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Managing the Newly Diagnosed Patient in 2020

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Disclosures

- Consultancy
  - AMGEN, Jazz, Takeda, Novartis, KITE, Sanofi, CELGENE, Pfizer, GSK, Omeros, Acrotech, Actinuum
- Research Support
  - AMGEN, Takeda, Novartis, Sanofi, CELGENE, Pfizer, GSK, Actinuum, Miltenyi
- I am a transplanter

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Initial Presentation

- 75-year-old woman
- κ light chain multiple myeloma diagnosed January 2019
  - Durie-Salmon Stage IIIA, ISS Stage 2
- Laboratory findings
  - Total proteinuria 5.82 g/day
  - Bence Jones protein (BJP) 3.6 g/day
  - Hypogammaglobulinemia
  - Albumin 3.9 g/dL
  - β2-microglobulin 4.7 mg/L
  - Creatinine 1.7 mg/dl
  - No paraprotein peak but kappa light chain 120000 with lambda light chain at 0.01
  - Kappa/lambda ratio=12000000

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Initial Presentation

- Bone marrow biopsy
  - Cellularity 80% with 25% plasma cells
  - Cytogenetics 46, XX, inversion 9 (p11;q13)
- FISH no abnormalities
- Skeletal survey: extensive lytic bone disease with healing fractures of left 7th and the 8th ribs
- MRI of the spine: diffuse hyper-intense homogenous signal on STIR sequence
- MRI of the pelvis: diffuse marrow infiltrative changes due to myeloma
- Comorbidities: Diabetic on metformin, no history of coronary artery disease or other comorbidities

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Maintenance of Certification Question

- In this newly diagnosed 75 year old with ISS Stage 2 Myeloma what would be the treatment strategy most likely to achieve a complete remission
- 1. Double therapy induction x 6 months followed by lenalidomide maintenance
- 2. Triple therapy with an alkylator a proteasome inhibitor and steroids followed by lenalidomide maintenance
- 3. Triple therapy with an alkylator a proteasome inhibitor and steroids followed by high dose melphalan and auto HCT followed by lenalidomide maintenance
- 4. Triple therapy with lenalidomide, bortezomib and dexamethasone followed by high dose melphalan and auto HCT followed by lenalidomide maintenance

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Maintenance of Certification Answer

- In this newly diagnosed 75 year old with ISS Stage 2 Myeloma what would be the treatment strategy most likely to achieve a complete remission
- The correct answer is 4 which in randomized trials has shown deeper responses than the other alternatives.
- Doublet therapy is inferior to 3 drug therapy and should be limited to frail and debilitated patients
- In this patient high dose melphalan and autologous HCT would deepen the response
- Option 3 is reasonable due to her increase creatinine but would be associated with a lower CR rate.

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Is she transplant eligible?
If yes
Is there an optimal induction?

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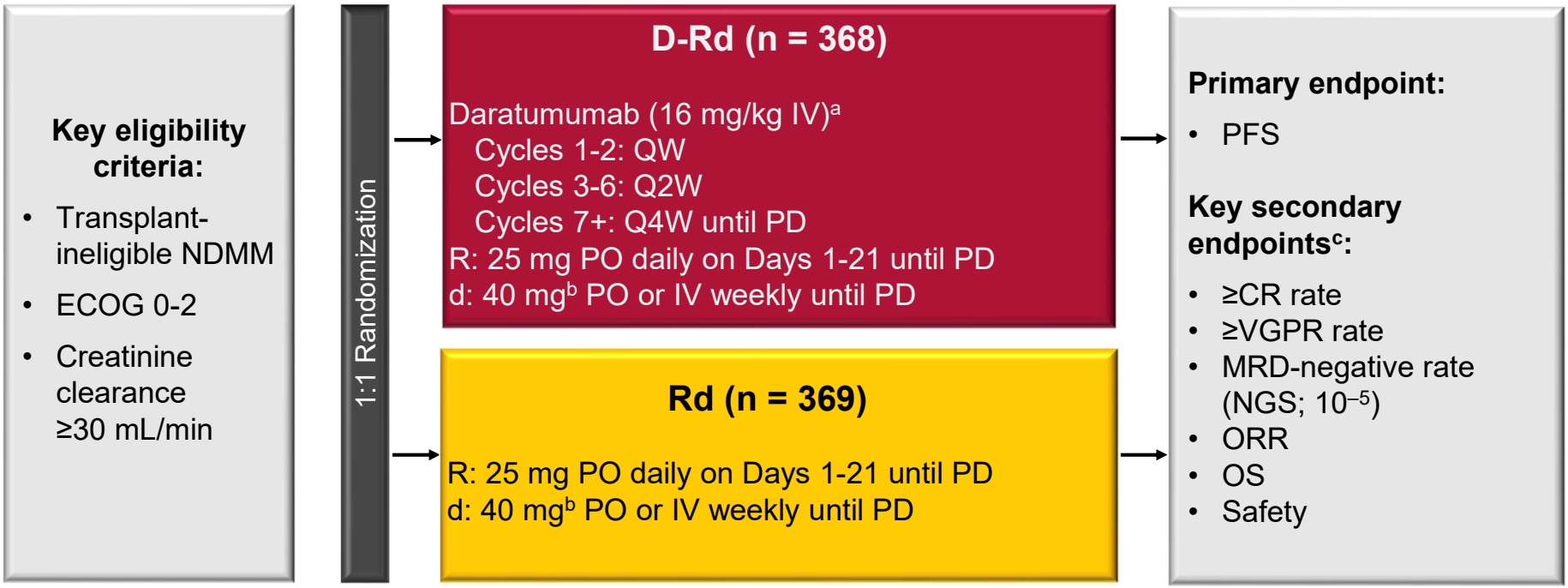
MAIA Study Design

- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



Stratification factors
- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥75 years)

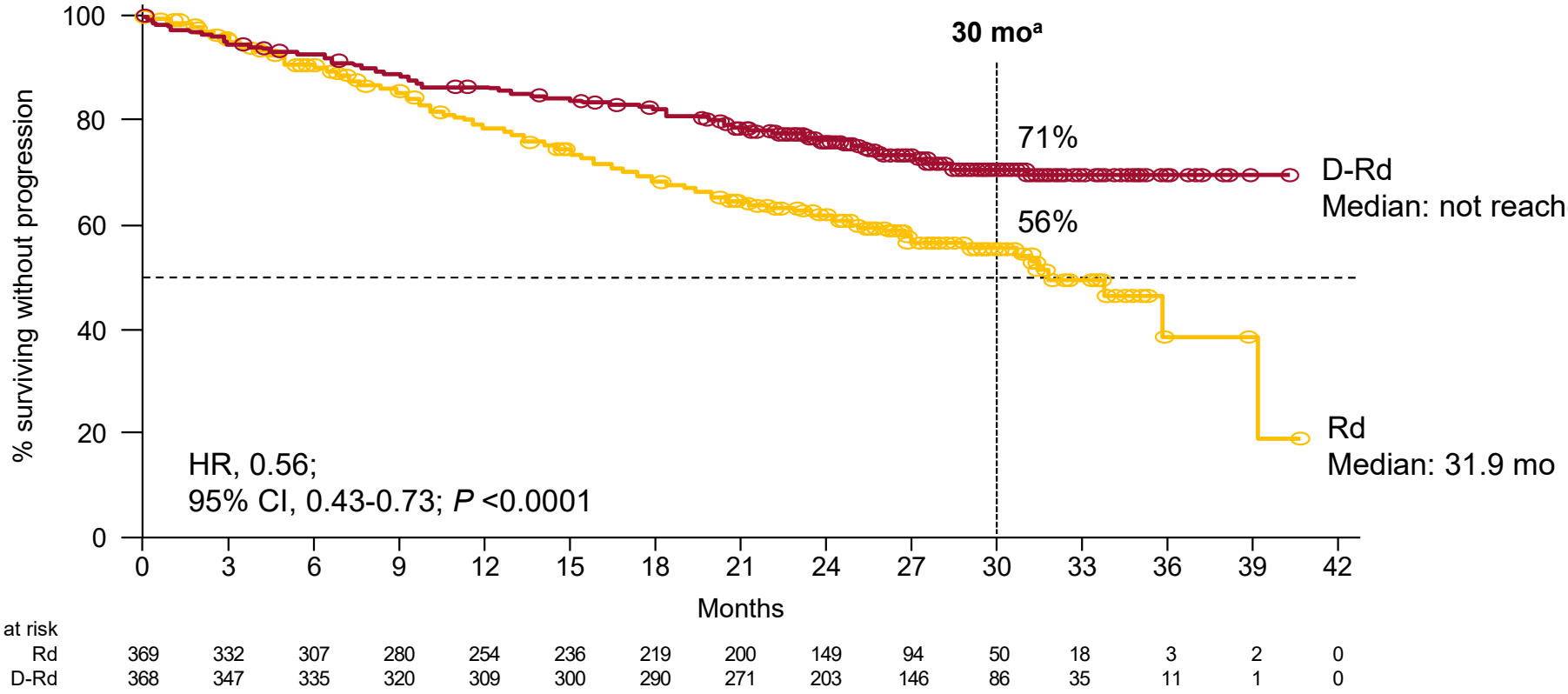
Cycle: 28 days

[a]On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
[b]For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c]Efficacy endpoints were sequentially tested in the order shown.

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, North America; IV, intravenously; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, orally; CR, complete response; VGPR, very good partial response; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; BMI, body mass index.

Efficacy: PFS

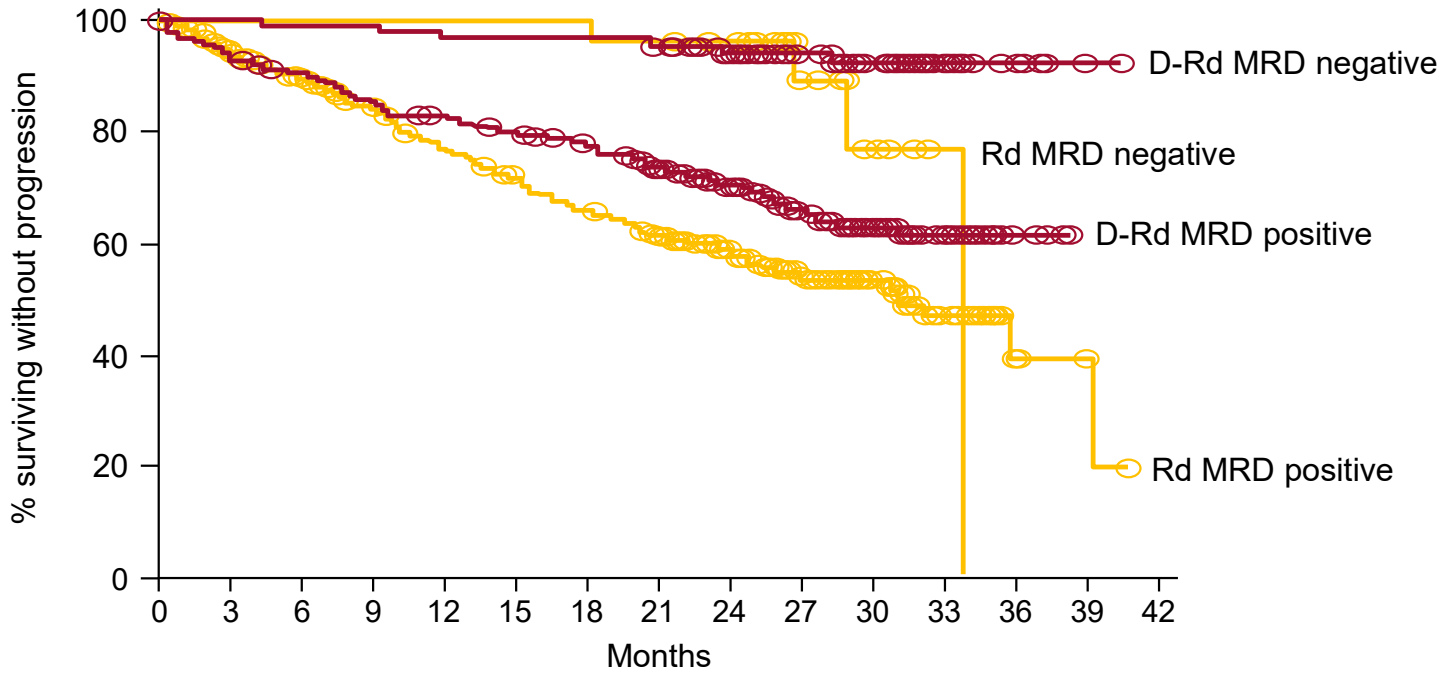
Median follow-up: 28 months (range: 0.0-41.4)



44% reduction in the risk of progression or death in patients receiving D-Rd

CI, confidence interval.
[a]Kaplan-Meier estimate.

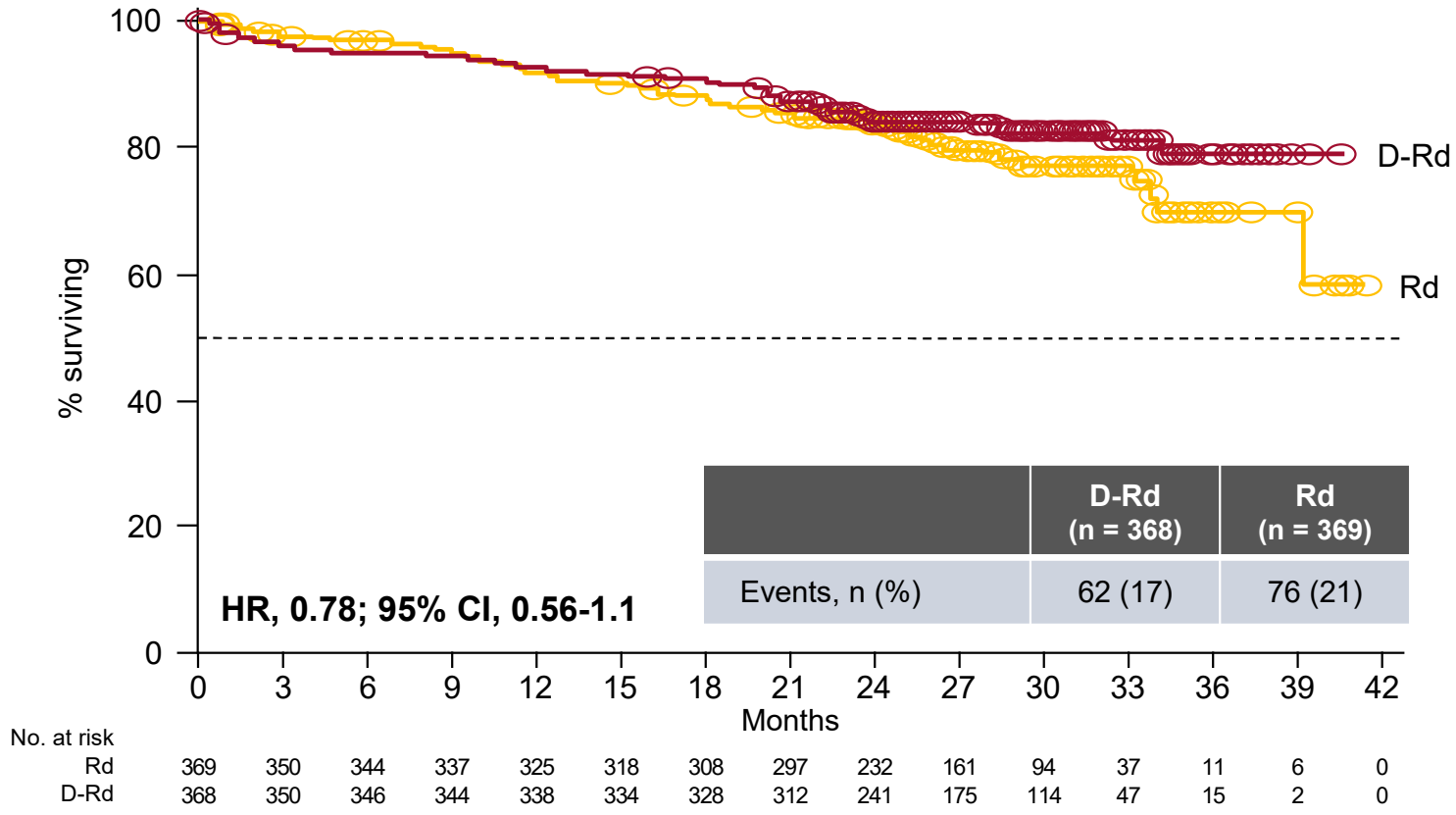
Efficacy: PFS by MRD Status



No. at risk															
Rd MRD negative	27	27	27	27	27	27	27	25	21	12	5	1	0	0	0
D-Rd MRD negative	89	89	88	88	86	86	86	84	70	55	33	12	5	1	0
Rd MRD positive	342	305	280	253	227	209	192	175	128	82	45	17	3	2	0
D-Rd MRD positive	279	258	247	232	223	214	204	187	133	91	53	23	6	0	0

- **>3-fold higher MRD negativity achieved with D-Rd**
- **Lower risk of progression or death with MRD negativity**

Efficacy: OS at Median Follow-up of 28 Months



	D-Rd (n = 368)	Rd (n = 369)
Events, n (%)	62 (17)	76 (21)

No. at risk															
Rd	369	350	344	337	325	318	308	297	232	161	94	37	11	6	0
D-Rd	368	350	346	344	338	334	328	312	241	175	114	47	15	2	0

Data are immature after median follow-up of 28 months

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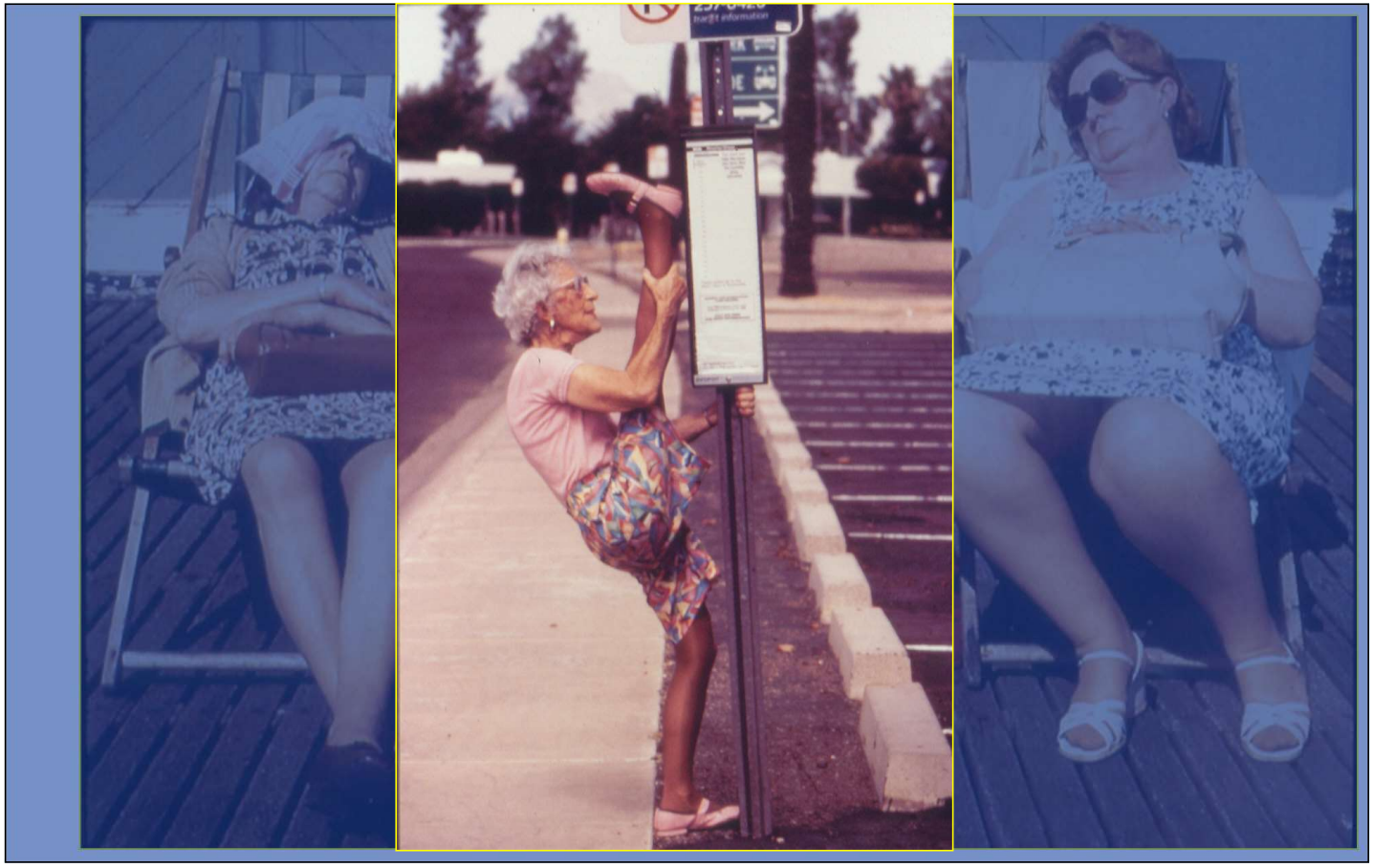
FUNCTIONAL ASSESSMENT



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Goals of Induction Therapy: The Potential Transplant Patient

- Rapid responses
- Depth of responses (high response rates)
- Durable responses
- Improve performance status
- Not limit PBSC mobilization
  - No use of alkylating agents in induction therapy
- Overall goal of multiple myeloma therapy: Extend survival while maintaining quality of life

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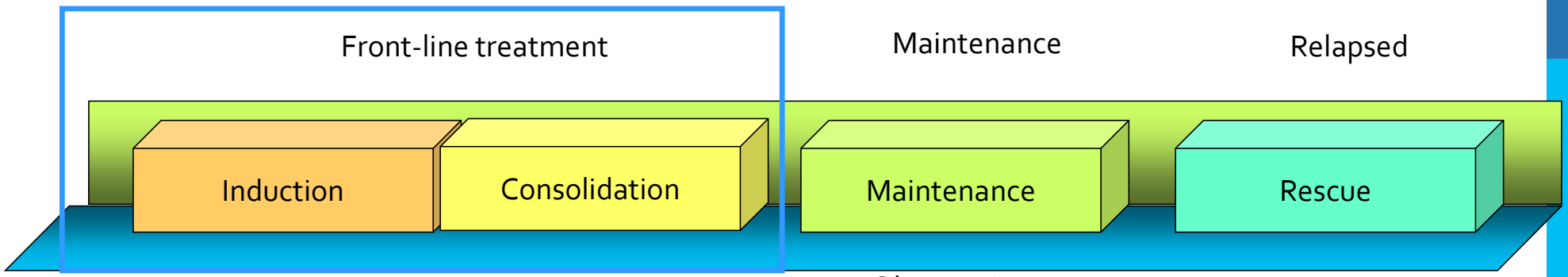
Phase III Trials Now Informing Induction



VTD vs VCD
RVD vs RD
RVD vs KRD?
Dara RVD vs RVD
Dara KRD

SCT

Observation
IMID: Thal-Len
Proteosome Inh: Bor-Ixa-Car
Steroids: Dex-Pred
Monoclonals: Dara-Elo

IMID: Thal-Len-Pom
Proteosome Inh: Bor-Car
Steroids: Dex-Pred
Alkylators: Mel-Cy-Benda
Monoclonals: Dara-Elo
Investigational

[a]Transplant eligible patients.
Bor = bortezomib; Dex = dexamethasone; Dox = doxorubicin; Thal = thalidomide; Len = lenalidomide; SCT = stem-cell transplant; Pred = prednsione; Lipo/Dox = liposomal doxorubicin.

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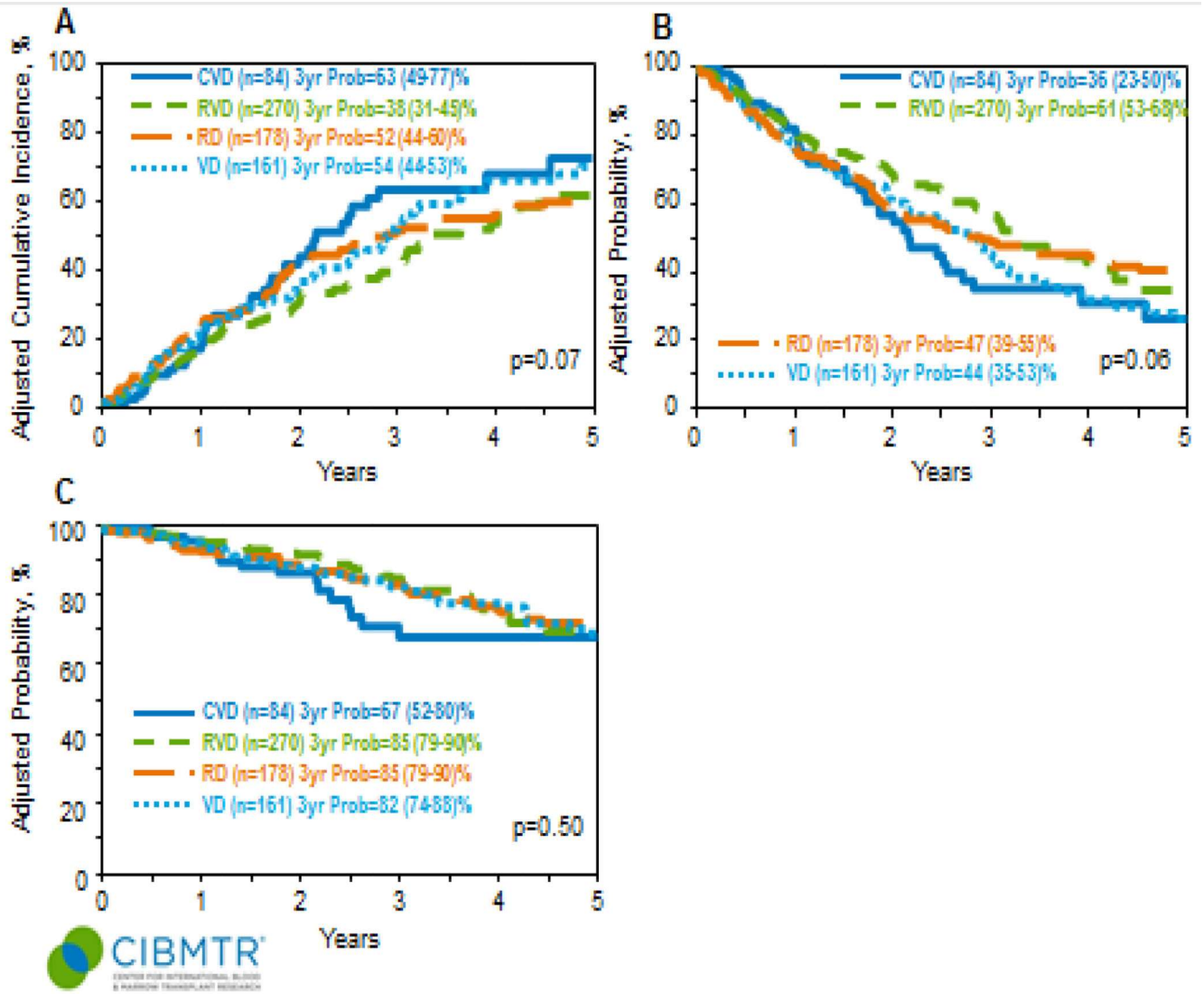

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She has a major response to induction (i.e VGPR) and sees 2 different specialist. One recommends HCT consolidation the other continued treatment.

Who is right? Why the contradiction?

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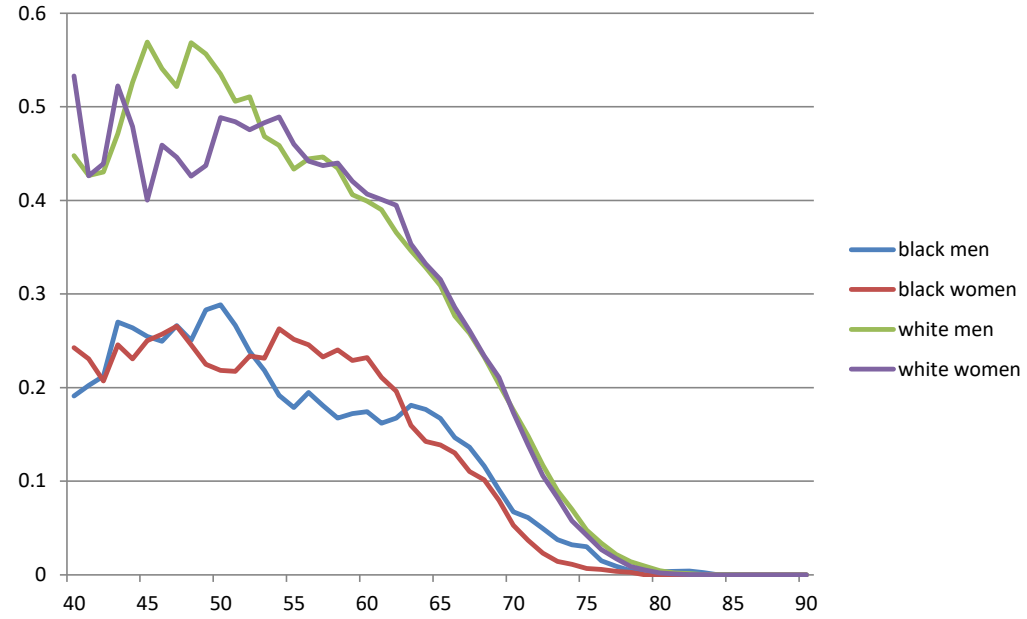
In 2020 who should receive high dose melphalan and auto HCT as consolidation?

- Everybody
- Nobody
- Only patient who fail to achieve MRD negativity after 6-8 cycles of highly effective induction therapy
- Response and risk adapted

Despite strong evidence supporting auto HCT in MM only 30% of potentially eligible patients undergo autograft. Even less if you are a minority or over 65 years of age
Costa et al. BBMT

AHPCT "utilization rate"



Why are patients not going to HCT?
Referral bias
Fear of side effects
Lack of access to an HCT program
Lack of awareness of treating physician

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What data do we have?

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EMN02/HO95 MM trial: study design

VCD x three-four 21-d cycles
Bort 1.3 mg/sm twice weekly; CTX 500 mg/sm d1-8;
Dex 40 mg on day of and after bort

CTX (2-4 g/sm) + G-CSF + PBSC collection

R1

VMP x 4 cycles

HDM x 1-2 courses

R2

VRD x two 28-d cycles
Bort 1.3 mg/sm, twice weekly;
len 25 mg d1-21;
dex 20 d1-2-4-5-8-9-11-12

No consolidation therapy

Lenalidomide 10 mg/day, d1-21/28

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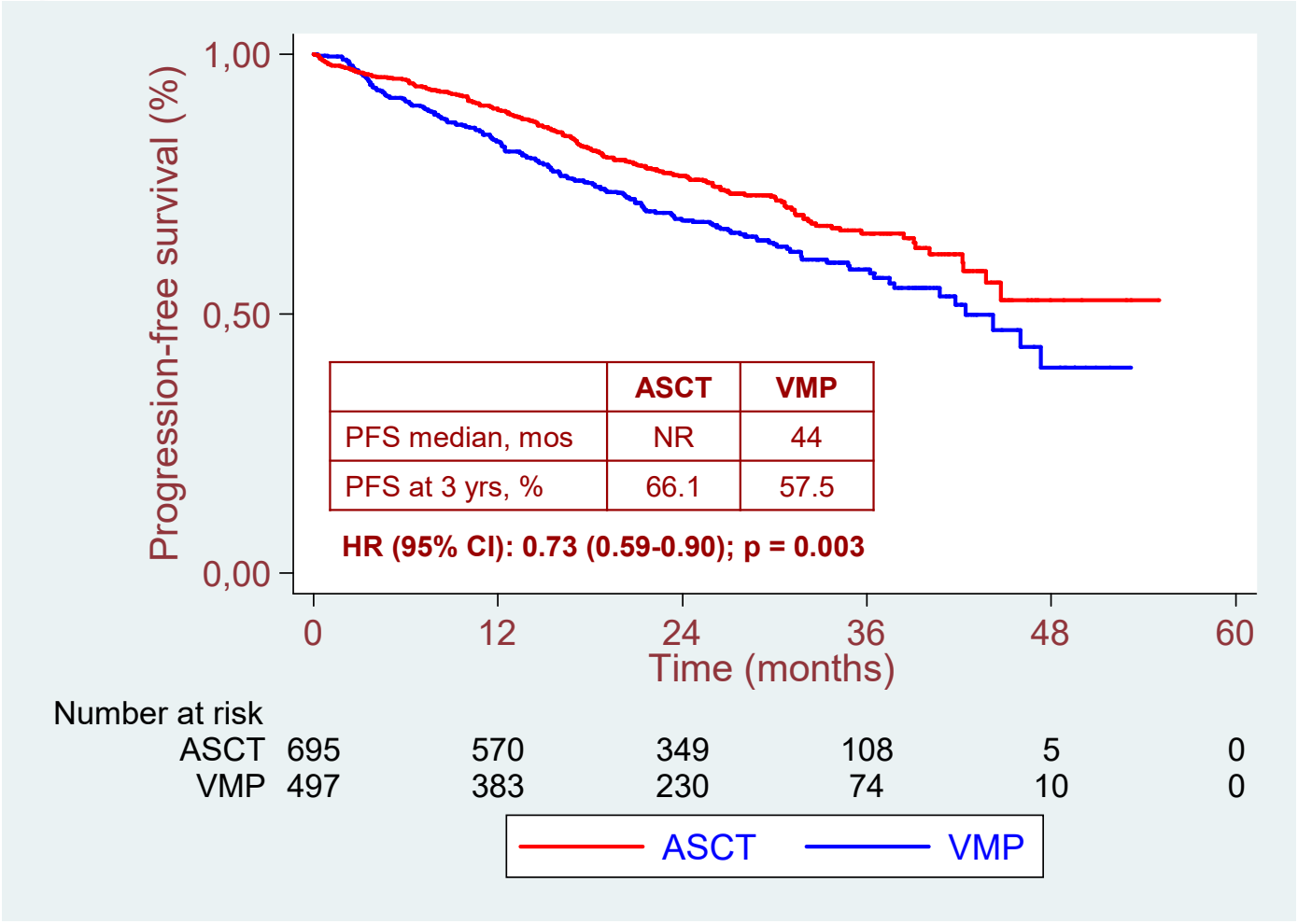
PFS by Randomization



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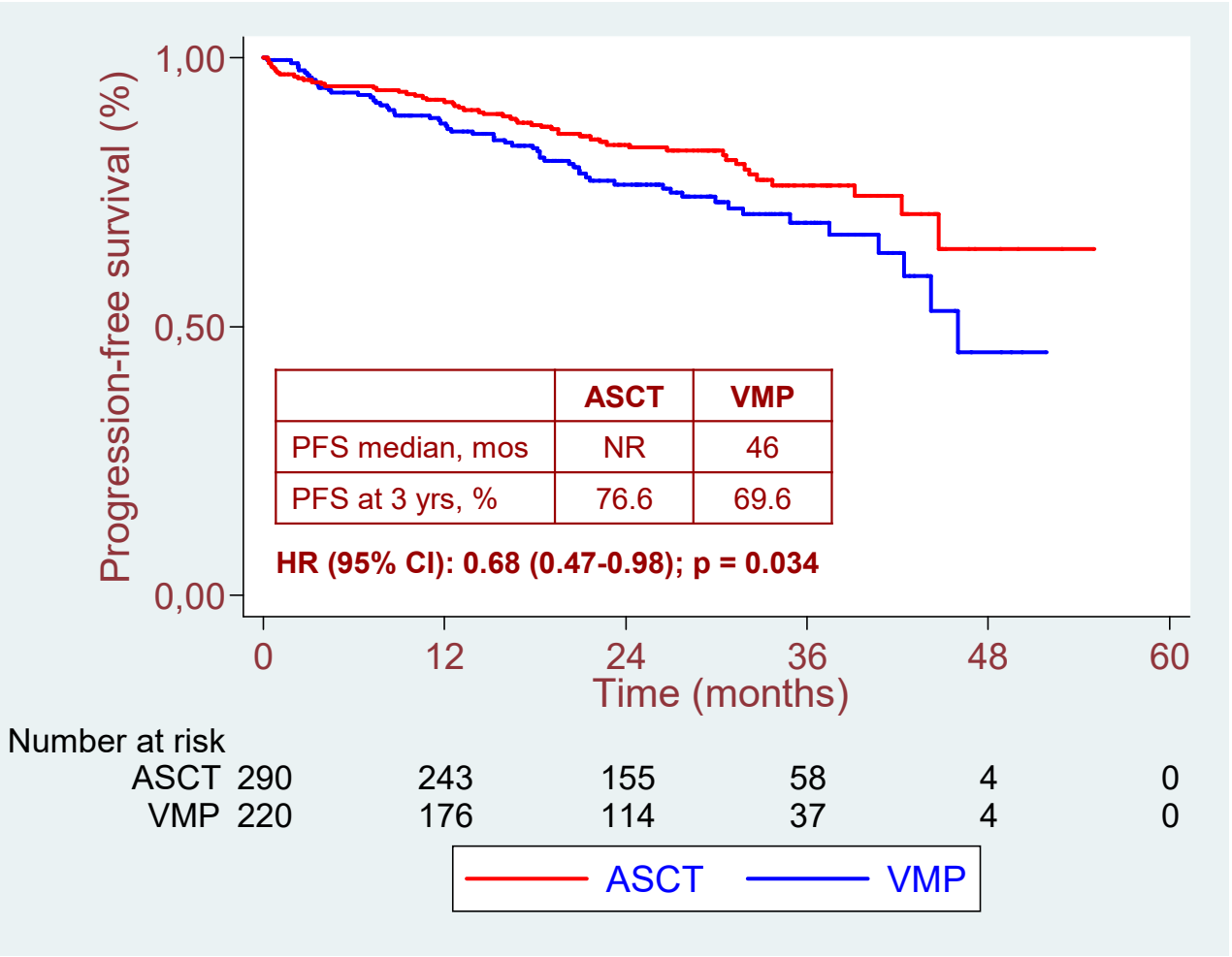
PFS by cytogenetics (standard risk)



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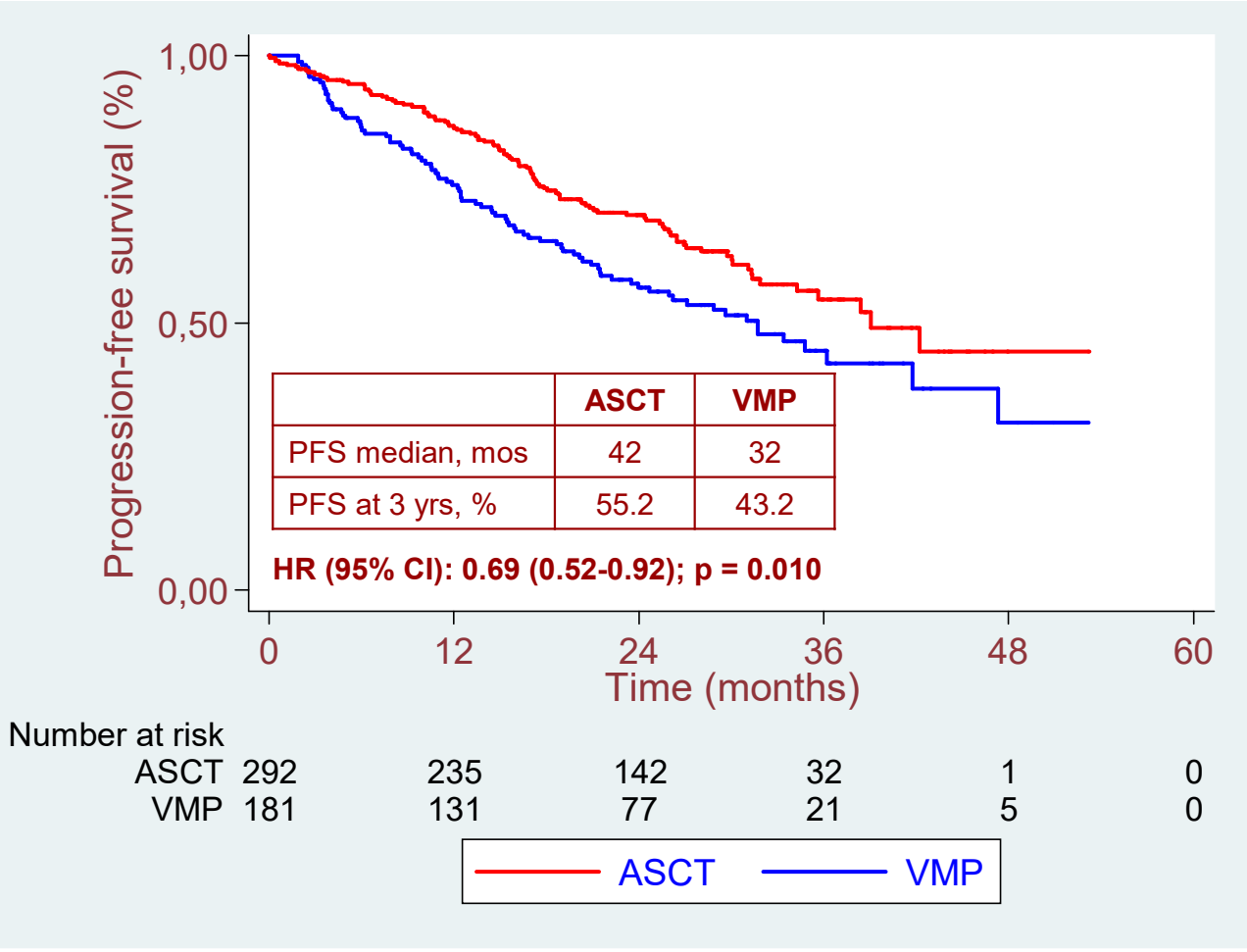
PFS by cytogenetics (high risk)



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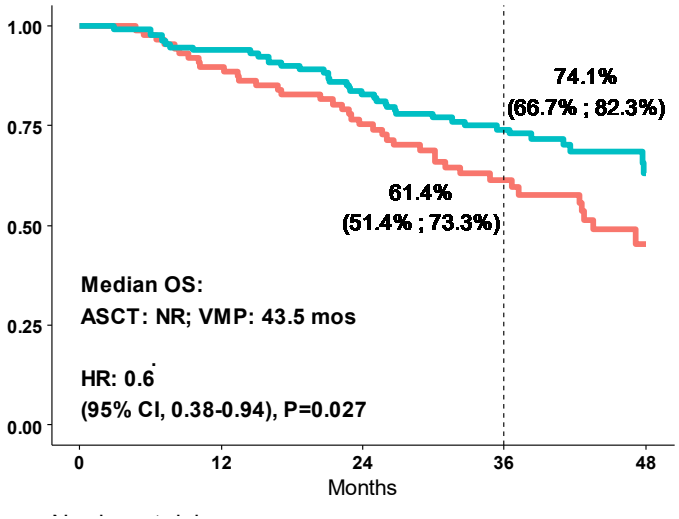
NOTE – High Dose Melphalan Independent Prognostic Variable

Variables affecting PFS	HR	95% CI	*P*-value
Best CR+sCR	0.22	0.16-0.30	<0.001
Standard Risk cytogenetics	0.44	0.34-0.57	<0.001
Randomization to ASCT	0.54	0.42–0.68	<0.001
ISS I	0.60	0.43-0.83	0.002

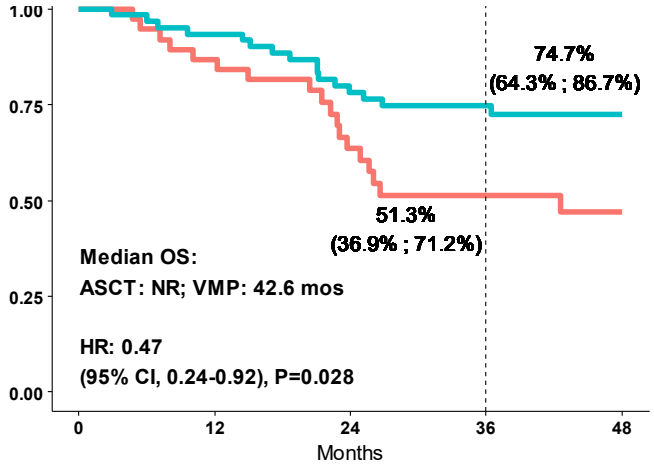
OS by randomization in high risk subgroups

VMP ASCT

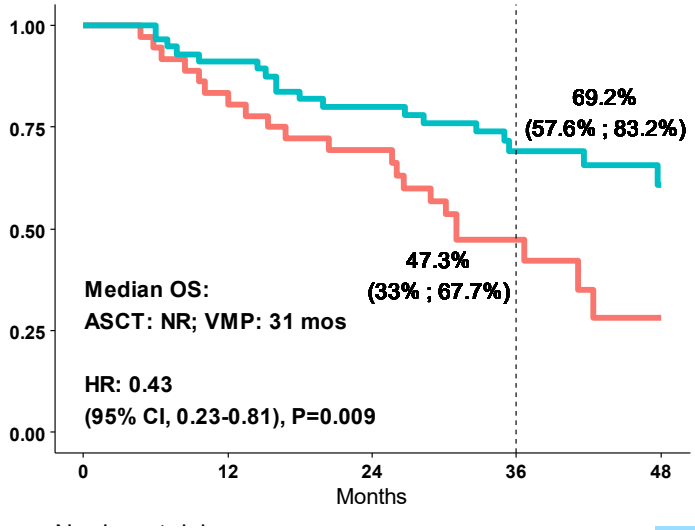
Del(17p) and/or t(4;14) and/or t(14;16)



Del(17p) positivity



R-ISS III



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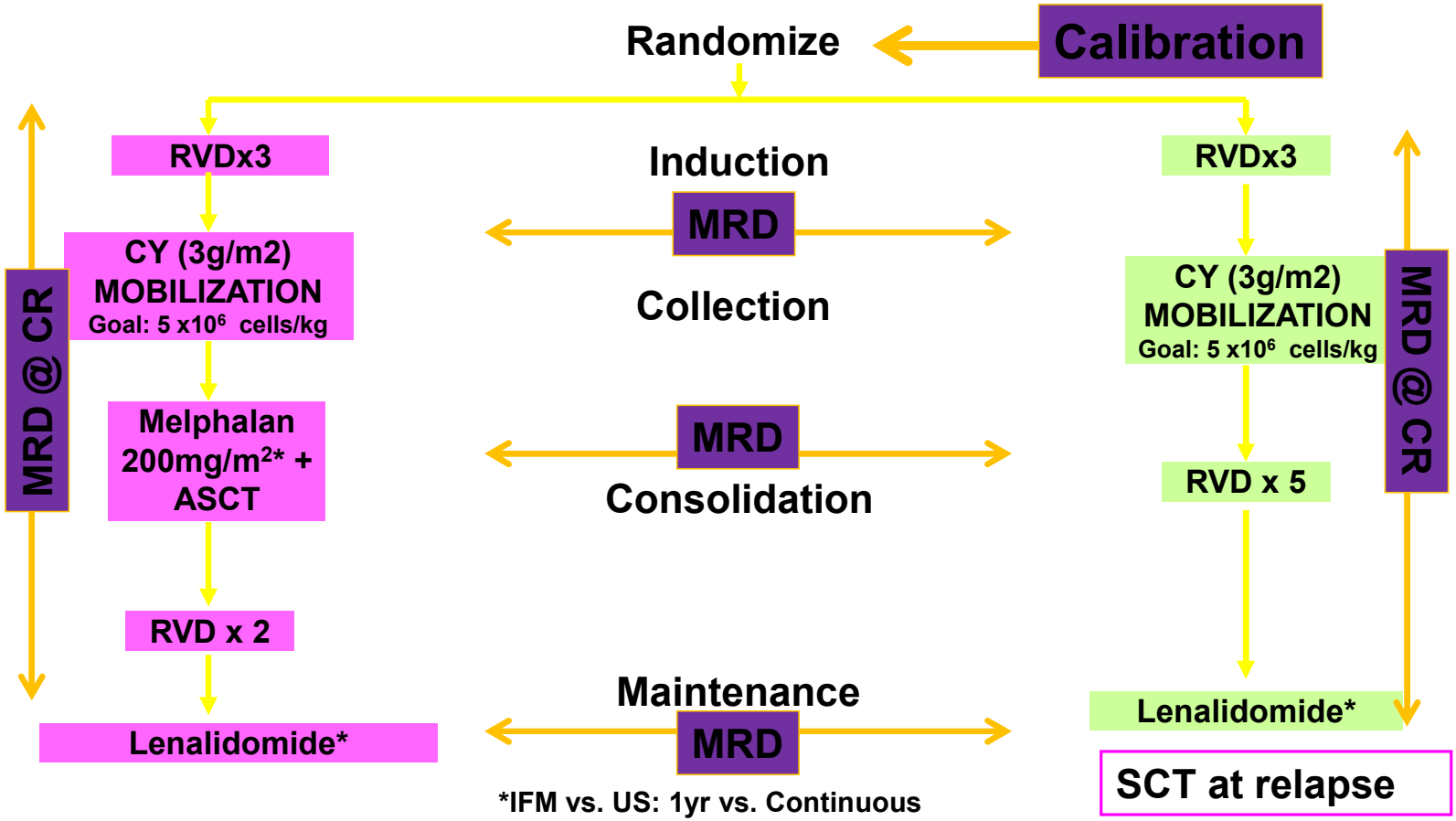
IFM/DFCI 2009 Study (US and France)
Newly Diagnosed MM (N=1,360)



*IFM vs. US: 1yr vs. Continuous

Moreau P, et al. *Blood.* 2014;124: Abstract 3359.

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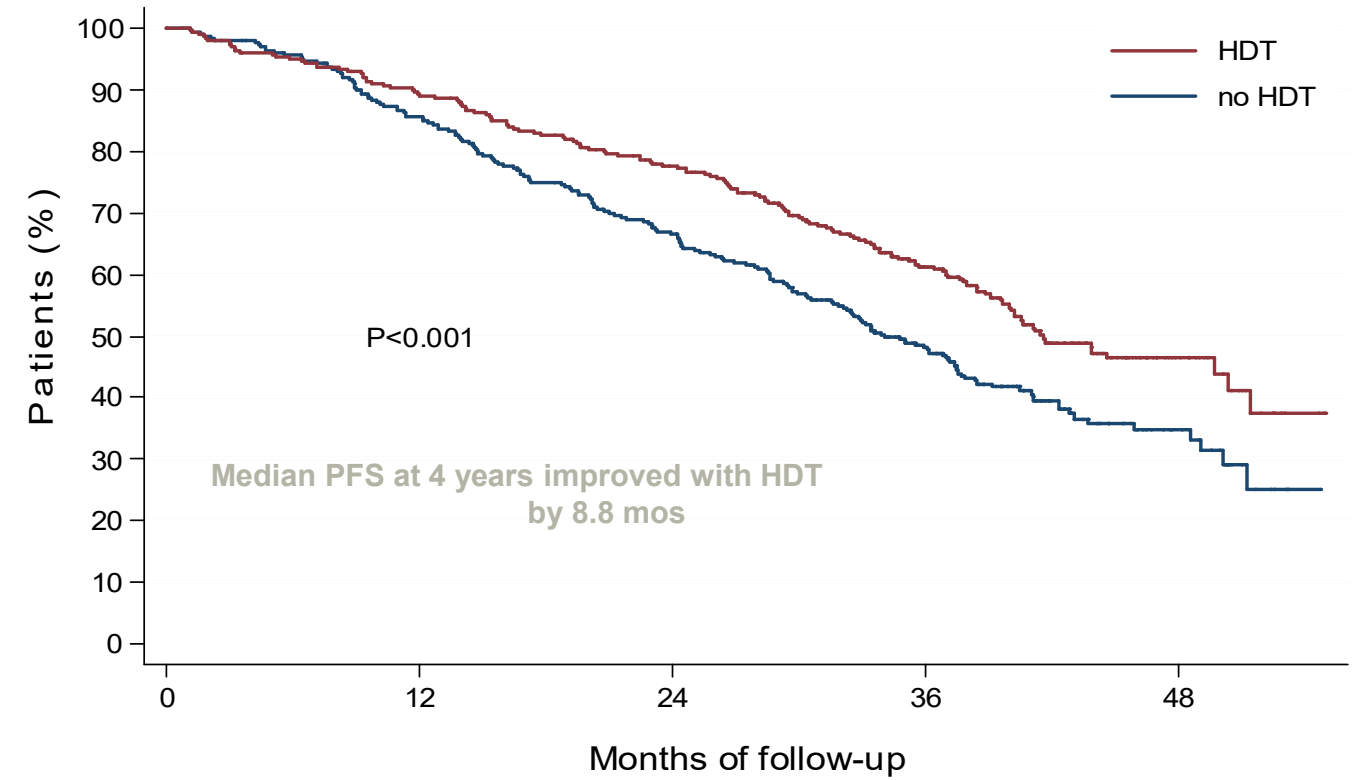
ASH 2015 (Attal et al): IFM 2009: PFS (9/2015)



N at risk					
HDT	350	309	261	153	27
no HDT	350	296	228	128	24

Attal M, et al. *Blood.* 2015;126: Abstract 391.

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ASH 2015: IFM 2009: Best Response

	RVD arm N=350	Transplant arm N=350	*P* value
CR	49%	59%	
VGPR	29%	29%	.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	.001

Attal M, et al. *Blood.* 2015;126: Abstract 391.

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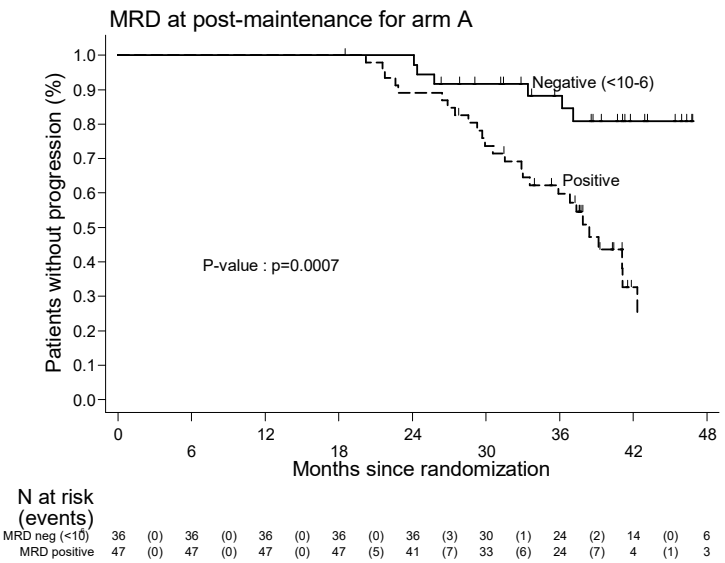
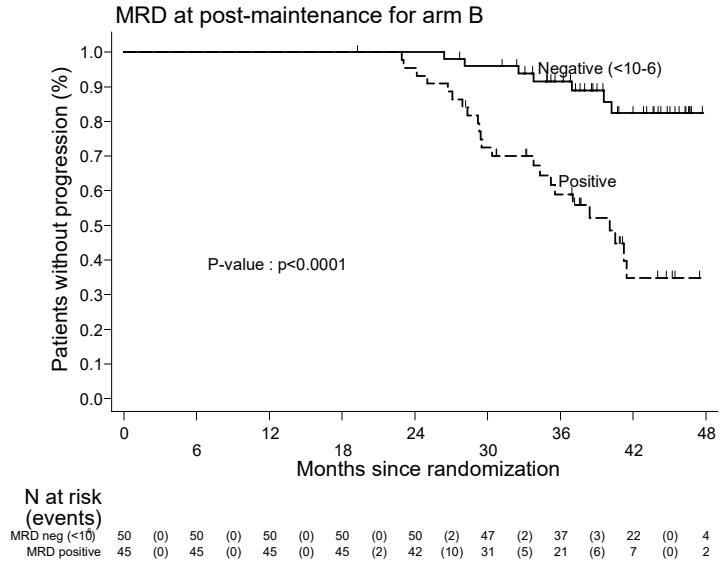
IFM/DFCI 2009 ~ PFS according to MRD Post Maintenance

RVD Arm



Transplant Arm



Avet-Loiseau H, et al *Blood.* 2015;126: Abstract 191.

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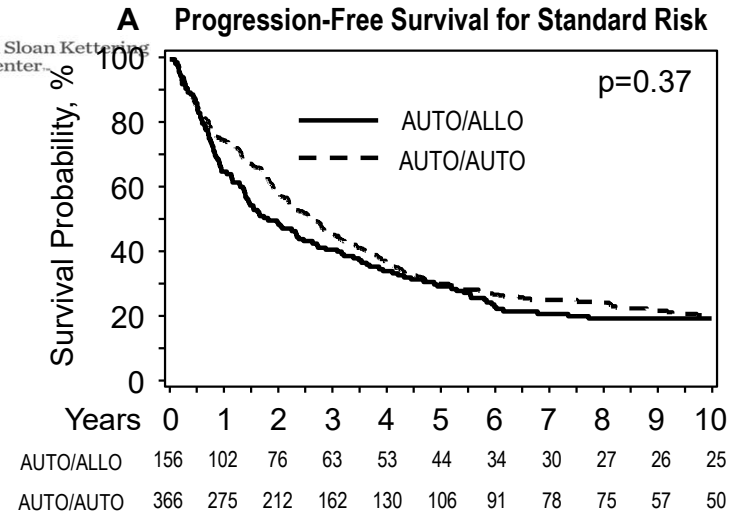

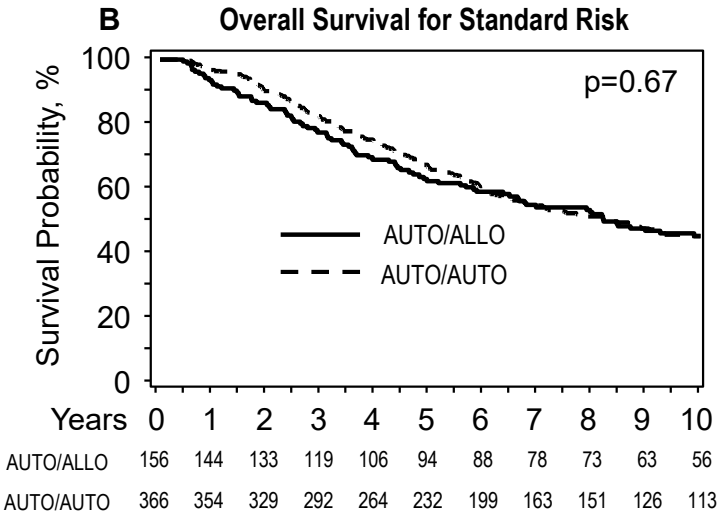

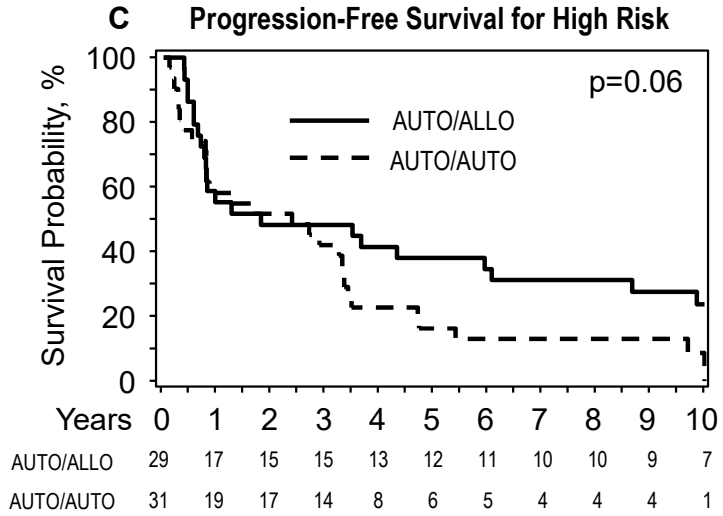

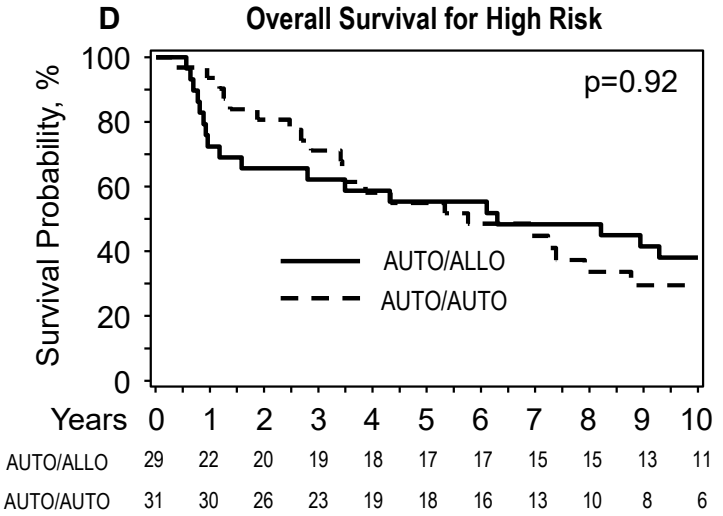

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Rationale for Delayed HCT-PROS

- 10% of patients don't derive significant benefit from high dose melphalan
- 10% of patients can achieve long term disease control without high dose melphalan
- Avoids exposure and potentially SPMs in patients
- Subsequent high dose melphalan is possible if cells are collected early
- 1% treatment related mortality
- 5-10% significant morbidity
- No clearly demonstrated survival benefit in the context of modern treatment
  - This may be impossible to determine due to efficacy of salvage therapy

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Rationale for Delayed HCT-CONS

- 10% of patients can achieve long term disease control without high dose melphalan
- 20% of patients who opt for delayed HCT do not get the procedure
- 50% of patients who opt for delayed HCT are receiving it within the first 24 months of the decision
- Toxicities are likely to be higher with delayed HCT
- Overall burden of therapy may actually be higher.

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…but RVD will no longer be the standard KRD and KRD Dara will be the next standard induction…

What data do we have for HCT in this setting?

Treatment Schema – 28-day Cycle

CFZ	Days 1-2, 8-9, 15-16 20 mg/m²* → 36 mg/m²	Days 1-2, 8-9, 15-16 LTD	Days 1-2, 15-16 LTD	
LEN	Days 1-21 25 mg	Days 1-21 15 mg Cycle 5 → LTD	Days 1-21 LTD	Days 1-21 LTD
dex	Weekly 40 mg	Weekly 20 mg or LTD	Weekly LTD	

*Days 1-2 of Cycle 1 only

G-CSF, granulocyte-colony stimulating factor; LTD=last tolerated dose; SCC=stem cell transplant

KRd+ASCT considered promising: improvement of ***sCR at the end of 8 cycles*** from historical rate of ***30% for KRd without transplant*** to ***50% for KRd+ASCT***

Efficacy of Carfilzomib Lenalidomide Dexamethasone (KRd) With or Without Transplantation in Newly Diagnosed Myeloma According to Risk Status: Results from the FORTE Trial

Francesca Gay,[1] Chiara Cerrato,[1] Maria Teresa Petrucci,[1] Renato Zambello,[1] Barbara Gamberi,[1] Stelvio Ballanti,[1] Paola Omedé,[1] Salvatore Palmieri,[1] Rossella Troia,[1] Stefano Spada,[1] Alessandro Gozzetti,[1] Tommaso Caravita,[1] Antonio Spadano,[1] Antonio Palumbo,[2] Vittorio Montefusco,[1] Pellegrino Musto,[1] Michele Cavo,[1] Mario Boccadoro.[1]

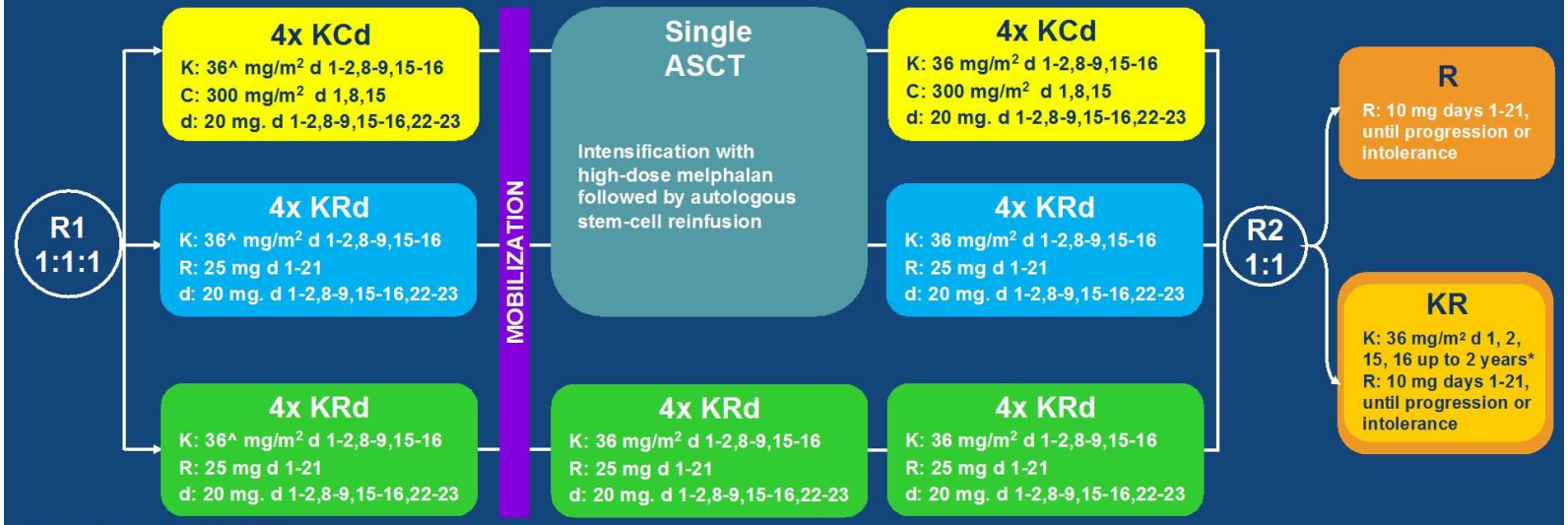
Correspondence: fgay@cittadellasalute.to.it

1. GIMEMA / European Myeloma Network, Italy; 2. University of Torino, Torino, Italy - Currently Takeda Pharmaceuticals Co.

Presented By Francesca Gay at 2019 ASCO Annual Meeting

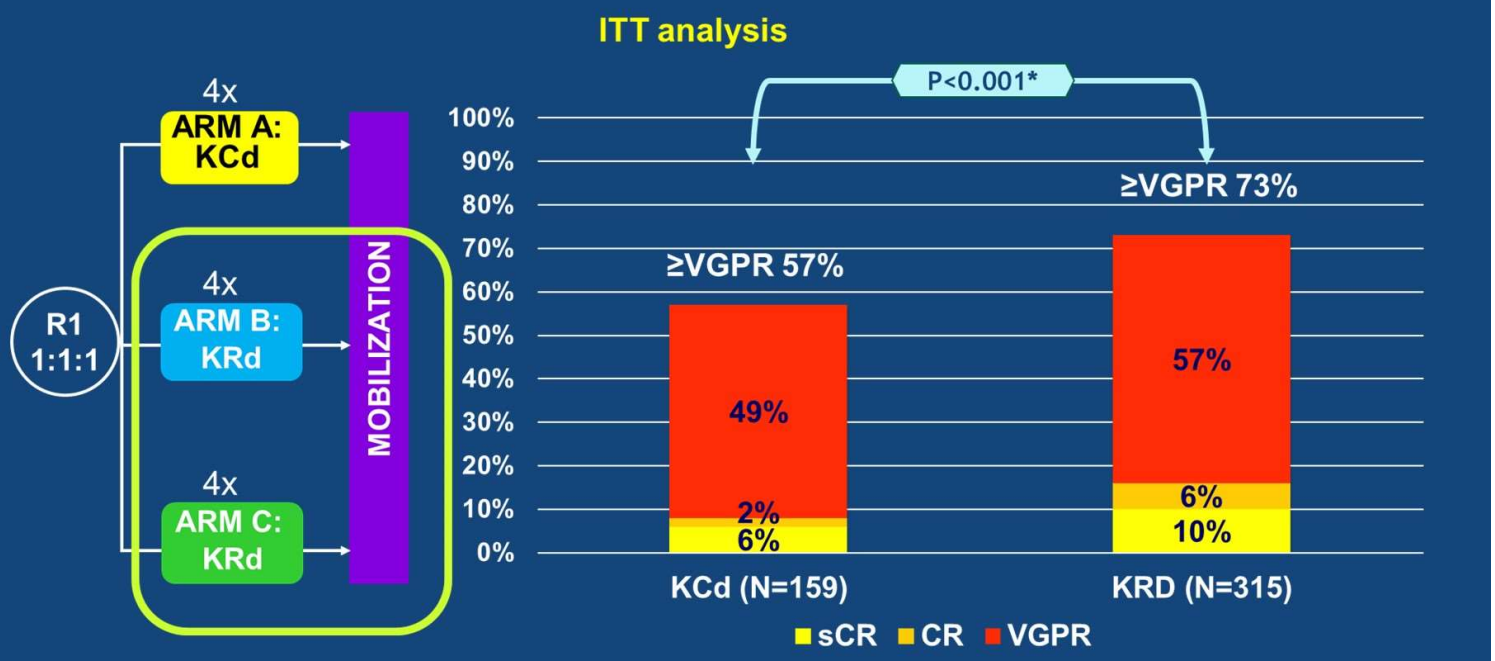
Trial design

NDMM patients, transplant-eligible and younger than 65 years



^20 mg/m² on days 1-2, cycle 1 only.
*Carfilzomib 70 mg/m² days 1, 15 every 28 days up to 2 years for patients that have started the maintenance treatment from 6 months before the approval of Amendment 5.0 onwards.
R1, randomization 1; R2, Randomization 2; IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT: autologous stem-cell transplantation; R, lenalidomide; KR, carfilzomib, lenalidomide. NDMM, newly diagnosed multiple myeloma; VGPR, very good partial response.

Post-induction response rate



*adjusted for International Staging System Stage, fluorescence in situ hybridization (FISH) analysis and age.
R1, randomization 1; KCd, carfilzomib, cyclophosphamide, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; ITT, intention to treat.

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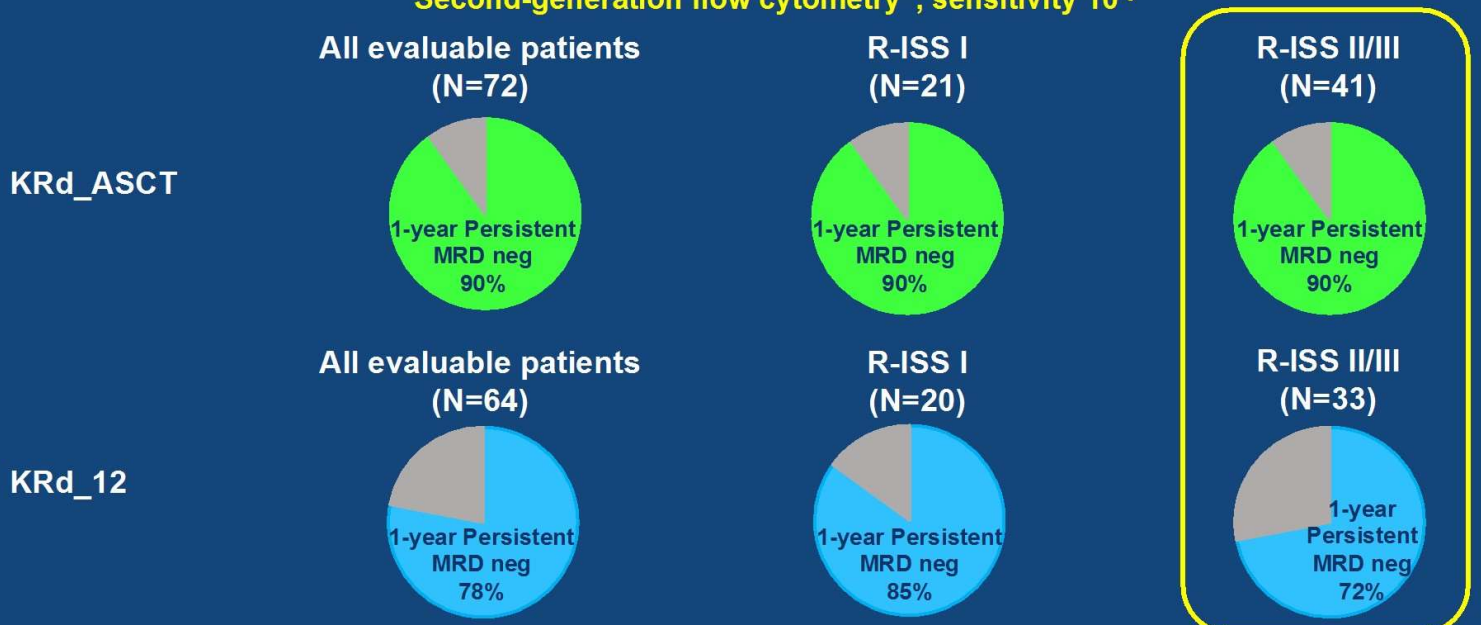
Persistent 1-year MRD negativity rate

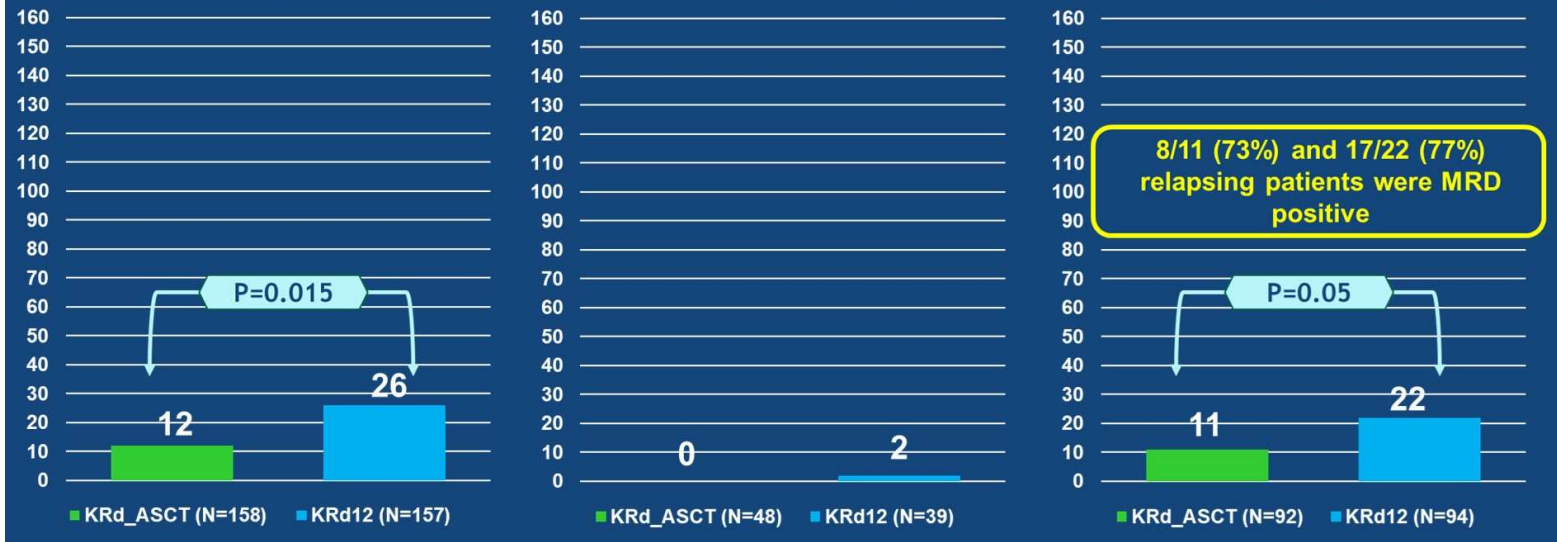
"Second-generation flow cytometry", sensitivity 10^{-5}



In KRd_ASCT 10 pts evaluable for persistent MRD negativity at 1 year have R-ISS not available due to missing FISH or LDH data
In KRd_12 11 pts evaluable for persistent MRD negativity at 1 year have R-ISS not available due to missing FISH or LDH data
ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; d, dexamethasone; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; R-ISS, Revised International Staging System, neg, negative.

Early relapse

Number of patients relapsing ≤ 18 months after Random 1



ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; d, dexamethasone; KRd_ASCT_KRd, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; R-ISS, Revised International Staging System; MRD, minimal residual disease.

1 Krd_ASCT and 2 KRd12 patients experiencing early relapse had R-ISS not available.

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Early relapse

Multivariate Logistic Regression Model*

	OR	95% CI	P-value
R-ISS II/III vs R-ISS I	3.78	1.71-8.35	0.001
KRd-ASCT vs KRd12	0.41	0.19-0.88	0.022
MRD negative (10^{-5})	0.21	0.12-0.40	<0.001

Increased risk of early relapse

Reduced risk of early relapse

*The model was also adjusted for the presence/absence of plasmacytoma and for age as continuous variable.
ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; d, dexamethasone; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; R-ISS, Revised International Staging System; OR, odds ratio; CI, confidence interval.

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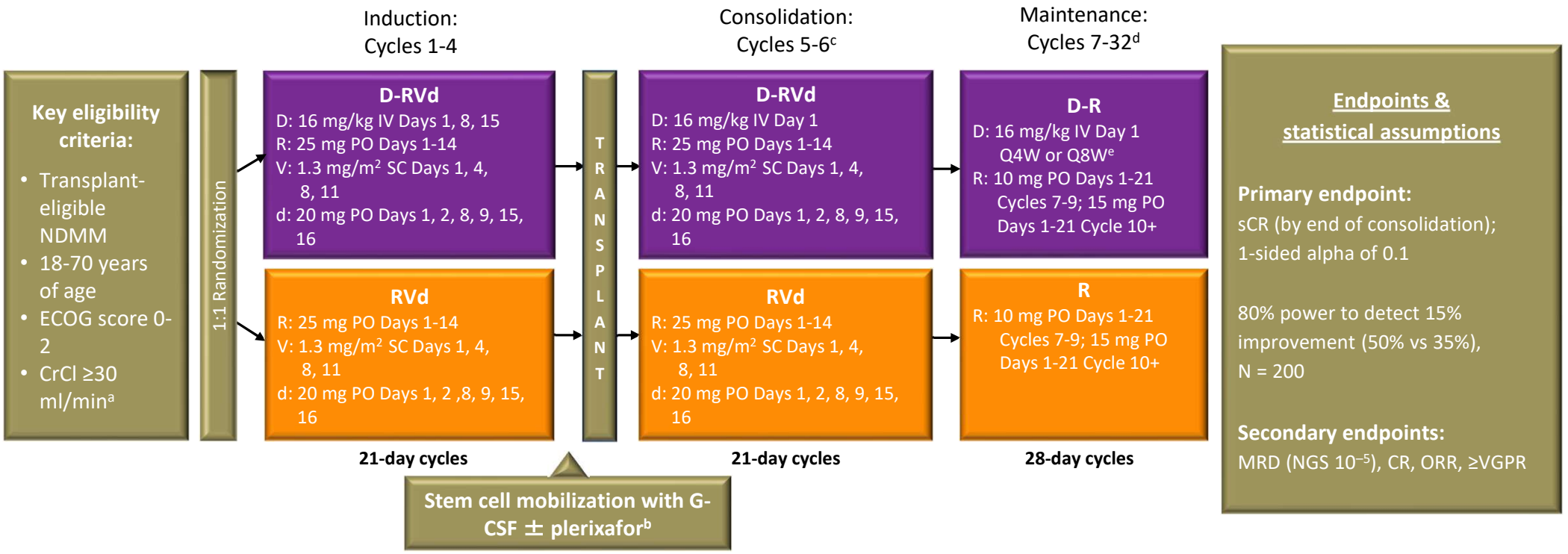
GRIFFIN (NCT02874742): Randomized Phase

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018

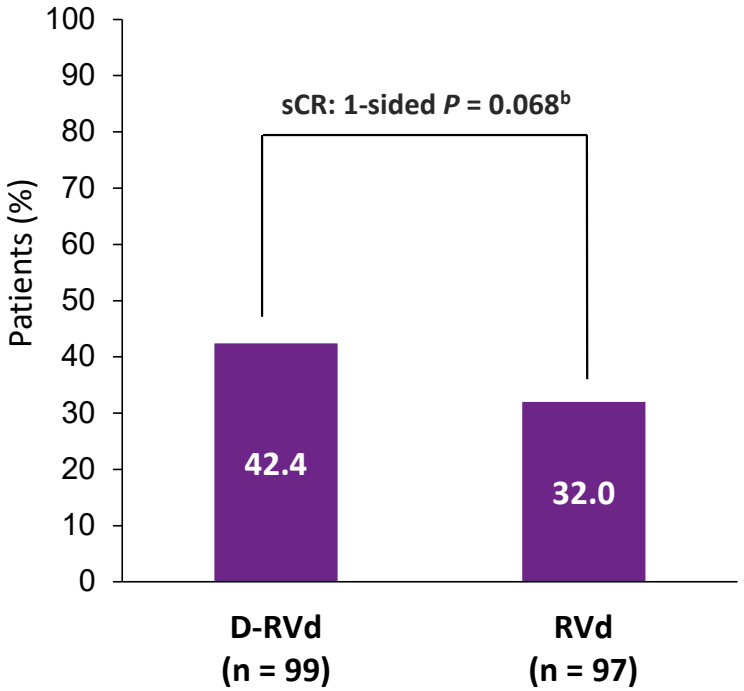


D-RVd, daratumumab-lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.

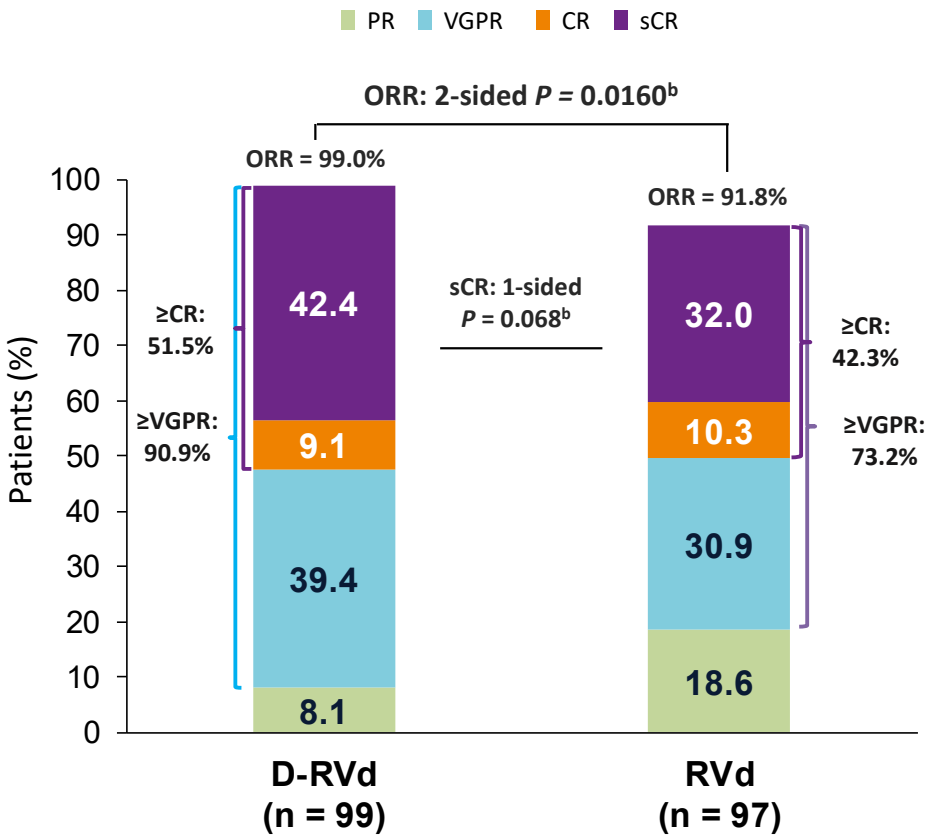
[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post transplant. [d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

Primary Endpoint: sCR by the End of Consolidation[a]

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]



Post-consolidation depth of response[a]



PR, partial response.
[a]Included patients in the response-evaluable population (all randomized patients with a confirmed diagnoses of MM, measurable disease at baseline, received ≥1 dose of study treatment, and had ≥1 post-baseline disease assessment).
[b]*P* values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A 1-sided *P* value is reported for sCR; for all other responses, 2-sided *P* values not adjusted for multiplicity are reported.

Post-Consolidation MRD Negativity

MRD-Negative Status (10^{-5}),[a] n (%)	D-RVd	RVd	Odds Ratio (95% CI)	*P* value[b]
In ITT population				
MRD negative regardless of response	46/104 (**44.2**)	15/103 (**14.6**)	4.70 (2.38-9.28)	<0.0001
MRD negative with CR or better	30/104 (**28.8**)	10/103 (**9.7**)	3.73 (1.71-8.16)	0.0007
In patients achieving CR or better	30/51 (**58.8**)	10/41 (**24.4**)	4.65 (1.76-12.28)	0.0014
In patients who received ASCT	45/94 (**47.9**)	14/78 (**17.9**)	4.31 (2.10-8.85)	<0.0001

D-RVd improved MRD-negativity (10^{-5}) rates at the end of consolidation

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. [b]*P* values were calculated from the Fisher's exact test.

Stem Cell Collection and Transplantation

	D-RVd	RVd
$CD34^+$ cell yield,[a,b] median (10^6 cells/kg)	8.1	9.4
$CD34^+$ cells transplanted,[c] median (10^6 cells/kg)	4.2	4.8
Patients receiving plerixafor for mobilization,[d] n (%)	66 (70)	44 (55)
Patients receiving cyclophosphamide,[d] n (%)	5 (5)	4 (5)
Days to neutrophil (0.5×10^9/L) engraftment, median	12	12
Days to platelet (20×10^9/L) engraftment, median	13	12

DARA did not impact time to engraftment

[a]Among patients who underwent peripheral blood stem cell apheresis (D-RVd, n = 94; RVd, n = 80). [b]One patient in the D-RVd group had a stem cell yield <3x10^6 cells/kg; no patients in either group had a stem cell yield <2x10^6 cells/kg. [c]Among patients receiving transplant (D-RVd, n = 94; RVd, n = 78). [d]Among patients who underwent mobilization (D-RVd, n = 95; RVd, n = 80). Patients underwent stem cell mobilization with G-CSF with or without plerixafor, according to institutional standards; if unsuccessful, cyclophosphamide-based mobilization was permitted.

Weekly KRd-daratumumab (all pts received 8 cycles)

Cycle 1	Cycle 2	Cycle 3-4	Cycle 5-6	Cycle 7-8 *(28-day cycles)*
Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m^2 day 2 and 56 mg/m^2 days 8 and 15; Lenalidomide 25 mg days 1-21; Dexamethasone 40 mg weekly	Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 56 mg/m^2 days 1, 8, and 15; Lenalidomide 25 mg days 1-21; Dexamethasone 40 mg weekly	Daratumumab 16 mg/kg days 1 and 15; Carfilzomib 56 mg/m^2 days 1, 8, and 15; Lenalidomide 25 mg days 1-21; Dexamethasone 40 mg weekly	Daratumumab 16 mg/kg days 1 and 15; Carfilzomib 56 mg/m^2 days 1, 8, and 15; Lenalidomide 25 mg days 1-21; Dexamethasone 20 mg weekly	Daratumumab 16 mg/kg day 1; Carfilzomib 56 mg/m^2 days 1, 8, and 15; Lenalidomide 25 mg days 1-21; Dexamethasone 20 mg weekly

For fit patients, stem cell collection recommended after 4 to 6 cycles; therapy resumed after collection to a total of 8 cycles

- **Bi-weekly and weekly arms had comparable efficacy and safety with a substantial reduction of the number of infusion days (total of 51 *vs.* 27) favoring weekly arm**
- **We closed the bi-weekly arm after fully enrolling the first stage**

Clinicaltrials.gov #NCT03290950

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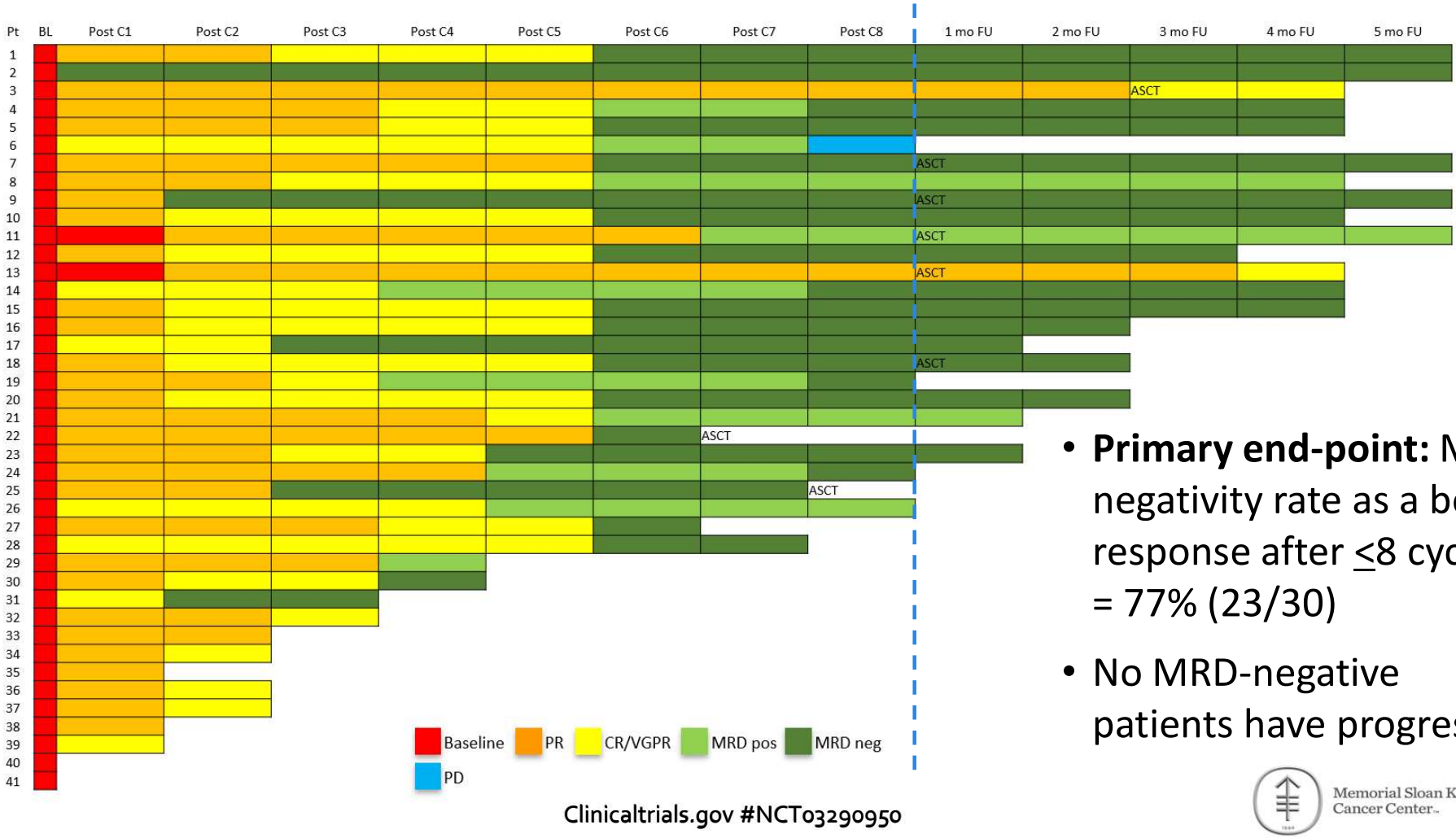
Results: response to therapy, by number of cycles



Clinicaltrials.gov #NCT03290950

- **Primary end-point:** MRD-negativity rate as a best response after ≤8 cycles = 77% (23/30)
- No MRD-negative patients have progressed

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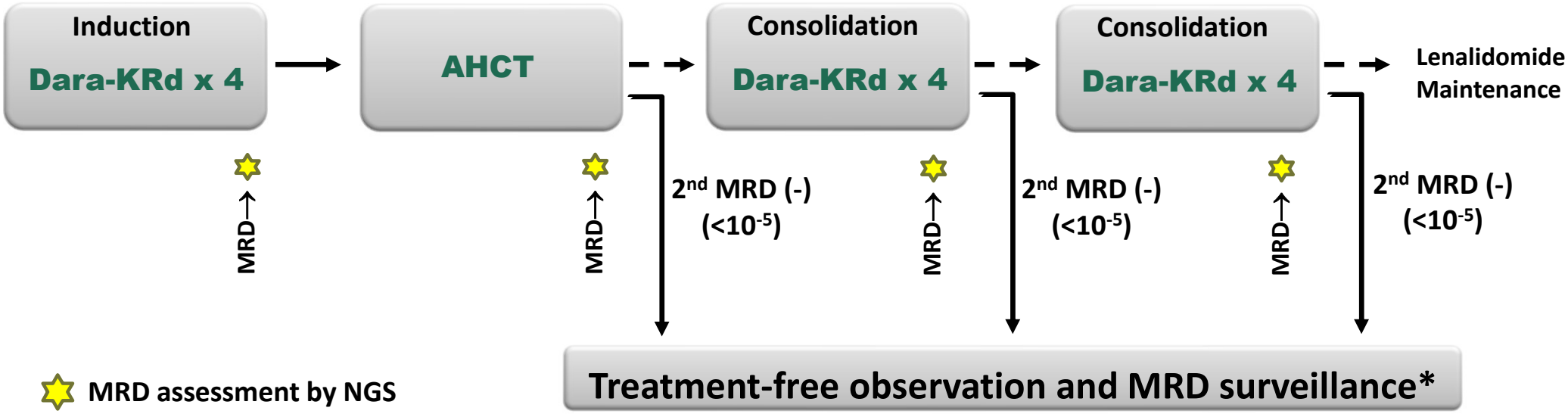
Treatment

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22

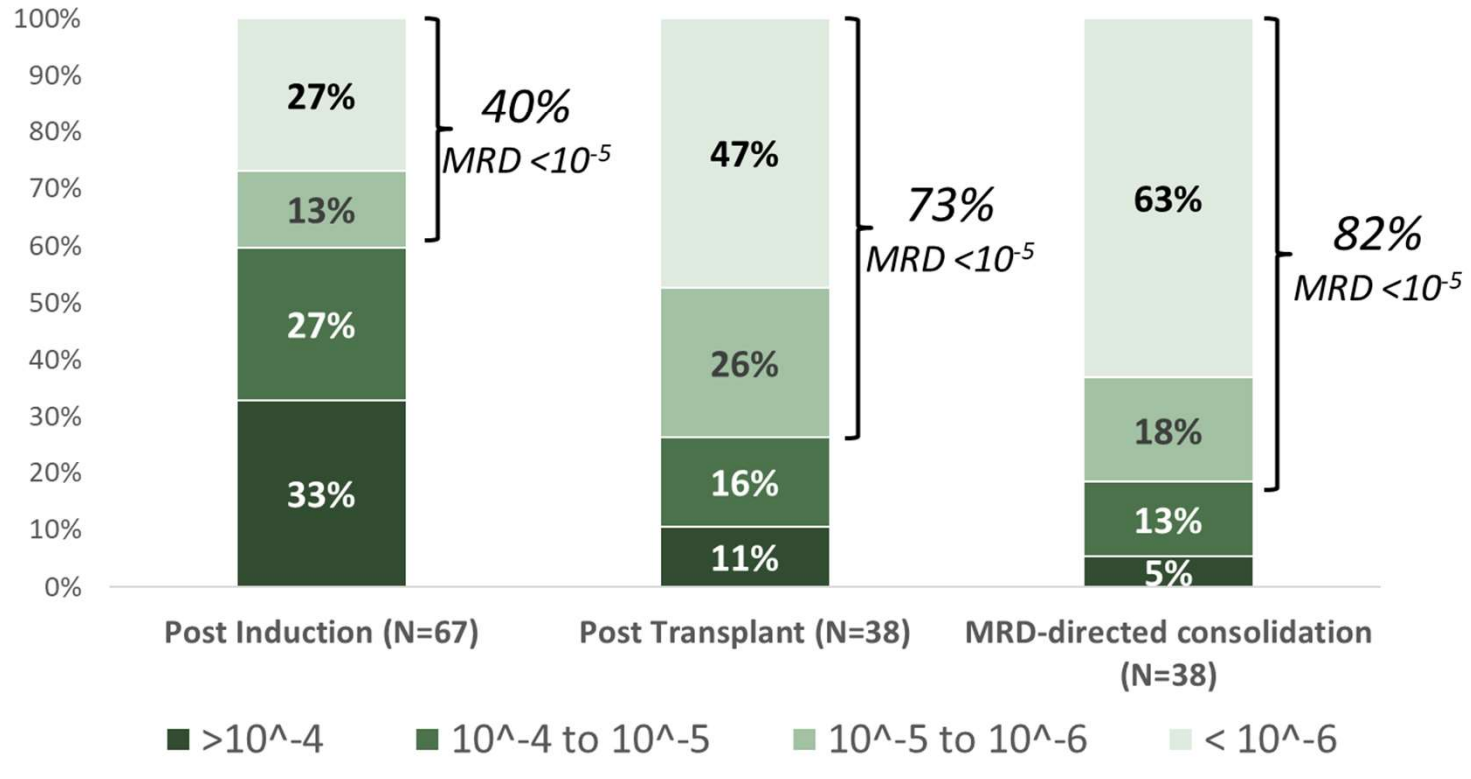


*24 and 72 weeks after completion of therapy

MASTER trial

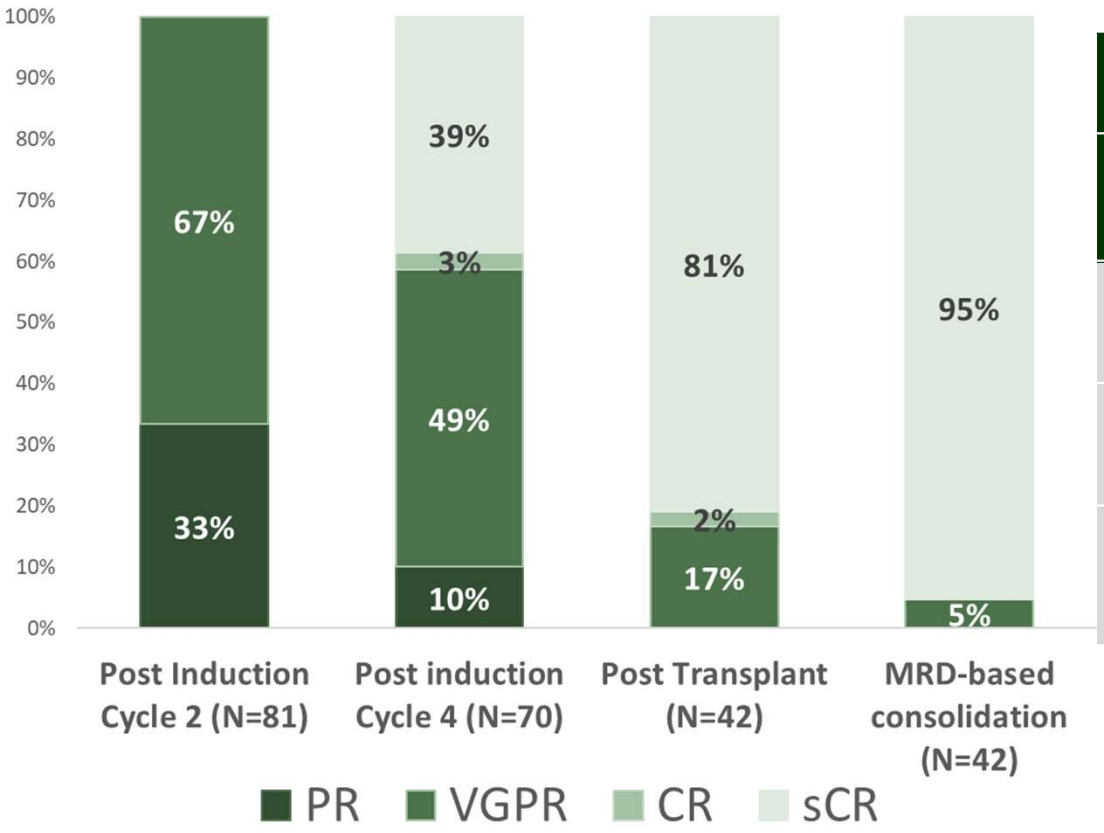
Best MRD response by phase of therapy

- MRD trackable by NGS clonoSEQ® in 78/81 patients (96%)
- 100% of datapoints obtained in patients with trackable MRD



MASTER trial

Best IMWG response by phase of therapy



sCR Rates			
	Post Induction	Post Transplant	MRD-based consolidation
All patients	39% (N=70)	81% (N=42)	95% (N=42)
Standard-risk	44% (N=50)	79% (N=29)	97% (N=29)
High-Risk [t(4;14), t(14;16), del17p]	25% (N=20)	85% (N=13)	91% (N=13)

- 1 progression at post-AHCT evaluation

MASTER trial

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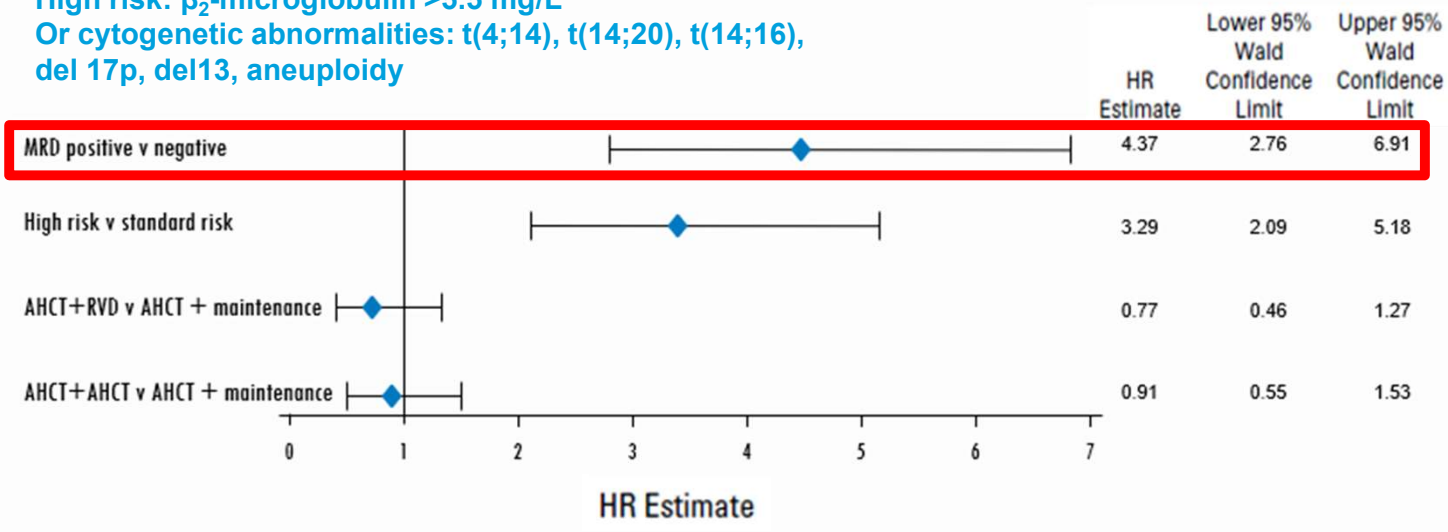
What about MRD Directed Therapy?

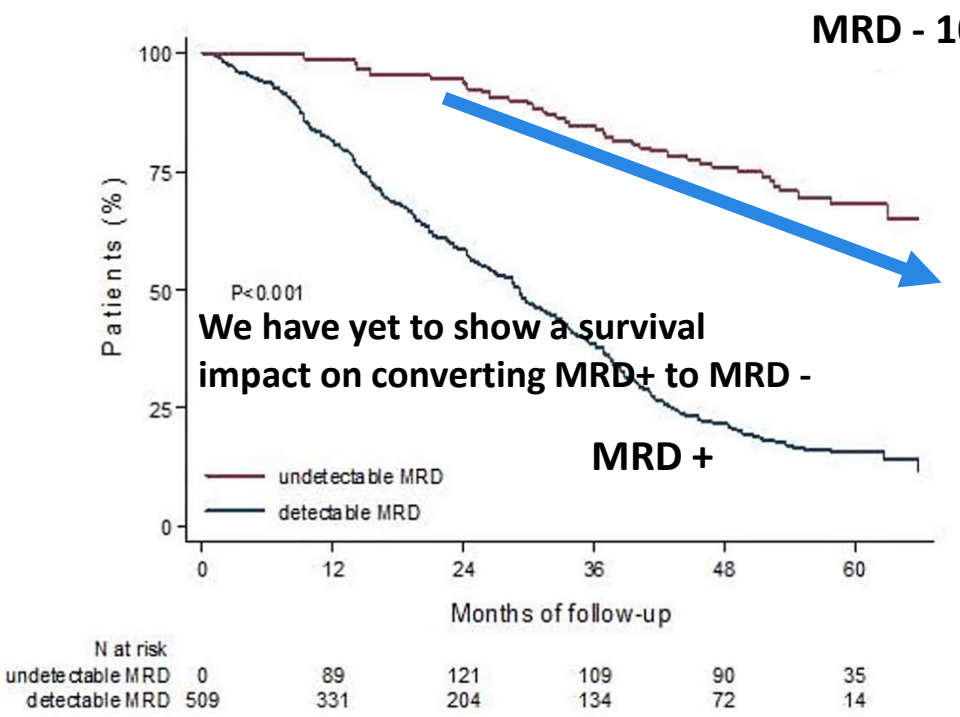
Multivariable analysis PFS at 1 Year - PRIMeR

High risk: β_2-microglobulin >5.5 mg/L
Or cytogenetic abnormalities: t(4;14), t(14;20), t(14;16), del 17p, del13, aneuploidy



Support provided by #U10HL069294 to BMT CTN from NHLBI/NCI, and #R01HL107213 from NHLBI

"MRD negativity is not the same as "cure" or even "long term disease control" and it's ability to inform practice is not the same for each patient.



At median follow-up of 55 months, median PFS for MRD negative patients not reached, *versus* 29 months for MRD positive patients

MRD negativity obtained in 30% (73/245) with VRd + transplant and 20% (54/264) with VRd alone

Perrot A, et al. Presented at ASH 2017.

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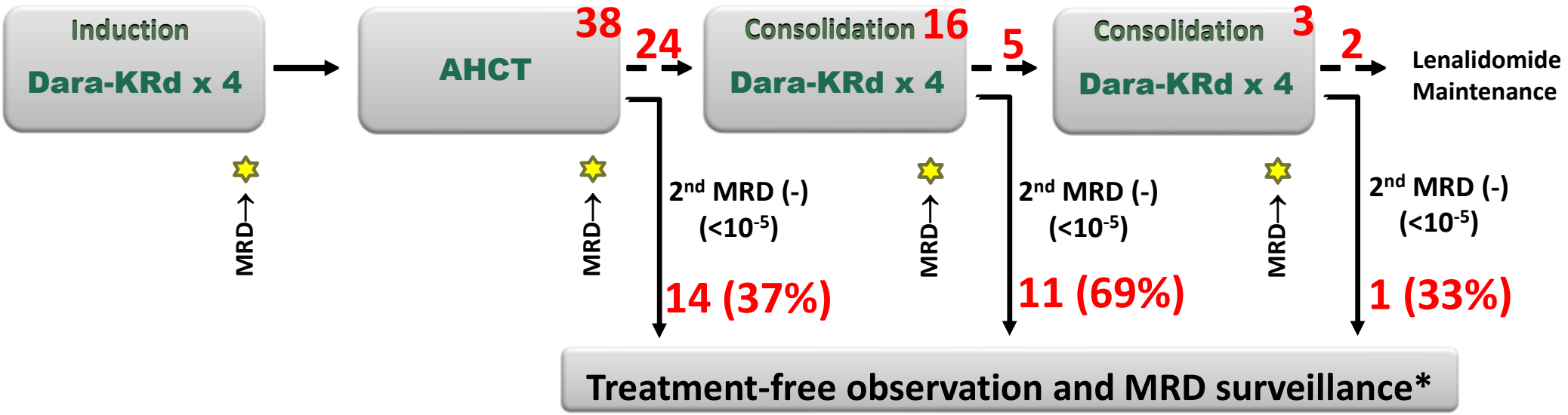
Observation/MRD surveillance

- 26 patients (19 SR, 7 HR) have reached confirmed MRD (-) and entered observation/MRD surveillance.
- Median follow up on observation 4.9 months (0.2-12.2) - <u>No relapse or resurgence of MRD</u>

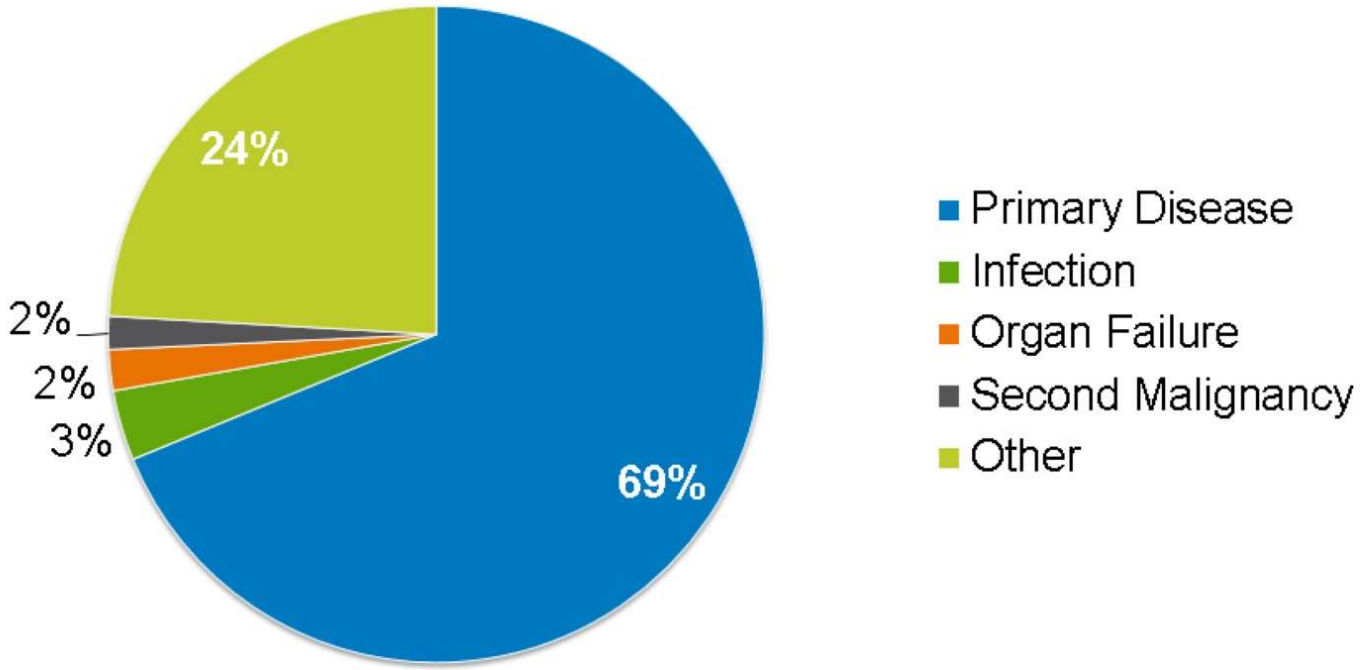


*24 and 72 weeks after completion of therapy

MASTER trial

Improving Outcomes

Causes of Death after Autologous HCT done in 2013-2014



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Relapse Prevention

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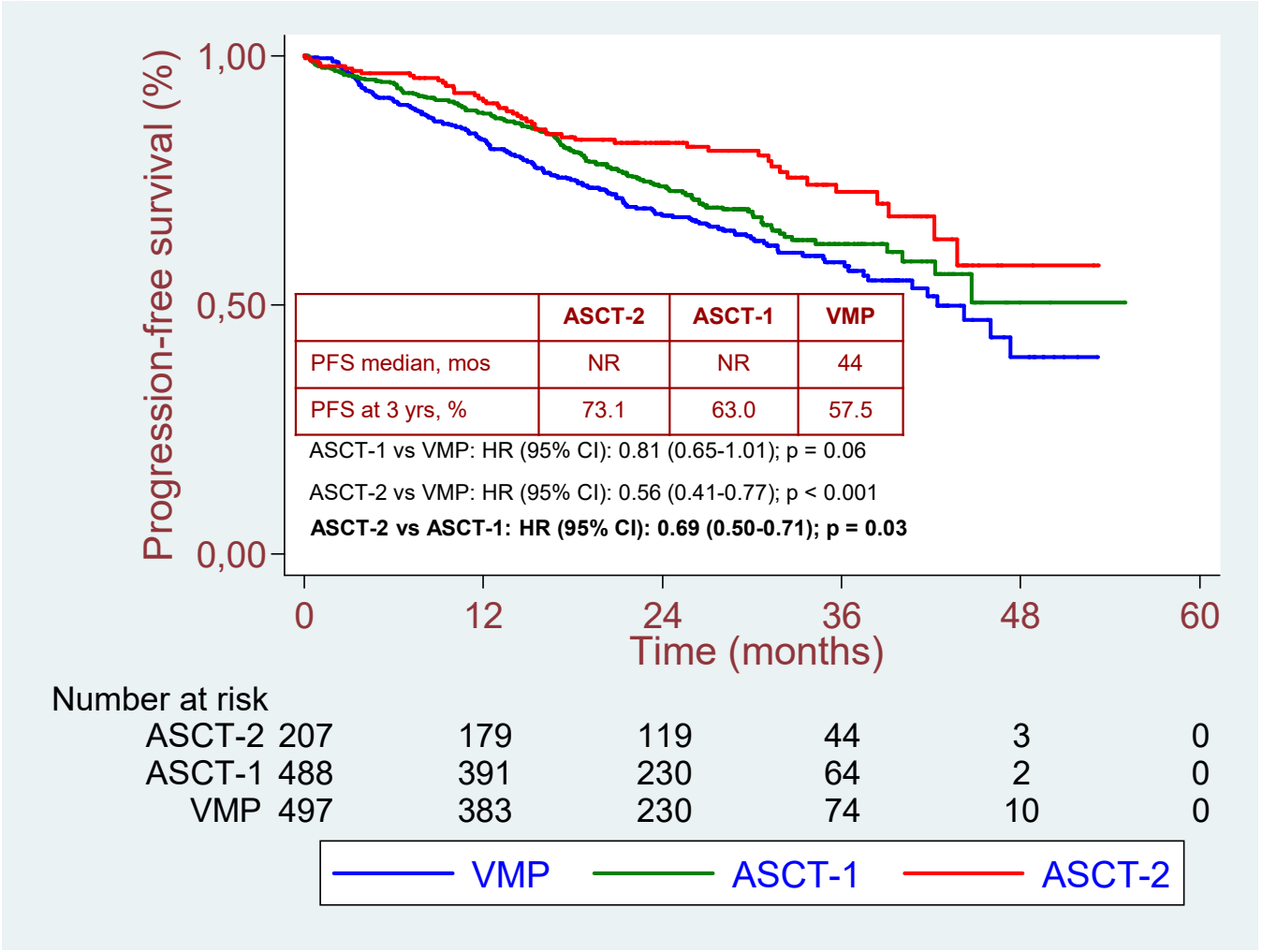
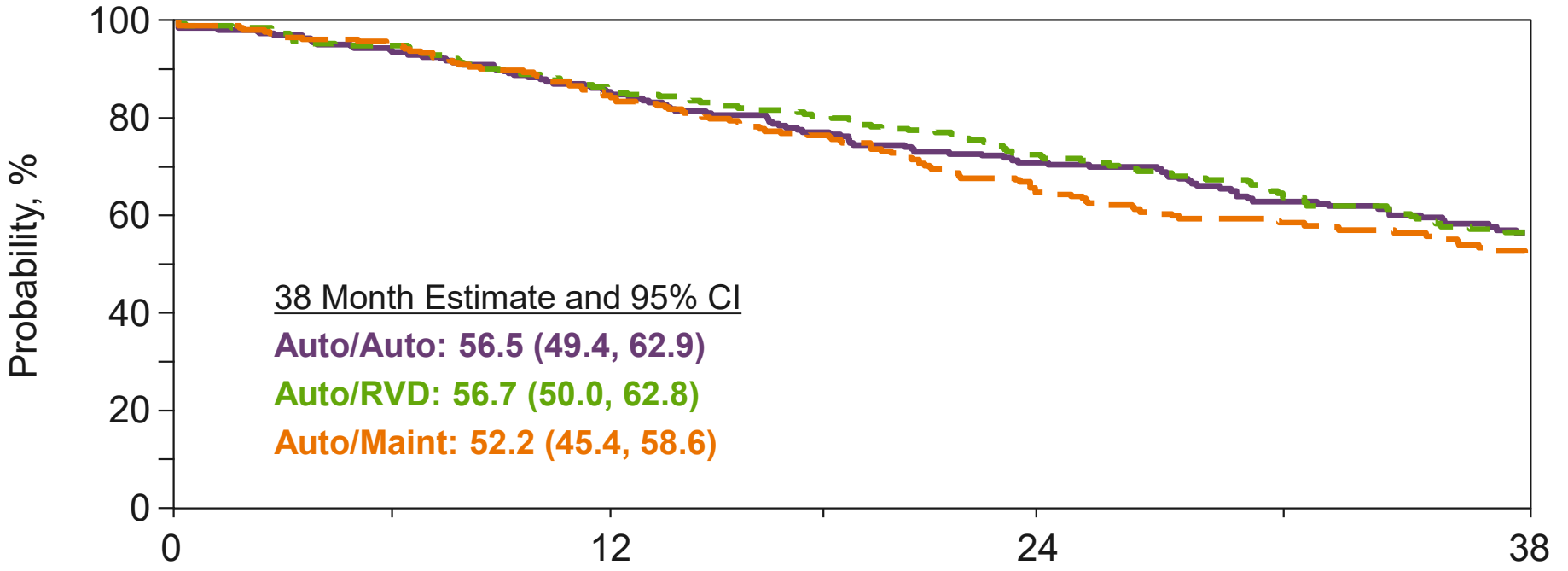
PFS by Randomization to ASCT-1 or ASCT-2



Primary Endpoint: Progression-free Survival



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

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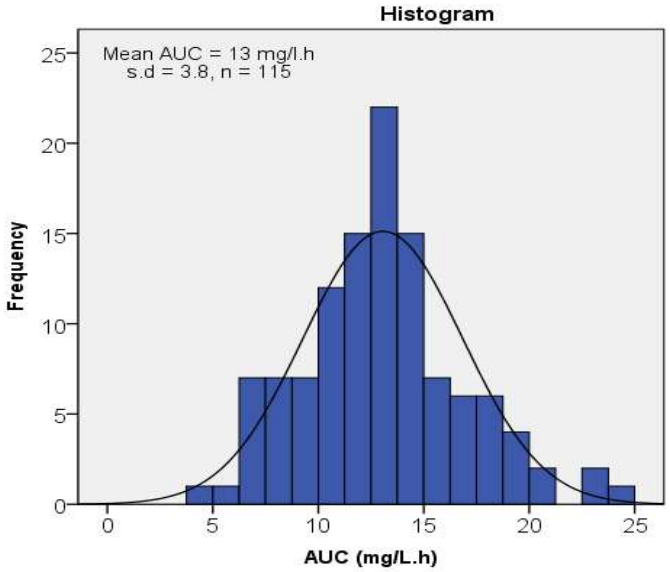
Wide Variability in Melphalan AUC

- Higher dose intensity associated with improved disease response
- Significant risk factors for severe mucositis
  - Melphalan dose
  - Renal impairment



- AUC range: 5 – 25 mg/L.h
- Same 5 fold variation as: Carbo, Fludarabine, Busulfan, Amphotericin

*Shaw BBMT 2012;18(2):S207

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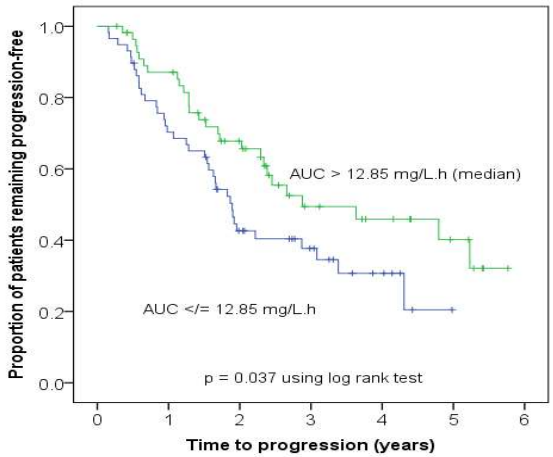
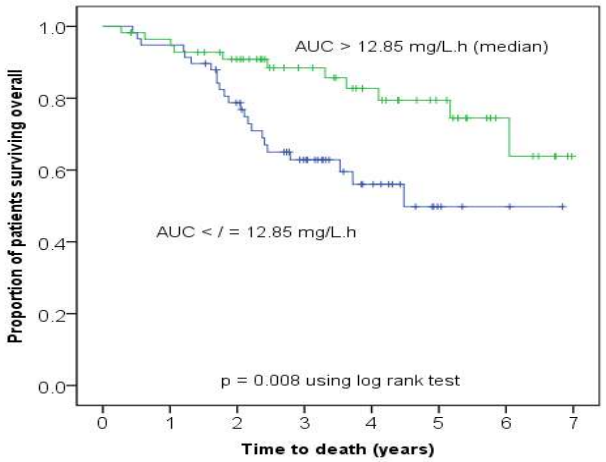
Higher Melphalan AUC Predicts Time to Progression, Overall Survival, and Toxicity





- Melphalan median AUC 12.85 mg/L.h
- Mucositis >= Grade 3
  - 12% clinical, 20% functional
  - Multivariate analysis Melphalan AUC (continuous), HR 1.2, p = 0.004

*Shaw BBMT 2012;18(2):S207

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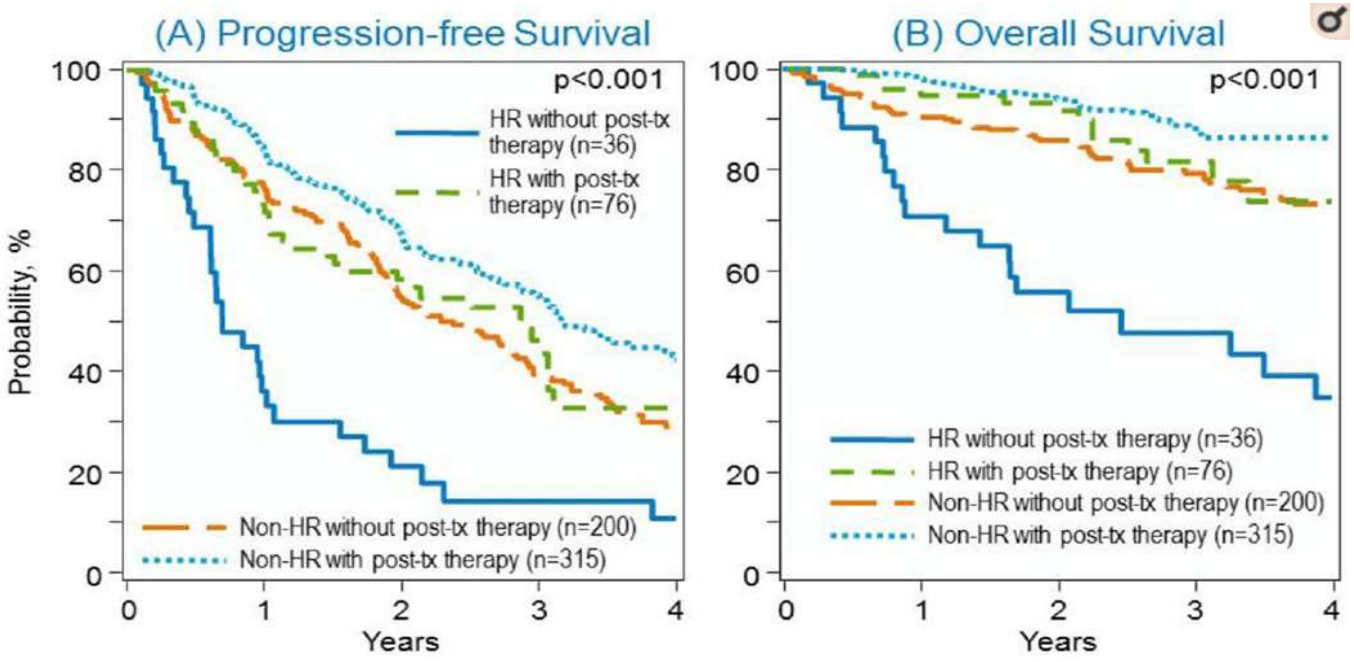
Post-transplant outcomes in high-risk compared to non-high risk multiple myeloma, a CIBMTR analysis

Emma C. Scott[1], Parameswaran Hari[2], Manish Sharma[3], Jennifer Le-Rademacher[2,4], Jiaxing Huang[2], Dan Vogl[5], Muneer Abidi[6], Amer Beitinjaneh[7], Henry Fung[8], Siddhartha Ganguly[9], Gerhard Hildebrandt[10], Leona Holmberg[11], Matt Kalaycio[12], Shaji Kumar[13], Robert Kyle[13], Hillard Lazarus[14], Cindy Lee[15], Richard T. Maziarz[16], Kenneth Meehan[17], Joseph Mikhael[18], Taiga Nishihori[19], Muthalagu Ramanathan[20], Saad Usmani[21], Jason Tay[22], David Vesole[23], Baldeep Wirk[24], Jean Yared[25], Bipin N. Savani[26], Cristina Gasparetto[27], Amrita Krishnan[28], Tomer Mark[29], Yago Nieto[30], and Anita D'Souza[2]



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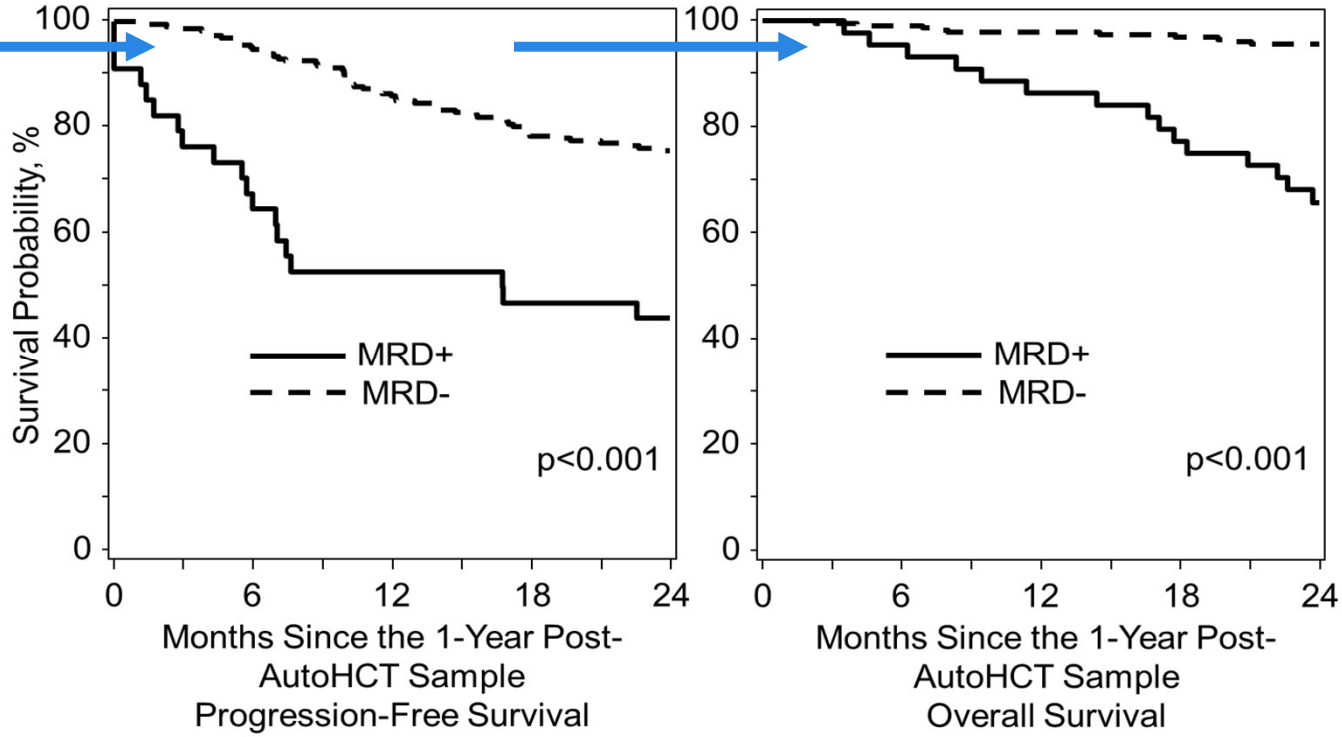
PRIMeR Results:
PFS (Left) and OS (Right) by MRD Status at 1-Year

PFS

Can pre-emptive intervention make a difference?



OS

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Support provided by #U10HL069294 to BMT CTN from NHLBI/NCI, and #R01HL107213 from NHLBI

Summary

- We are now at the dawn of a new era in hematopoietic cell transplantation for myeloma
- We have strategies that can now impact the major causes of treatment failure (relapse, infections and toxicities)
- The way forward will require more personalized approaches to develop the optimal strategy for each patient and each specific disease.
- Only prospective trials and well curated large datasets will allow us to develop the knowledge necessary to perform such transplants
- We need substitute our current Triple P Transplants where we Push the drugs, Pour the Cells and Pray that it all works out to a modern Triple P Strategy of Precise, Personalized and Predictable transplant.
- I predict that dose intense therapy will continue to be an important component of a curative strategy for myeloma with both autologous and allogeneic stem cell transplantation.

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Questions or referrals

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