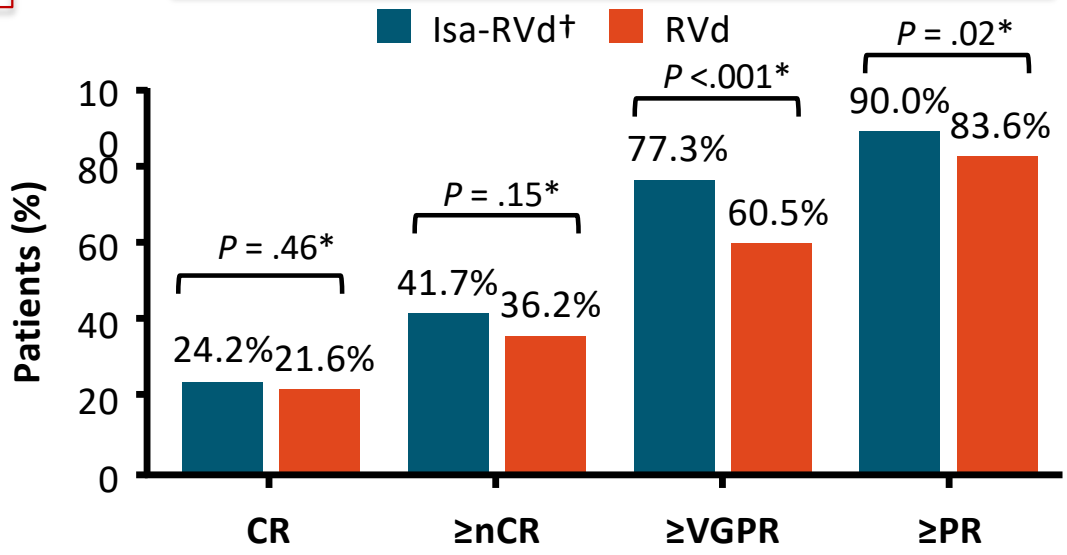
Patients with MRD Negativity at End of Induction



- Not assessable/missing* MRD status low: Isa-VRd, 10.6%; VRd, 15.2%

*Due either to loss to follow-up, missing bone marrow samples, or technical failures in measurement counted as nonresponders.

Response Rates at End of Induction



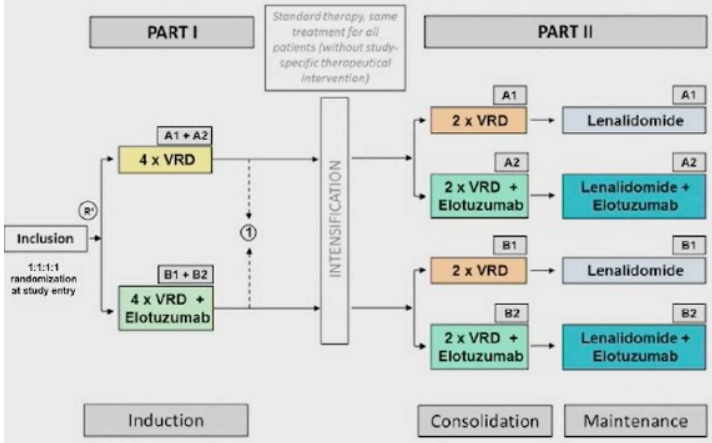
- Significant increase in ≥VGPR with Isa-VRd
- Significant increase in ORR

Goldschmidt. ASH 2021. Abstr 463.

Elotuzumab in Combination with Lenalidomide, Bortezomib, Dexamethasone and Autologous Transplantation for Newly-diagnosed Multiple Myeloma: Results from the Randomized Phase III GMMG-HD6 Trial

Elo-VRD vs VRD

GMMG-HD6: flow chart, eligibility criteria and endpoints



Key eligibility criteria

- TE NDMM 18 – 70 years
- WHO performance status 0-2 or 3 if MM-related

Primary efficacy endpoint

- PFS from randomization

Secondary endpoints (selection)

- OS from randomization
- CR rates after induction / consolidation
- best response on treatment

Response rates on study

(n / %)	RVD (N=278)	RVD + Elotuzumab (N=278)	p
≥ PR	237 / 85.2	230 / 82.7	0.54
≥ VGPR	147 / 52.9	163 / 58.6	0.14
CR	9 / 3.3	9 / 3.2	1.00
PD	8 / 2.9	6 / 2.2	0.79

post induction therapy

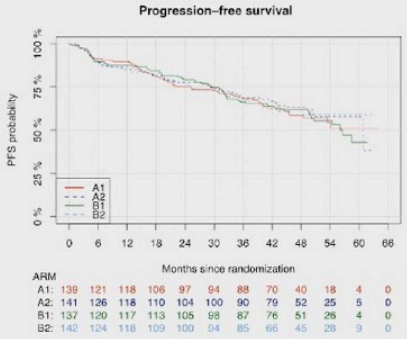
(n / %)	A1 (RVD+R) (n=123)	A2 (RVD+EloR) (n=124)	B1 (Elo-RVD+R) (n=119)	B2 (Elo-RVD+EloR) (n=124)	p
≥ VGPR	97 / 78.9	97 / 78.2	97 / 81.5	100 / 80.7	0.95
≥ PR	116 / 94.3	114 / 91.9	113 / 95.0	113 / 91.1	0.48

prior to consolidation therapy

Addition of elotuzumab to RVd did not increase high-quality responses (≥VGPR) after induction or consolidation compared to RVd alone

RVd, lenalidomide, bortezomib, dexamethasone; Elo, elotuzumab; R, lenalidomide; WHO, World Health Organization; PR, partial response; VGPR, very good partial response; CR, complete response; PD, progressive disease.

Progression-free survival



3-year PFS rates

Overall: 67.7% (95% CI: 63.7-71.7%)

A1: 68.8% (95% CI: 60.9-76.8%)

A2: 68.5% (95% CI: 60.7-76.4%)

B1: 66.2% (95% CI: 58.2-74.3%)

B2: 67.2% (95% CI: 59.2-75.2%)

Primary endpoint „to detect a difference between the four treatment arms" (adjusted logrank p value stratified by ISS at randomization, p=0.86)

A1: RVd+R; A2: RVd+EloR; B1: Elo-RVd+R; B2: Elo-RVd+EloR; RVd, lenalidomide, bortezomib, dexamethasone; elo, elotuzumab; PFS, progression-free survival; ISS, International Staging System; 95 % CI: 95% confidence interval.

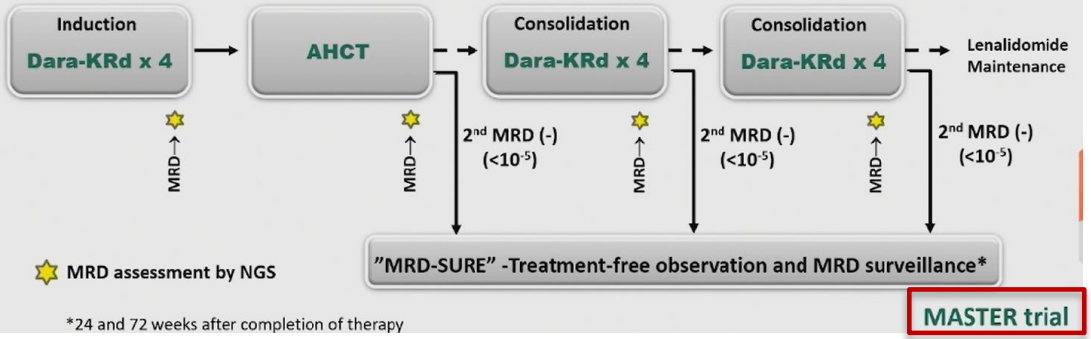
Dara-KRD

18th IMW

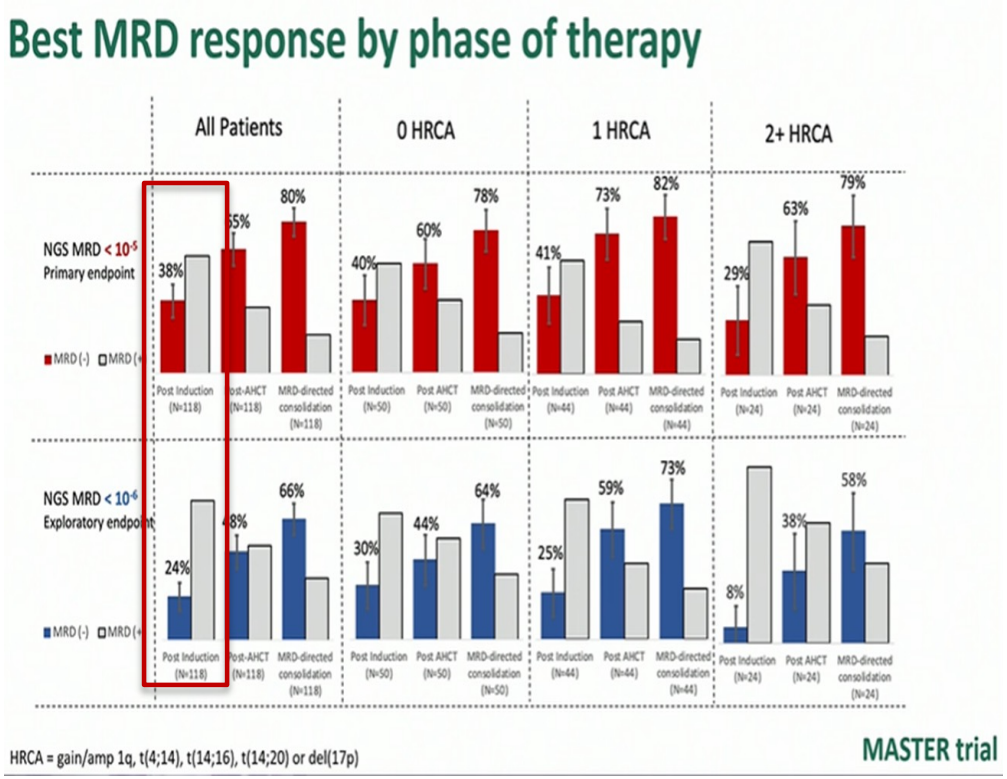
Treatment

Dara-KRd

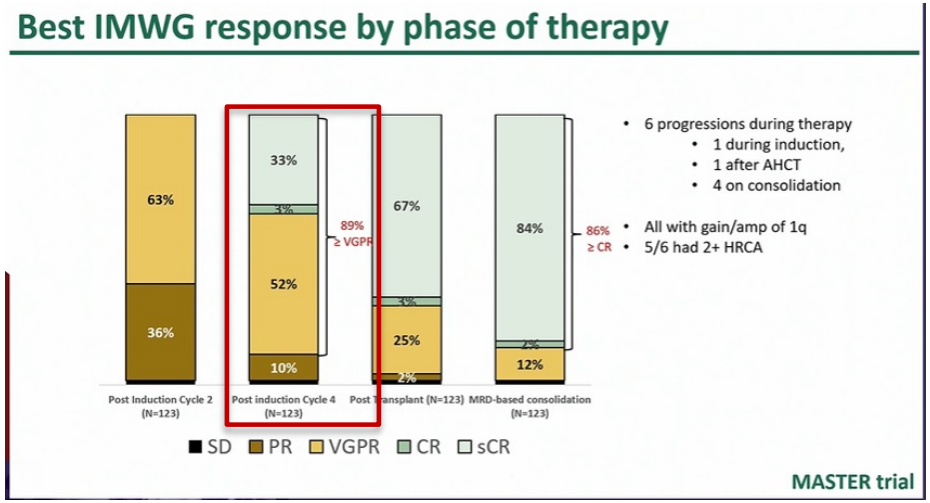
- Daratumumab 16 mg/m² days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m² Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



Best MRD response by phase of therapy

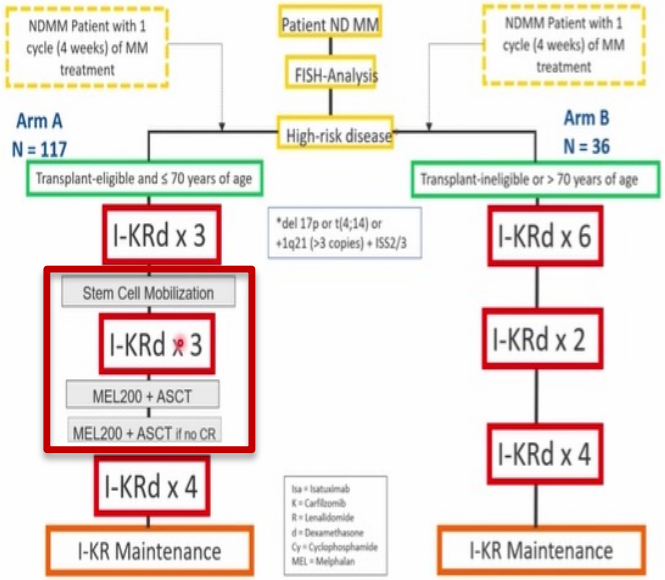


Best IMWG response by phase of therapy



Post induction: 89% > VGPR, 38% MRD- 10^{-5} (primary end-point), 24% 10^{-6} (exploratory end-point), including HR disease

Study Design – GMMG CONCEPT (NCT03104842)



Isa-KRd Induction

Cycle 1

Isatuximab	10 mg/kg	day 1, 8, 15, 22
Carfilzomib	20 mg/m²	day 1, 2
Carfilzomib	36 mg/m²	day 8, 9, 15, 16
Lenalidomide *	25 mg	day 1-21
Dexamethasone**	40 mg*	day 1, 8, 15, 22

28-day-cycle

Isa-KRd Induction

Cycle 2-6

Isatuximab	10 mg/kg	day 1, 15
Carfilzomib	36 mg/m²	day 1, 2, 8, 9, 15, 16
Lenalidomide **	25 mg	day 1-21
Dexamethasone***	40 mg*	day 1, 8, 15, 22

28-day-cycle

* Cy-based mobilisation was moved in an amendment to time point after 3 induction cycles
**Dose adaption of lenalidomide according to renal function
***20 mg in patients ≥75 years

Isa-KRD

Leipoldt LB et al, EHA 2021

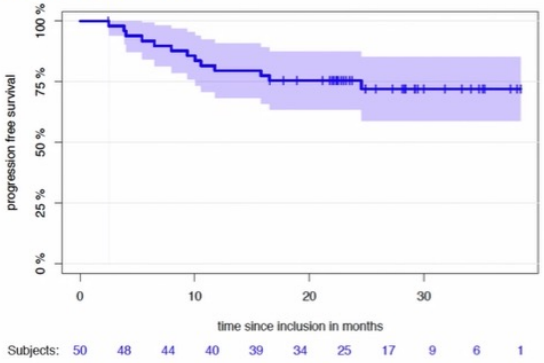
Results: Best response to therapy, 6 induction cycles

All evaluable patients: n = 50

- Overall response rate (ORR, ≥ PR): 100%
- ≥ VGPR : 90%; CR/sCR: 46%
  - Arm A: 41/46 ≥ VGPR
  - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
  - 20 patients MRD negative
  - 11 patients MRD positive **60% MRD neg**
  - 2 not assessable

Results of MRD assessments after induction treatment are not reported and available yet

Progression-free Survival



Median follow-up: 24.9 months

- 12-month PFS: 79.6% (68.3%; 90.9%)
- 24-month PFS: 75.5% (63.5%; 87.6%)

Data cut-off: Jan. 26, 2021
(95%-confidence level)

40/50 patients were relapse-free after 1 year

63rd ASH
Annual Meeting

Daratumumab, Cyclophosphamide, Bortezomib, Lenalidomide, Dexamethasone (Dara-CVRd), V-Augmented Autologous Stem Cell Transplant (V-ASCT) and Dara-VRd Consolidation in Ultra-High Risk (UHiR) Newly Diagnosed Myeloma (NDMM) and Primary Plasma Cell Leukemia (pPCL) Compared with Myeloma XI Trial Treatment for UHiR MM: the UK OPTIMUM/MUKnine Trial.

Martin F. Kaiser, Andrew Hall, Katrina Walker, Nicola Newnham, Ruth M De Tute, Sadie Roberts, Emma Ingleson, Kris Bowles, Mamta Garg, Anand Lokare, Christina Messiou, Graham Jackson, Gordon Cook, Guy Pratt, Roger G. Owen, Mark T Drayson, Sarah R Brown, Matthew W Jenner

OPTIMUM MUK9 INVESTIGATORS

Dara-CVRD vs Myeloma XI (KCRD or CRD) (Ultra-HR and PPCL, de-escalation)

Trial therapy

OPTIMUM

Bridging	Induction		Consolidation 1	Consolidation 2	Maintenance
Max 2 cycles	Max 6 cycles (incl bridging)		6 Cycles Start 100-120d post ASCT	12 Cycles	Until progression
SOC (VTD CVD)	**Dara-CVRd** Daratumumab iv 16 mg/kg Cycle 1&2: Days 1, 8, 15 Cycle 3+: Day 1 Cyclophosphamide po 500 mg Days 1, 8 Bortezomib sc 1.3 mg/m² Days 1, 4, 8, 11* Lenalidomide po 25 mg Days 1-14 Dexamethasone po 40 mg† Days 1, 4, 8, 11 21d cycles	Stem Cell Mobilisation	**V-HD-MEL +ASCT** Melphalan iv 200 mg/m² Day -1 Autologous Stem Cell Translantation Day 0 Bortezomib 1.3 mg/m² Days -1, +5, +14,* Weekly after haematopoietic recovery	**Dara-VRd** Daratumumab sc 1800 mg Day 1 Bortezomib sc 1.3 mg/m² Days 1, 8, 15, 22* Lenalidomide po 25 mg Days 1-21 Dexamethasone po 40 mg † Day 1, 8, 15, 22 28d cycles	**Dara-VR** Daratumumab sc 1800 mg Day 1 Bortezomib sc 1.3 mg/m² Days 1, 8, 15* Lenalidomide po 25 mg Days 1-21 28d cycles	**Dara-R** Daratumumab sc 1800 mg Day 1 Lenalidomide po 25 mg Days 1-21 28d cycles

*Permissive bortezomib dose reduction schedule 1.25mg for elderly/frailer

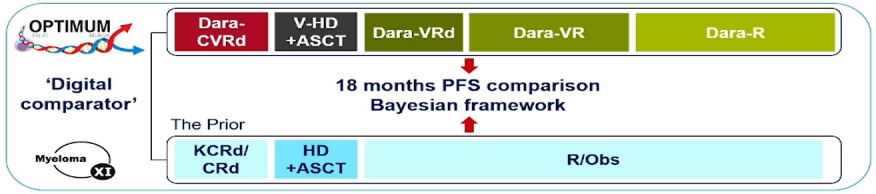
Trial objectives

Evaluate efficacy of Dara-(C)VRd before and after ASCT in Ultra High-Risk MM and PCL

- **Progression free survival at 18 months compared against The Prior**
- Response and MRD after induction and ASCT
- Determine safety and toxicity of Dara-CVRd induction and Dara-VRd consolidation

Brown S. et al., BMJ Open 2021 8

Digital comparator trial – OPTIMUM



OPTIMUM design:

Near-concurrent external dataset: 'winning' arms from large phase 3 Myeloma XI trial

- KCRd (carfilzomib, cyclophosphamide, lenalidomide, dexamethasone) or CRd induction
- **Recruited in same healthcare system**, same geography, virtually identical trial entry criteria

At time of OPTIMUM design, results for MyXI KCRd or CRd were **not yet analysed**

- Pre-define probability threshold for range of possible outcomes

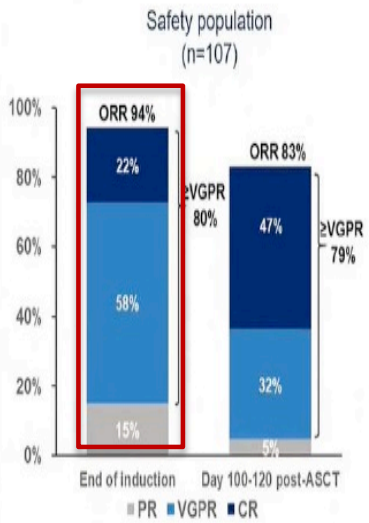
6

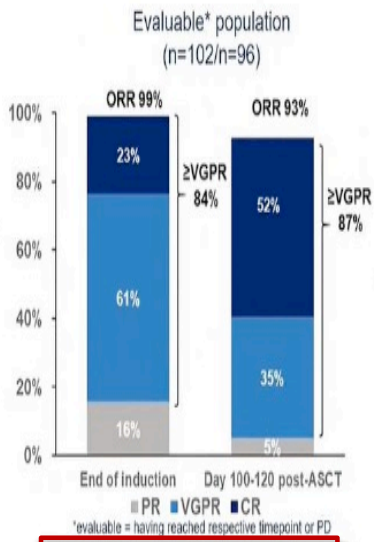
Brown S. et al., BMJ Open 2020
Jackson G., et al., PLOS Med 2021

Central response results

18th IMW

Response Safety Population (n=107)	End of induction	100-120 days post-ASCT
CR	23 (21.5%)	50 (46.7%)
VGPR	62 (57.9%)	34 (31.8%)
PR	16 (15.0%)	5 (4.7%)
PD	1 (0.9%)	7 (6.5%)
Timepoint not reached	5 (4.7%)	11 (10.3%)



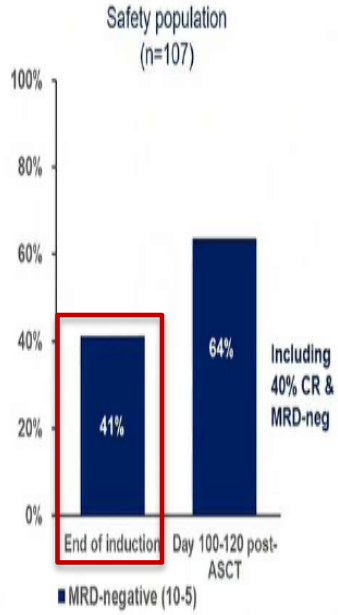


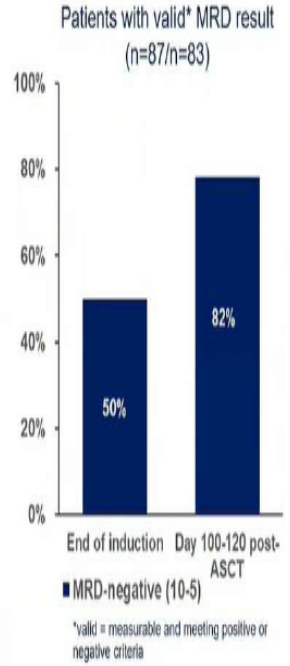
After induction ORR 94%, ≥ VGPR 80%

pPCL (evaluable D100-120; n=8)
- CR: 2 (25%)
- VGPR: 2 (25%)
- PR: 2 (25%)
- PD: 2 (25%)

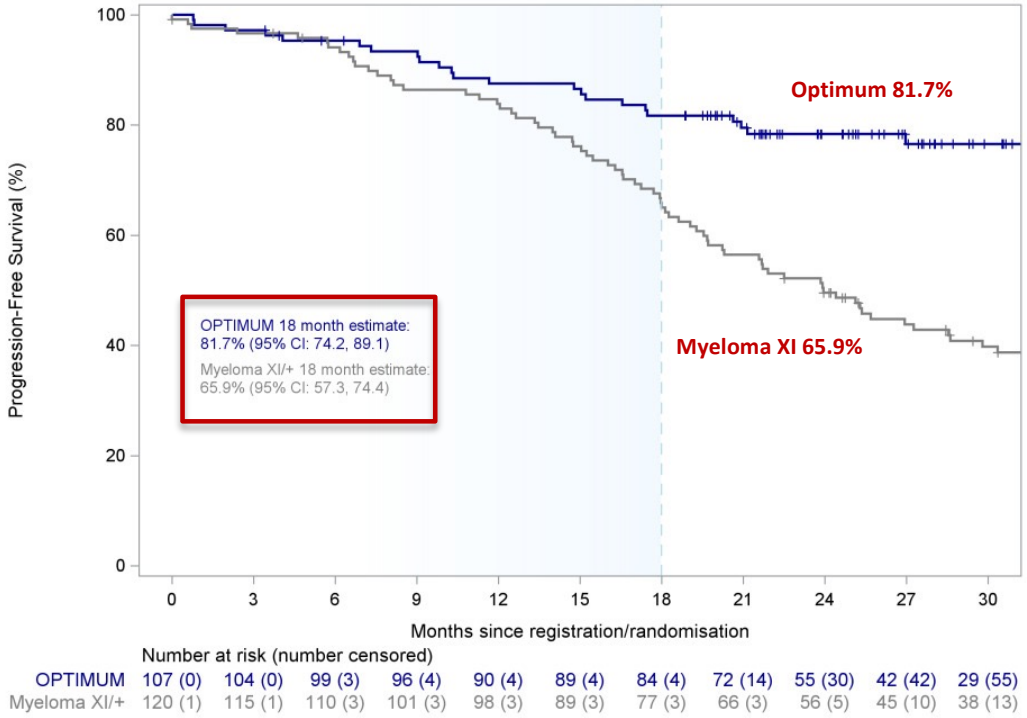
Central response results - MRD

MRD Safety Population (n=107)	End of induction	100-120 days post-ASCT
MRD-neg	44 (41.1%)	68 (63.6%)
MRD-pos	43 (40.2%)	15 (14.0%)
Inadequate or no sample	15 (14.0%)	13 (12.1%)
Timepoint not reached	5 (4.7%)	11 (10.3%)

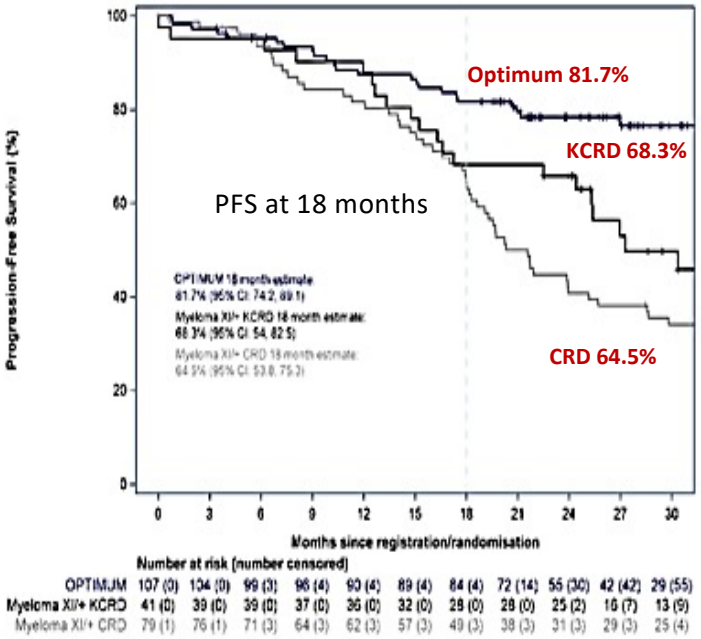




After induction MRD- 10^{-5} 41%



Dara-CVRd (OPTIMUM) vs. KCRd vs. CRd (Myeloma XI)



Presented by: Martin Kaiser, MD, FRCP, FRCPath
@MyMKaiser

Daratumumab Plus Ixazomib, Lenalidomide and Dexamethasone as Extended Induction and Consolidation Followed by Lenalidomide maintenance in Standard-Risk Transplant-Eligible Newly Diagnosed Multiple Myeloma Patients (IFM 2018-01): a phase II study of the IFM group

Dara-IRD (extended induction, standard risk)

IFM 2018-01 study design

NDMM < 66y
FISH screening
No t(4;14)
No t(14;16)
No del17p

Induction IRd-Dara_21d-cycles 1-6

Ixazomib 3mg	Lenalidomide 25mg	Dexamethasone 40mg	Daratumumab 16mg/kg (IV)
D1, D4, D8, D11	D1-D14	D1, D8, D15	C1-4: D1, D8, D15 ; C5-6: D1, D15

Mobilization & HSC collection

Cyclophosphamide 3g/m² IV	G-CSF 10 µg/kg/d	HSC collection

Intensification & ASCT

Melphalan 200 mg/m² IV D-2	HSC infusion D0	PegG-CSF D+2

Consolidation IRd-Dara_28d-cycles 7-10

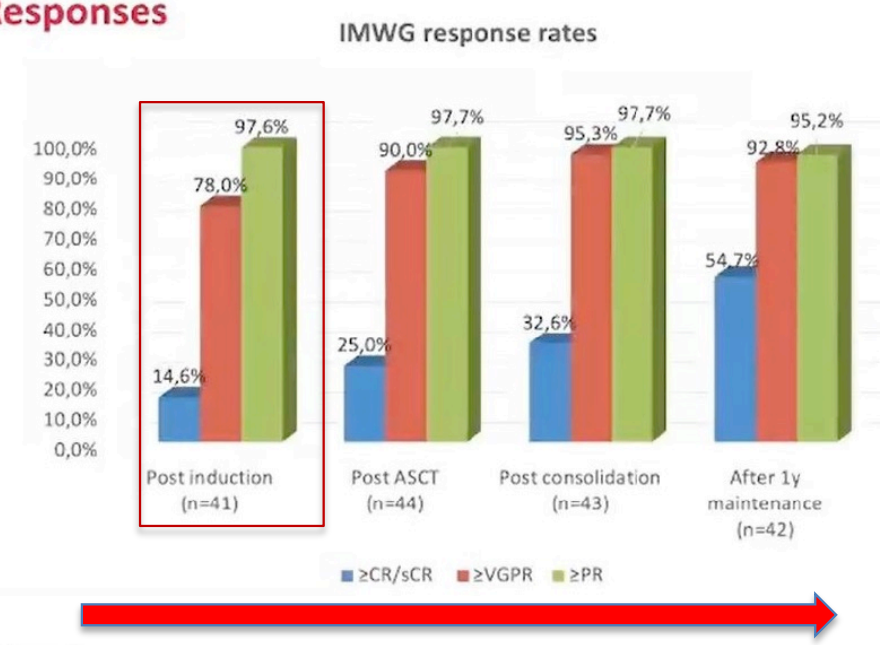
Ixazomib 4mg	Lenalidomide 25mg	Dexamethasone 20mg	Daratumumab 16mg/kg (IV)
D1, D8, D15	D1-D21	C7-8: D1, D8, D15, D22; C9-10: D1, D15	D1, D15

Maintenance 28d-cycles x 26 (2y) or until progression

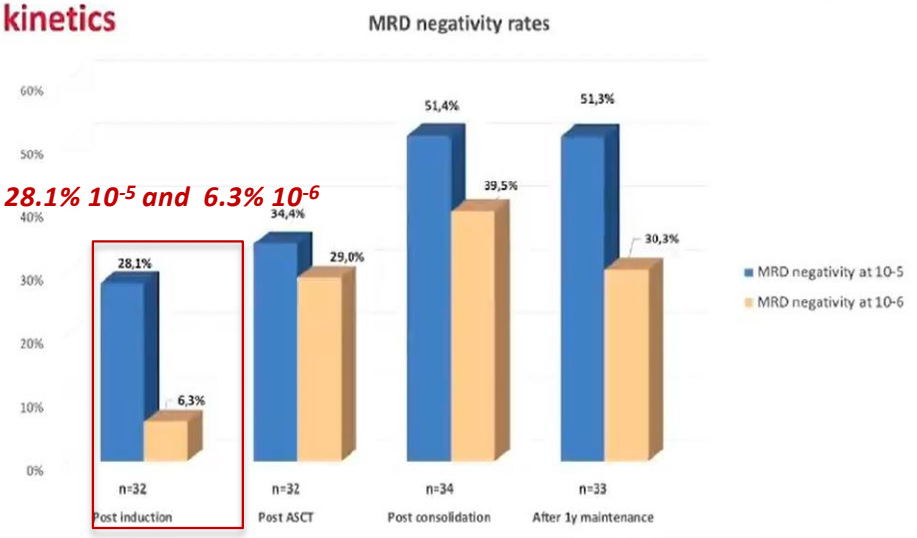
Lenalidomide 10 mg D1-D21

Perrot A et al, ASH 2021

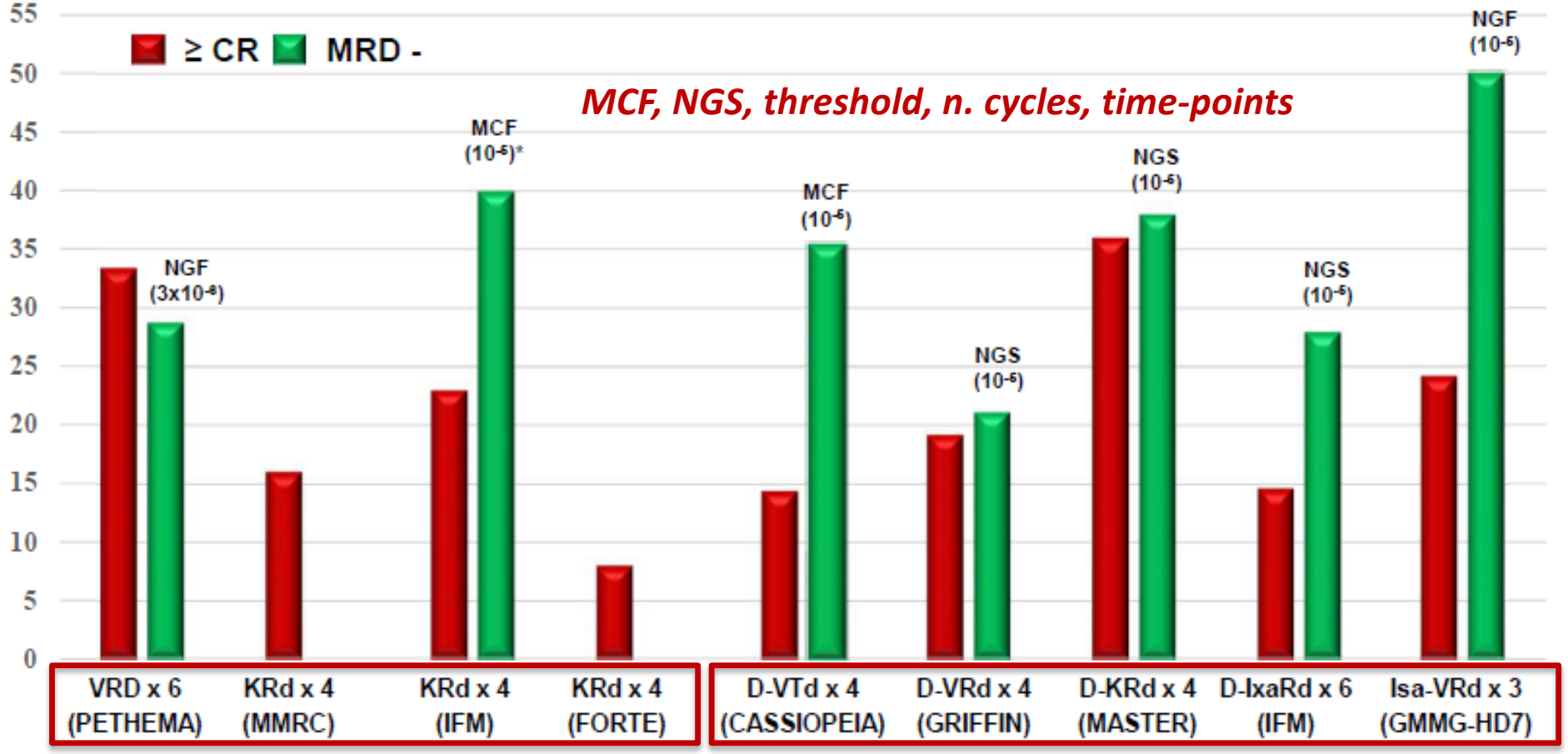
IMWG Responses



MRD kinetics



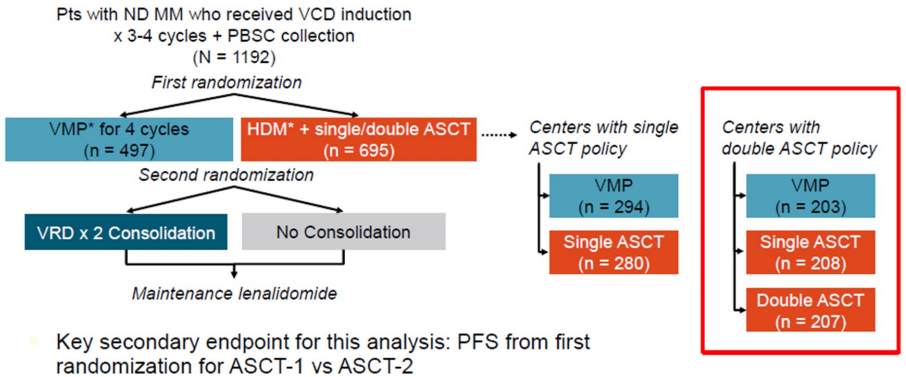
Response rates after induction of the main triplet and quadruplet drug combinations



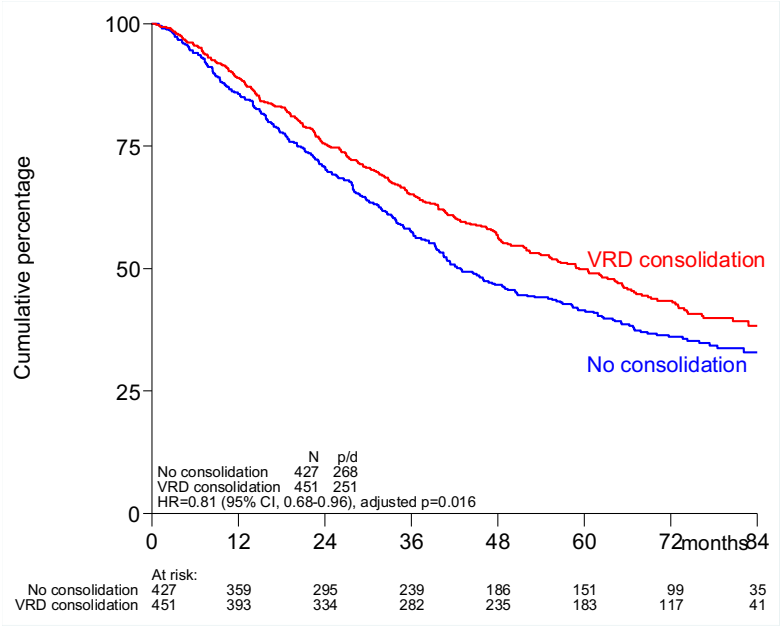
* Only patients with ≥ CR

Consolidation

EMN02/HO95: Phase III Study Design



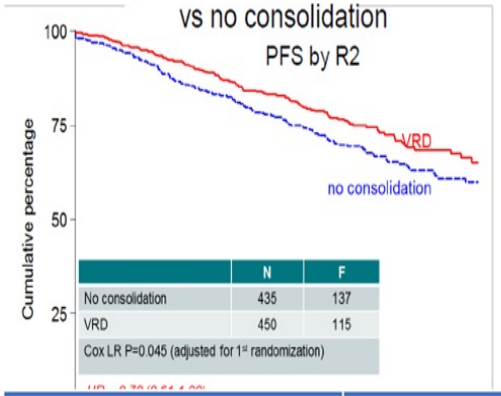
- Key secondary endpoint for this analysis: PFS from first randomization for ASCT-1 vs ASCT-2



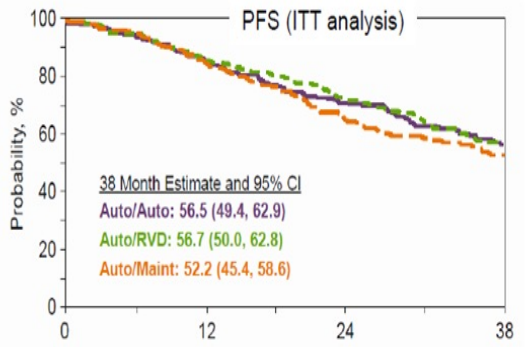
Sonneveld P, et al. JCO 2021

VTD: upgrade to CR by 30%
VRD: upgrade CR 38% vs 26%

EMN02 phase 3 study of VRD consolidation vs no consolidation

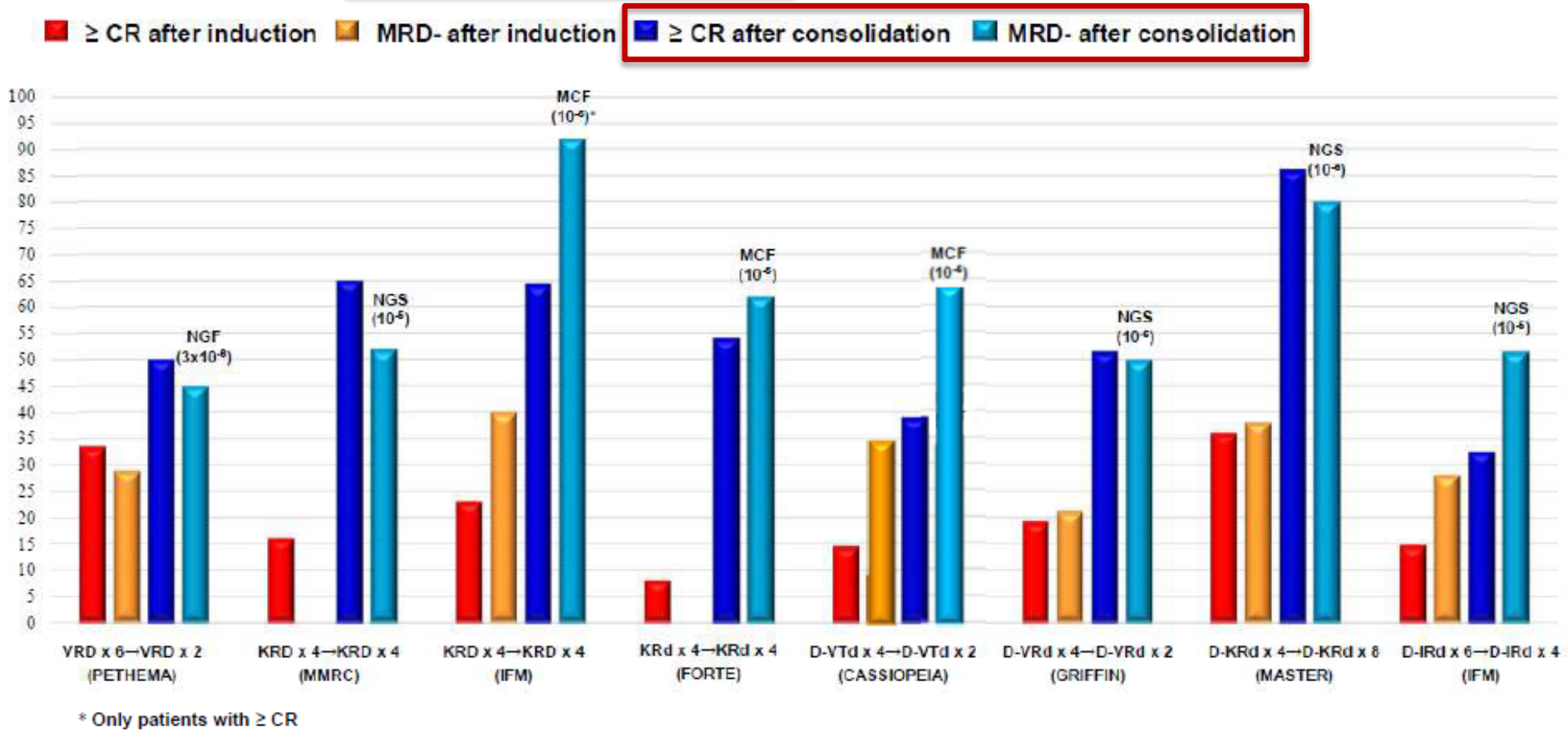


STaMINA phase 3 study of VRD consolidation vs no consolidation



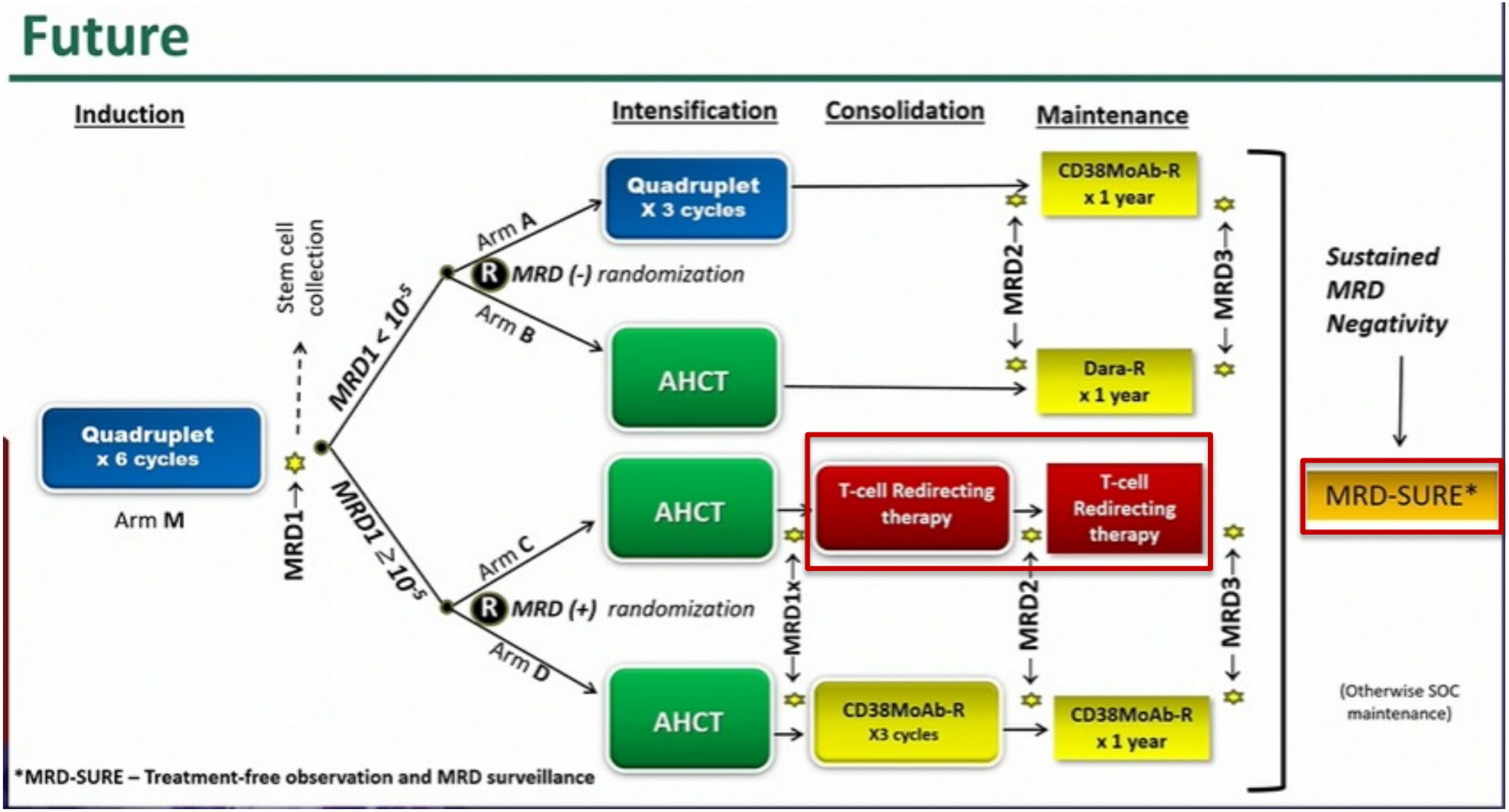
	EMN02	STAMINA
Induction regimen (%)	VCD (100)	VCD (13.4); VRD (57)
Pre-planned induction thp (mths)	2–3	2–12
Failure to receive double ASCT (%)	19.8	32
Double ASCT plus Consolidation (%)	50	0
Maintenance therapy	Len (10 mg)	Len (10–15 mg)

Response rates after induction and consolidation of the main triplet and quadruplet drug combinations



* Only patients with ≥ CR

Future


Induction
Intensification
Consolidation
Maintenance
Quadruplet
x 6 cycles
Arm M
Stem cell collection
MRD1→
MRD1 < 10-5
MRD1 ≥ 10-5
Arm A
Arm B
Arm C
Arm D
R MRD (-) randomization
R MRD (+) randomization
Quadruplet
X 3 cycles
AHCT
AHCT
AHCT
MRD1x→
T-cell Redirecting therapy
T-cell Redirecting therapy
CD38MoAb-R
X3 cycles
CD38MoAb-R
x 1 year
Dara-R
x 1 year
CD38MoAb-R
x 1 year
MRD2→
MRD2→
MRD3→
MRD3→
Sustained MRD Negativity
MRD-SURE*
(Otherwise SOC maintenance)
*MRD-SURE – Treatment-free observation and MRD surveillance

ANSWERS

- *Induction without transplant frontline?* ***No (not yet)***
- *Best induction treatment: will quadruplets substitute triplets?* ***Yes (five-drug combinations are under investigation)***
- *Therapeutic synergy of induction treatment: the renaissance of consolidation?* ***Probably yes***
- ***MRD: the new endpoint of (any?) treatment?***