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Treatment Conundrums in Myeloma
What's new in 2022?

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Disclosures

- Research Support
  - CELGENE, SANOFI, Johnson & Johnson, Actinuum, Millenium, AMGEN, TAKEDA
- Consulting
  - CELGENE, SANOFI, Johnson & Johnson, Actinuum, Millenium, AMGEN
  - Kite (Gilead), Novartis, BMS, Jazz, Pfizer,
- I am a transplanter

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Agenda

- The standard patient
  - When to treat?
  - High risk smoldering
- Induction
- Role of Consolidation
- Special populations
  - Transplant ineligible
  - Renal failure
- Young patient with high-risk disease
- Approach to the relapsing patient
- Managing most common toxicities

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Clinical Case

- MJ is a 42 year old female who is found on a routine physical to have the following lab values

CBC values

- **WBC count 3,300/µL**
- **Hemoglobin 10.3 g/dL**
- **Platelet count 158,000/µL**

Chemistry Values

- **Creatinine 1.0 g/dL**
- **Calcium 10.2 mg/dL**
- **Albumin 3.2 g/dL**
- **Total protein 10.9 g/dL**

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MJ

- Referred to a hematologist
- Ferritin low
- SPEP Ig G kappa 4.2 grms monoclonal peak
- 24-hour urine was normal < 0.16 g/24 hours
- β_2-microglobulin normal 2.6 mg/L
- BMA 60% plasma cells ; FISH no abnormalities
- Low iron stores
- *Bone Survey – Osteopenia*

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NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Multiple Myeloma

NCCN Guidelines Index
Table of Contents
Discussion

INITIAL DIAGNOSTIC WORKUP

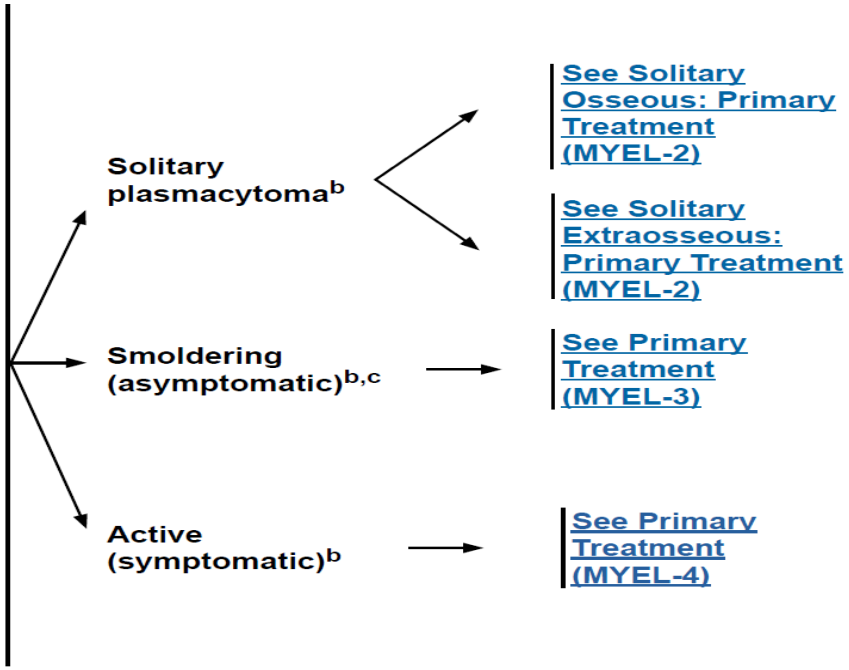
- History and physical exam
- CBC, differential, platelet count
- Exam of peripheral blood smear
- Serum BUN/creatinine, electrolytes, albumin, and calcium
- Creatinine clearance (calculated or measured directly)
- Serum uric acid
- Serum LDH and beta-2 microglobulin
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Skeletal survey or whole body low-dose CT scan
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Metaphase cytogenetics on bone marrow
- Plasma cell FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14:20), 1q21 amplification], 1p abnormality

Useful in Certain Circumstances

- Whole body or skeletal MRI or whole body PET/CT scan[a]
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Plasma cell proliferation
- Serum viscosity
- HLA typing
- Echocardiogram
- Evaluate for light chain amyloidosis, if appropriate

See NCCN Guidelines for Systemic Light Chain Amyloidosis

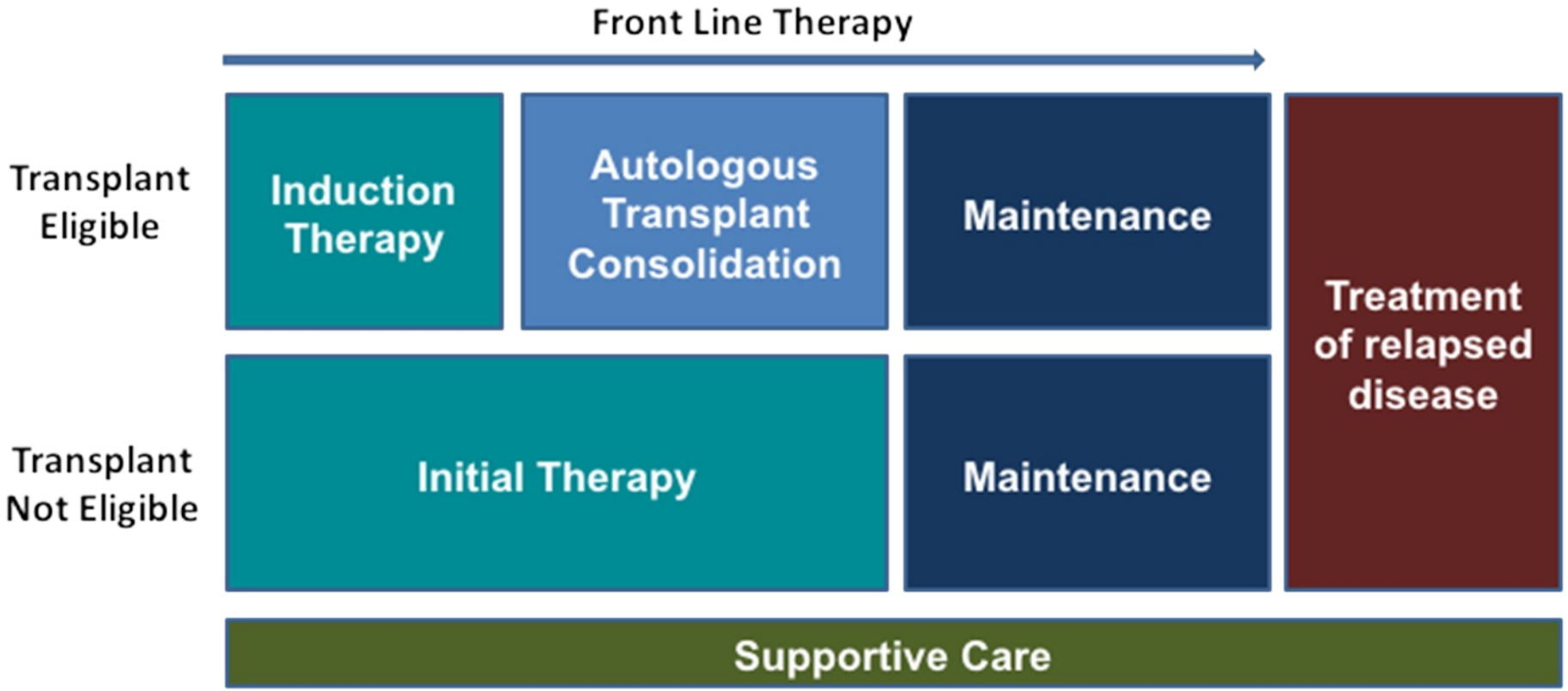
CLINICAL PRESENTATION



[a]Additional testing (whole body or skeletal MRI or whole body PET/CT scan) is recommended to discern active from smoldering myeloma, if skeletal survey is negative. Recommendations for MRI are with contrast.
[b]See Staging Systems for Multiple Myeloma (MYEL-B).
[c]See Definition of Multiple Myeloma (Smoldering and Active) (MYEL-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment Paradigm For Newly Diagnosed Multiple Myeloma



Staging and Cytogenetic Risk-Assessment

Stage[1]	R-ISS[1]
I	Serum albumin ≥3.5 g/dL^{-1} Serum β2M <3.5 mg/L^{-1} No high-risk cytogenetics Normal LDH level
II	Not stage I or III
III	Serum β2M >5.5 mg/L^{-1} High-risk cytogenetics: t(4;14), t(4;16), or del(17p) or elevated LDH

Risk[2]	Features
Standard	Trisomies t(11;14) t(6;14)
High	t(4;14) t(14;16) t(14;20) Del(17p) *p53* mutation Gain/Amp 1q High plasma cell S-phase GEP high-risk signatures Circulating Plasma Cells

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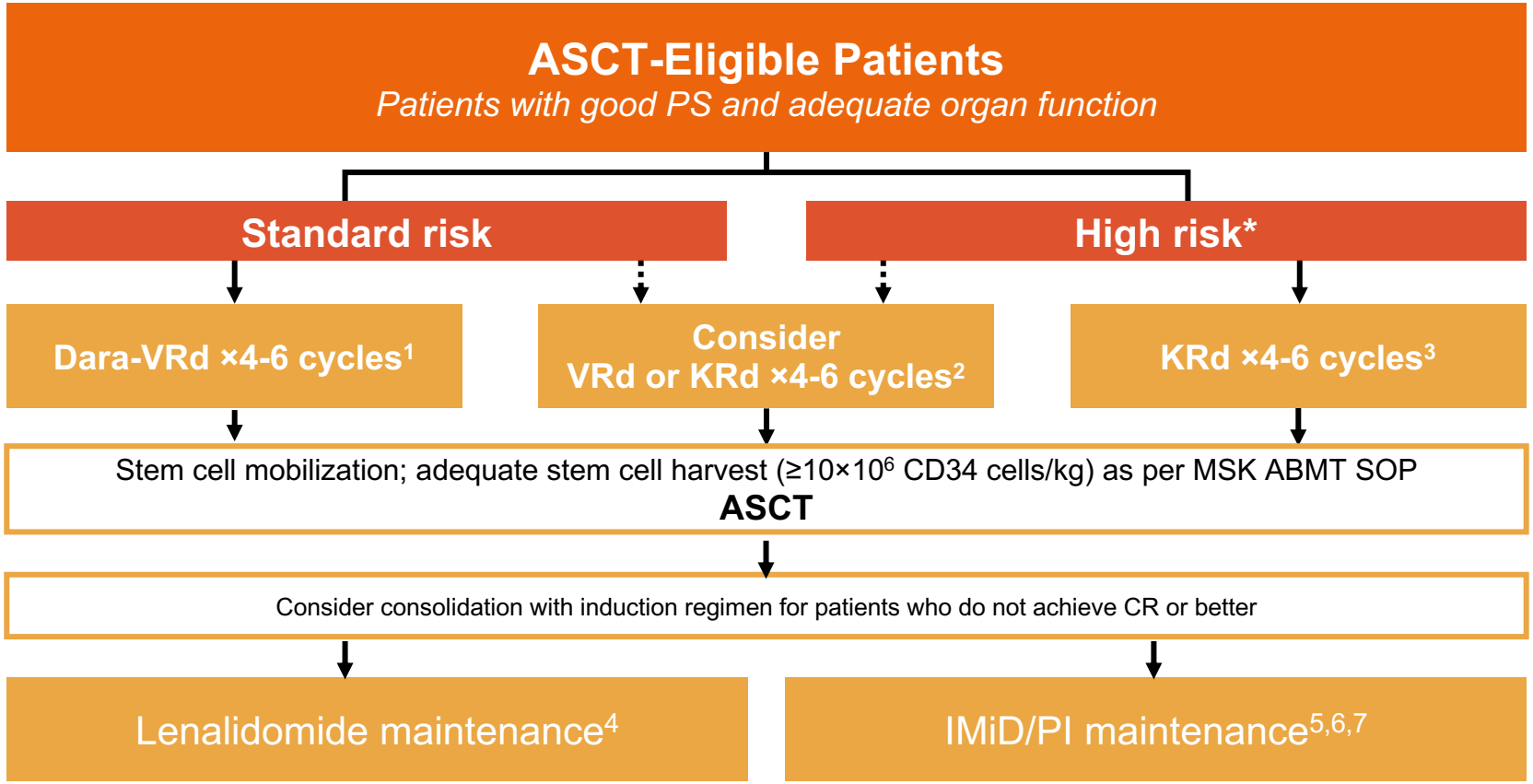
1. Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2869; 2. Costa LJ, Usmani SZ. J Natl Compr Canc Netw. 2020;18(12):1730-1737.

Approach to Transplant Eligible NDMM



- ASCT, autologous stem cell transplant; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PS, performance status; Tx, treatment.
- *By R-ISS staging (R-ISS II/III) and/or cytogenetics (t[4;14], t[14;16], or del[17p]), elevated LDH, primary plasma cell leukemia
- 1. Attal. *NEJM*. 2017;376:1311. 2. Voorhees PM. Blood 2020. Gay. ASH 2020. Abstr 294. 4. McCarthy. *J Clin Oncol*. 2017;35:3279. 5. Nooka. *Leukemia*. 2014;28:690. 6. Dimopoulos. ASH 2018. Abstr 301. 7. Usmani. *Lancet Haematol*. 2021 Jan;8(1):e45-e54.

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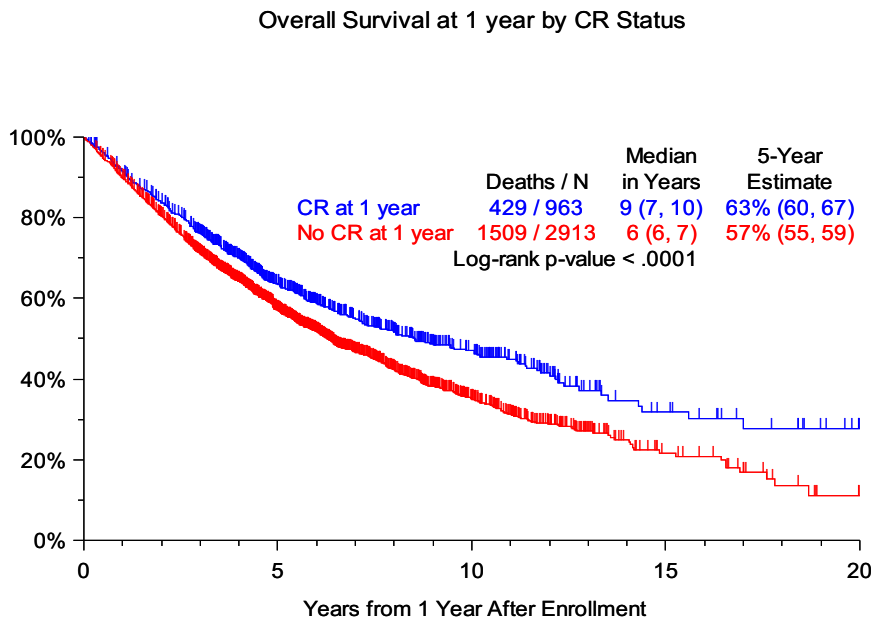
INDUCTION

- She opts for iron supplementation and observation despite recommendation to start treatment.
- 12 months later she complains of increasing fatigue
  - M peak 6.2 g/L
  - Hemoglobin 9.3 g/L
- PET – CT new FDG avid lesion in femur and pelvis
- What is the best induction ?
  - 2 agents vs 3 agents vs 4 agents
  - What class of drugs ?
- Goals of treatment " Longest life with the best quality of life with the least amount of treatment necessary"

Long-term Survivors Achieve CR Within 1 Year of Diagnosis

- Analysis of prospectively collected datasets with patients >10 years survival.
- 7,291 patients with survival data were considered for the analysis, age limit up to 75 years.
- Global study: Czech Republic, France, Germany, Italy, South Korea, Spain, the Nordic Myeloma Study Group (Sweden, Denmark, Norway) and the United States.
- Over 90% of the patients in the dataset were from the pre-novel therapy induction era and ~ 10% did received thalidomide as part of their upfront therapy (Total Therapy 2 thalidomide arm, GMMG-HD3 thalidomide arm and BO2002).

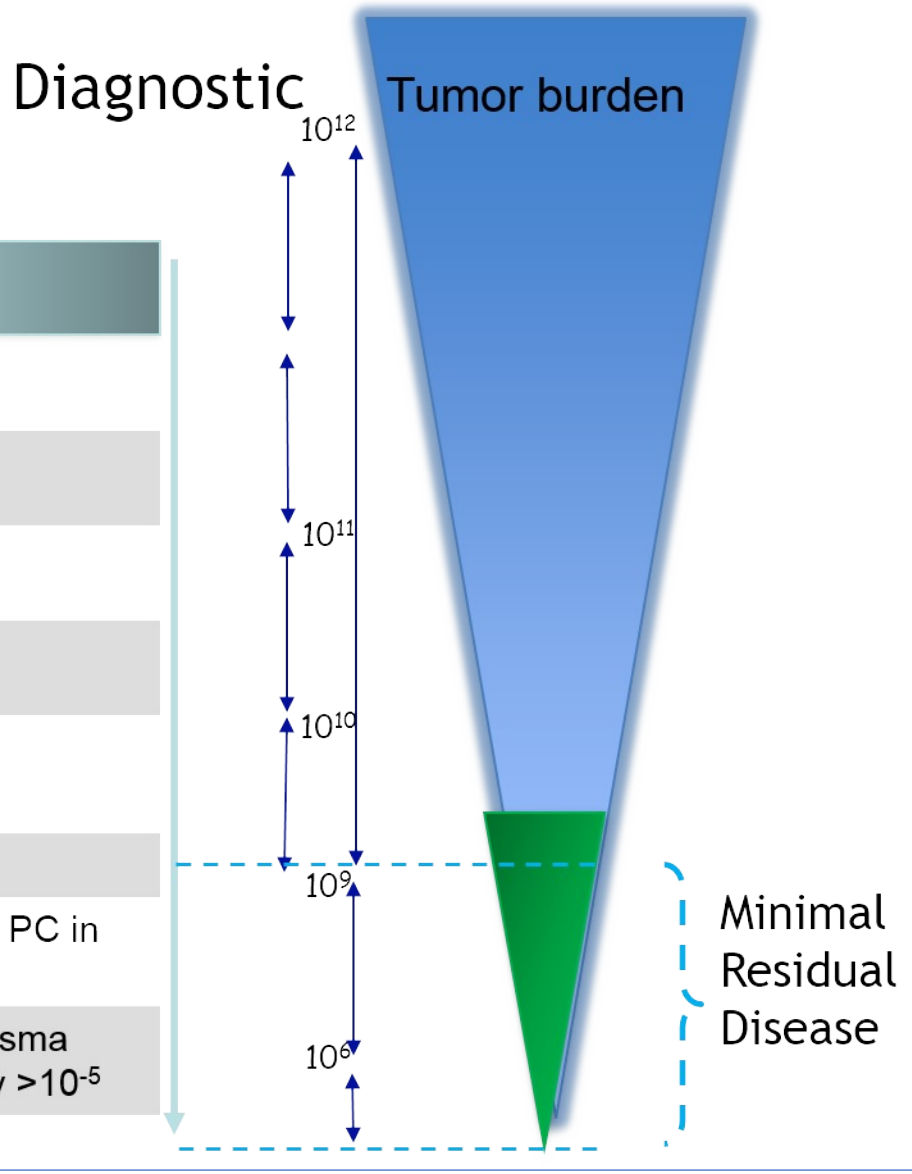


Usmani SZ et al. Blood Can J 2018 (*In press*)

Measurable Residual Disease MRD

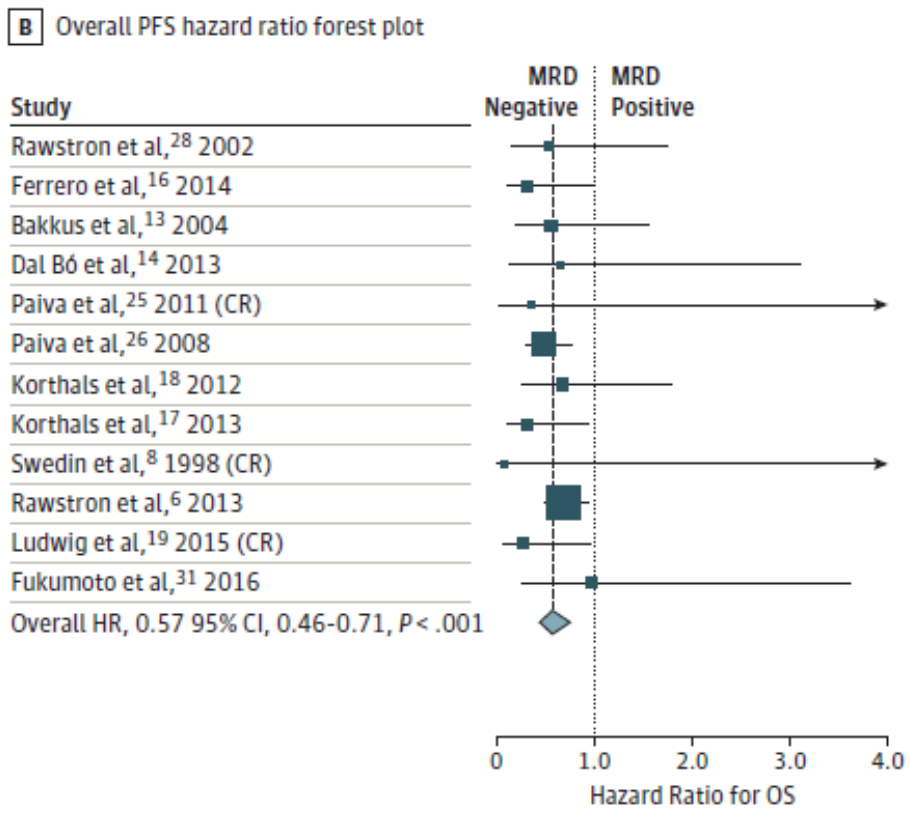
RESPONSE

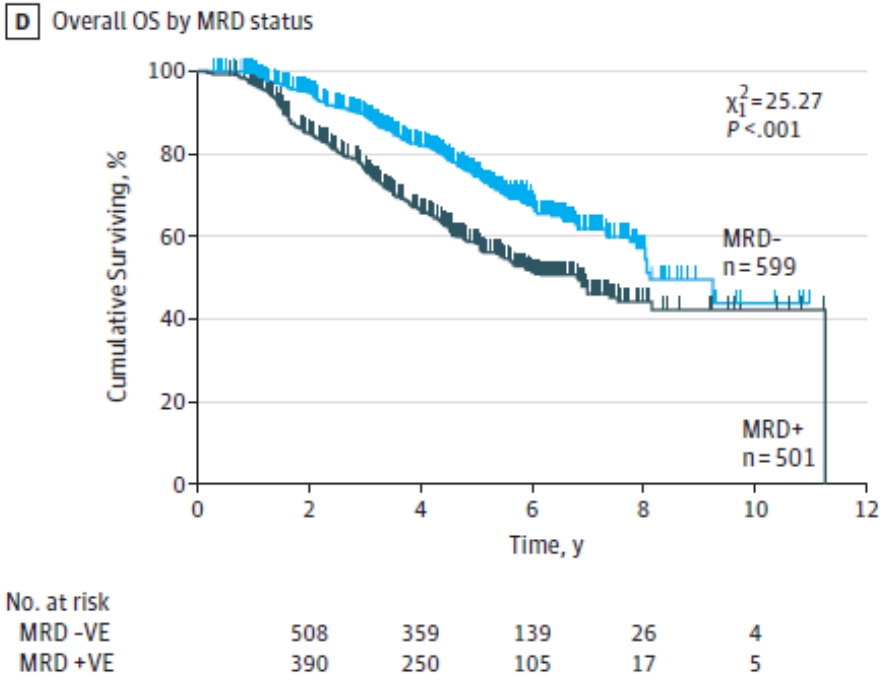
Category	Level of detection
SD	
PR	MC <50%
VGPR	MC <90%
nCR	MC 0.1 – 0.5 g/dl
CR	MC ≤ 0,5g/dl PC in BM<5%
Stringent CR	CMC ≤ 0.01g/dl
Immunophenotypic CR	sCR+ non aberrant PC in 1,000,000 cells
Molecular CR	CR+ non clonal plasma cells with sensitivity $>10^{-5}$



Rajkumar SV et al Blood 2011; Durie B et al Leukemia 2006; Blade J et al BJH 1998

MRD Negativity As Surrogate for OS





Munshi N et al, JAMA Oncology 2017:3(1):28-35

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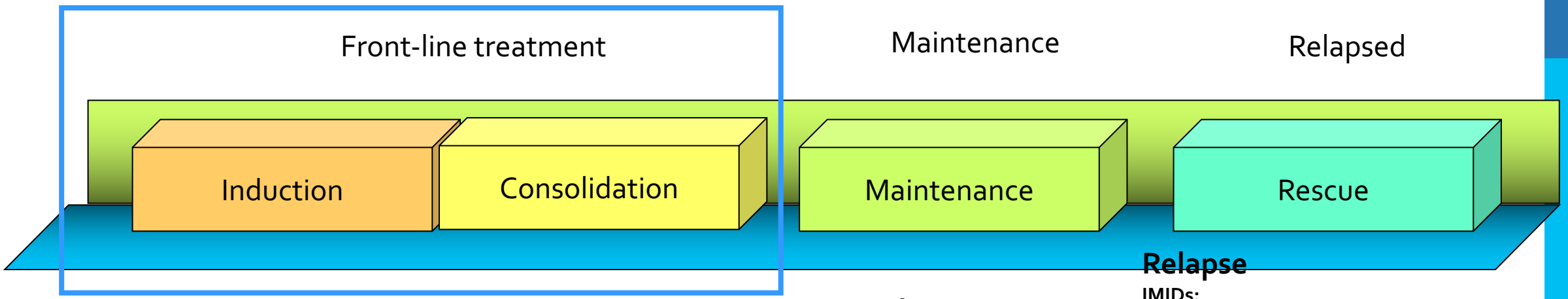
TREATMENT STRATEGIES FOR MYELOMA



Induction

Immunomodulador:
- **Thalidomide/Lenalidomide**

Proteosome Inhibitor
- **Bortezomib/Carfilzomib/Ixazomib**

Steroids
- **Dexa/Prednisone**

Alkylating Agents
- **Ciclophosphamide/Melphalan**

Anthracycline
- **Doxorubicin**

Monoclonals
- **Daratumumab**

Consolidation

High Dose Melphalan Transplant

Maintenance Observation

IMID: Thal-Len

Proteosome Inh: Bor

Steroids: Dex-Pred

Relapse

IMIDs:
- **Thalidomida/Lenalidomida**

Proteosome Inhibitor
- **Bortezomib/Carfilzomib/Ixazomib**

Steroids
- **Dexa/Prednisona**

Alkylating Agents
- **CyclophosphamideMelfalan**
- **DCEP / VDT PACE**

Anthracycline
- **Doxorubicin**

Monoclonals
- **CD38 Daratumumab/Isatuximab**
- **CS1: Elotuzumab**

ADC: BCMA: Belantemab

CAR T Cells

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Factors to Consider when Planning Induction Therapy for MM

- Basic Principles
  - Effective
  - Tolerable
  - Preserve Stem Cells
  - Available

- Clinical Factors
  - Renal Function
    - CyBORD as first cycle
  - Older Patient or Diabetic
    - Lower Steroid dose (20)
  - Bleeding or Clotting Disorder
    - IMID use
  - Neuropathy
    - bortezomib
- High Risk Features
    - Carfilzomib/Dara

What do the randomized trials tell us?

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

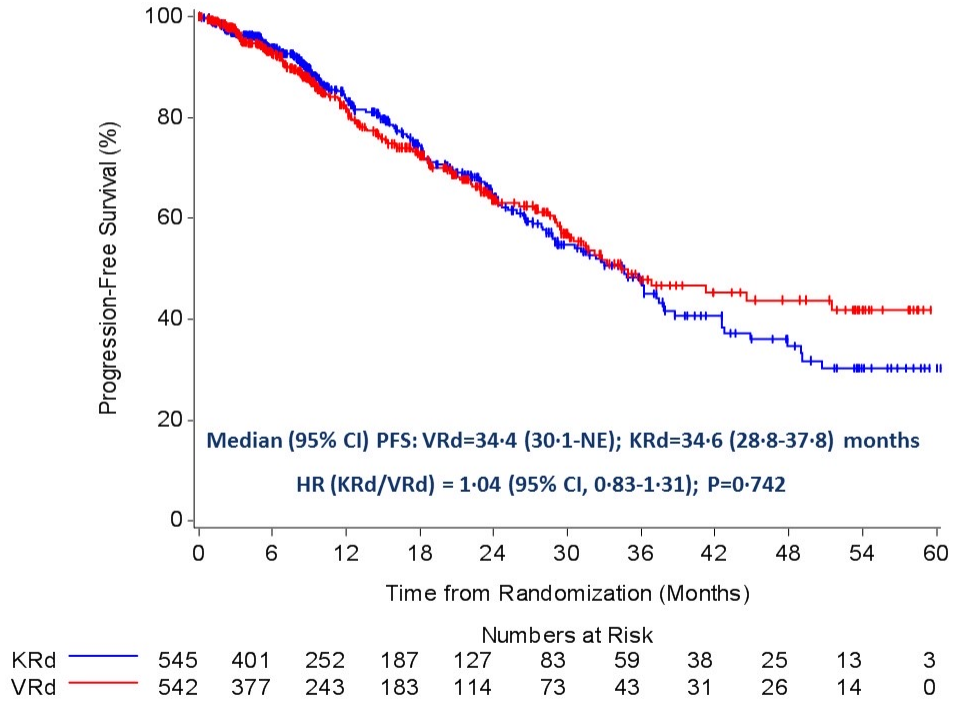
Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma: results of ENDURANCE (E1A11) phase 3 trial

Shaji K. Kumar, Susanna J. Jacobus, Adam D. Cohen, Matthias Weiss, Natalie Scott Callander, Avina A. Singh, Terri L. Parker, Alexander Menter, Alex Yang, Benjamin Marshall Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Seth Rosenberg, Jeffrey A. Zonder, Edward Anthony Faber, Sagar Lonial, Paul G. Richardson, Robert Z. Orlowski, Lynne I. Wagner, S. Vincent Rajkumar

Federally Funded Research

Presented By Shaji Kumar at TBD

Progression Free Survival from Induction Randomization

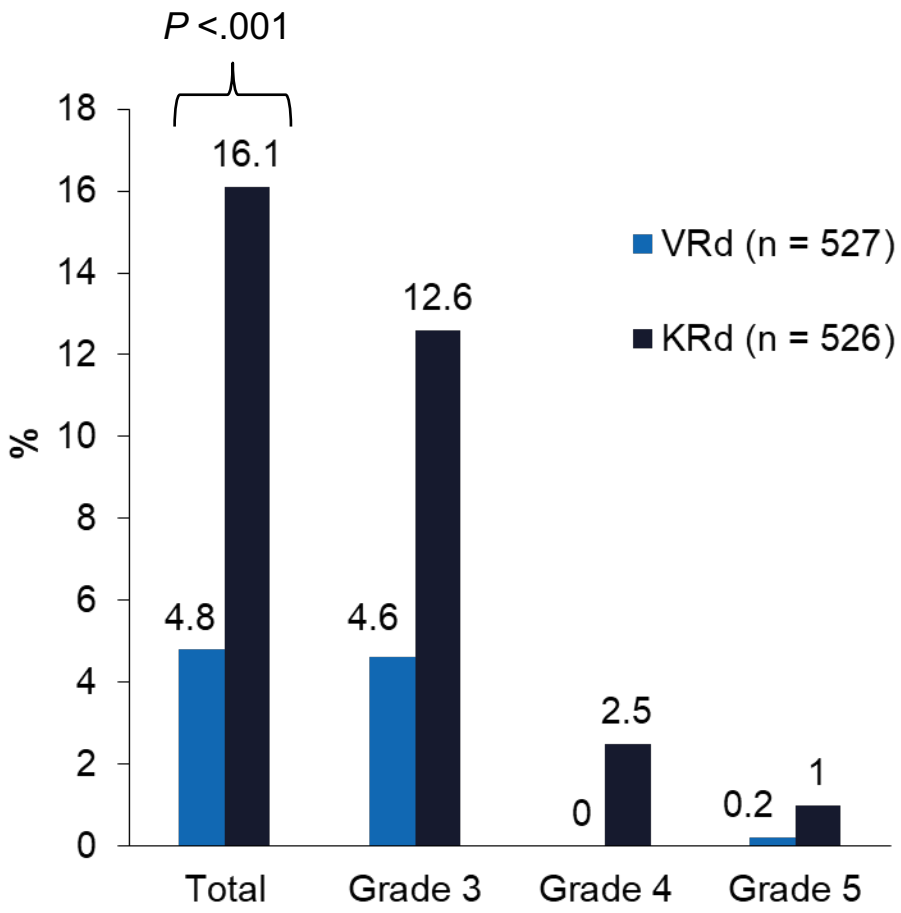


- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI)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

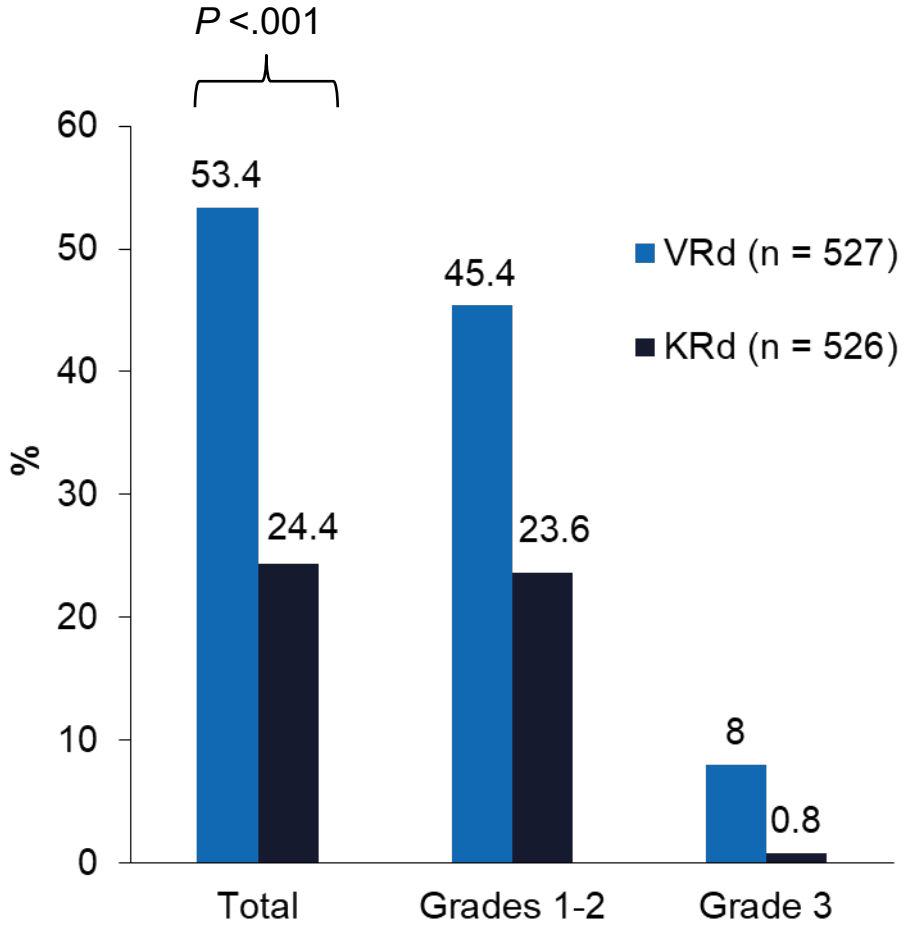
Presented By Shaji Kumar at TBD

ENDURANCE: Adverse Events of Interest

Cardiac, Pulmonary, and Renal



Peripheral Neuropathy



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Kumar S, et al. Lancet Oncol 2021.

62nd ASH Annual Meeting, December 5-8, 2020
Abstract #141

Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized FORTE Trial

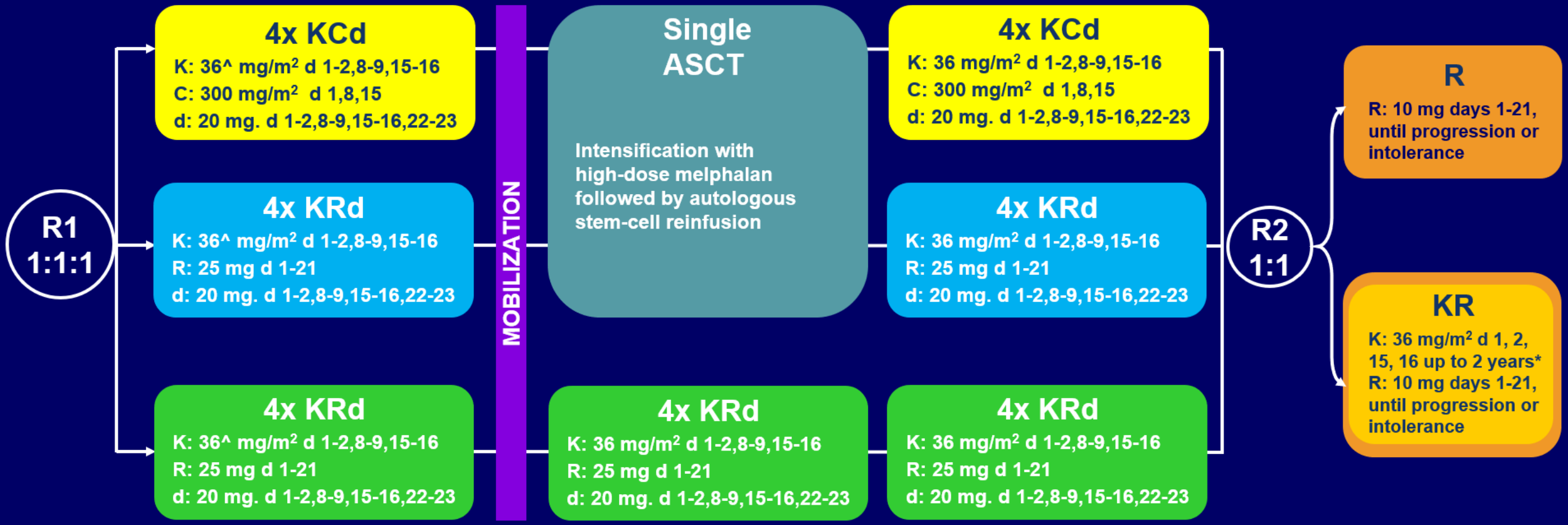
Francesca Gay[1]*, Pellegrino Musto[1], Delia Rota-Scalabrini[1], Monica Galli[1], Angelo Belotti[1], Elena Zamagni[1], Luca Bertamini[1], Renato Zambello[1], Micol Quaresima[1], Giovanni De Sabbata[1], Giuseppe Pietrantuono[1], Mattia D'Agostino[1], Daniela Oddolo[1], Andrea Capra[1], Anna Marina Liberati[1], Salvatore Palmieri[1], Franco Narni[1], Massimo Offidani[1], Michele Cavo[1], Mario Boccadoro.[1]

***Correspondence: fgay@cittadellasalute.to.it**

1. GIMEMA / European Myeloma Network, Italy

Trial design

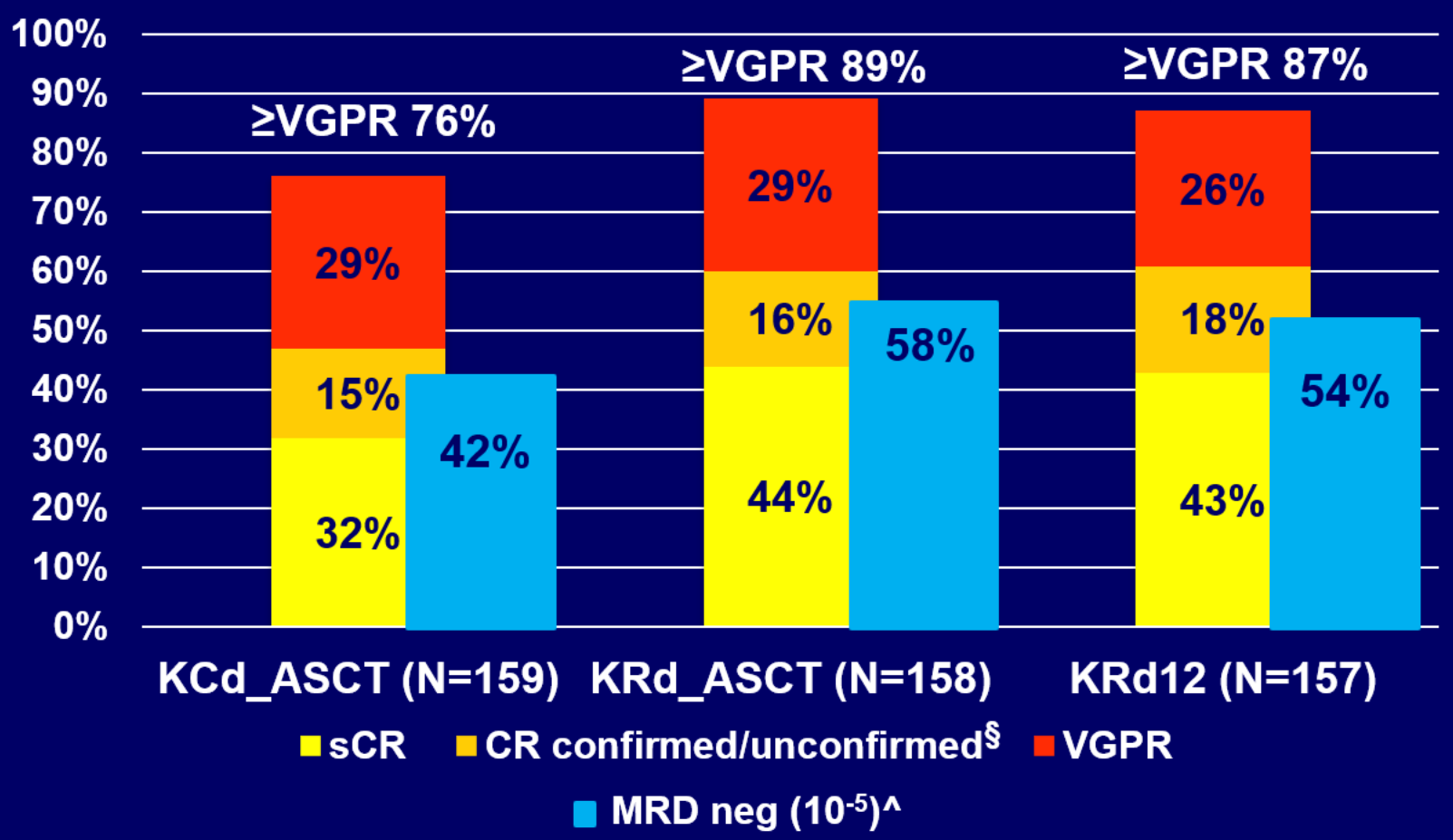
474 NDMM patients, transplant-eligible and younger than 65 years



^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. NDMM, newly diagnosed multiple myeloma, R1, first randomization (induction/consolidation treatment); R2, second randomization (maintenance treatment); IQR, interquartile range K, carfilzomib; C, cyclophosphamide; R, lenalidomide; d, dexamethasone; d, days; ASCT, autologous stem-cell transplantation.

KRd_ASCT vs. KRd12 vs. KCd_ASCT: Efficacy

Pre-maintenance response rate and MRD negativity
ITT analysis



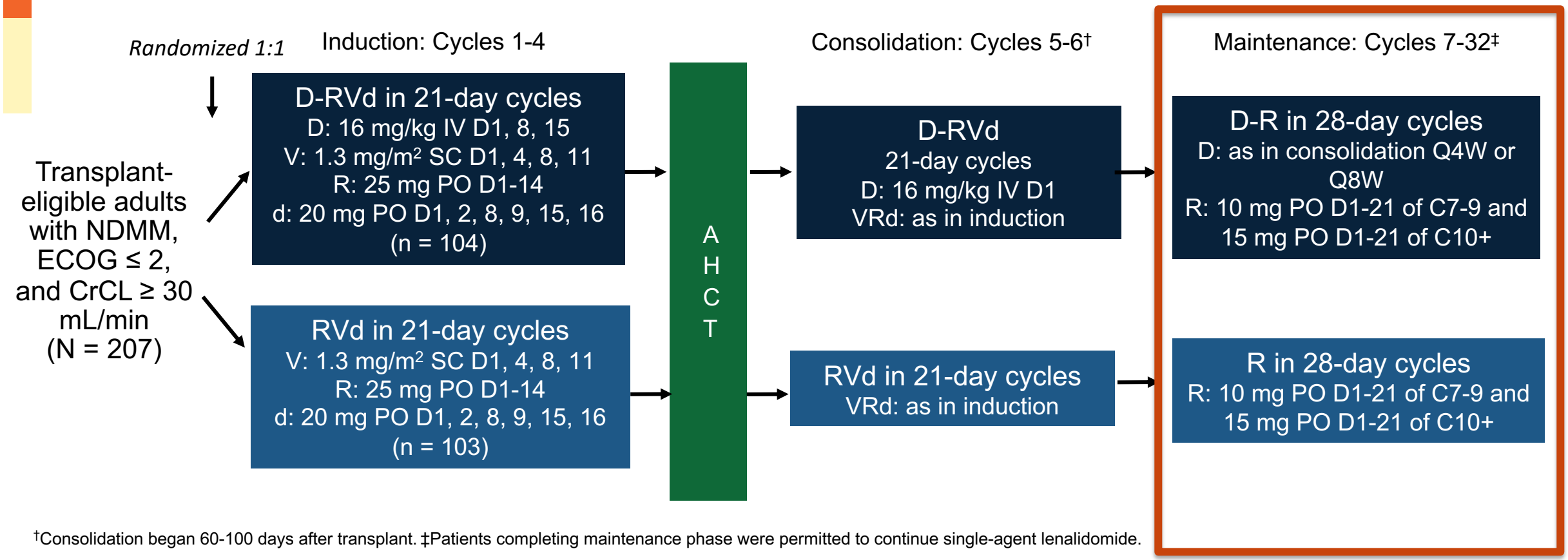
	OR	p-value*
≥VGPR		
KRd_ASCT vs KCd_ASCT	2.53	0.004
KRd12 vs KCd_ASCT	2.11	0.015
sCR		
KRd_ASCT vs KCd_ASCT	1.65	0.035
KRd12 vs KCd_ASCT	1.60	0.048

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

^Patients whose samples were not available (~10%) were considered as positive. *Adjusted for ISS, Age, FISH, LDH.
§ Unconfirmed CR/sCR: patients missing immunofixation/sFLC analysis needed to confirm CR/sCR (6% in KCd_ASCT_KCd; 8% in KRd_ASCT_KRd; 6% KRd_12).
ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; neg, negativity; ITT, intention to treat; sCR, stringent complete response; CR: complete response; VGPR: very good partial response; OR: odds ratio; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; FLC, free light chain, ISS, International Staging System.

Gay F et al. Blood. 2018;132(Supplement 1):Abstract #121 [ASH 2018 60th Meeting]. doi:10.1182/blood-2018-99-112093.

GRIFFIN 2-yr Maintenance Update



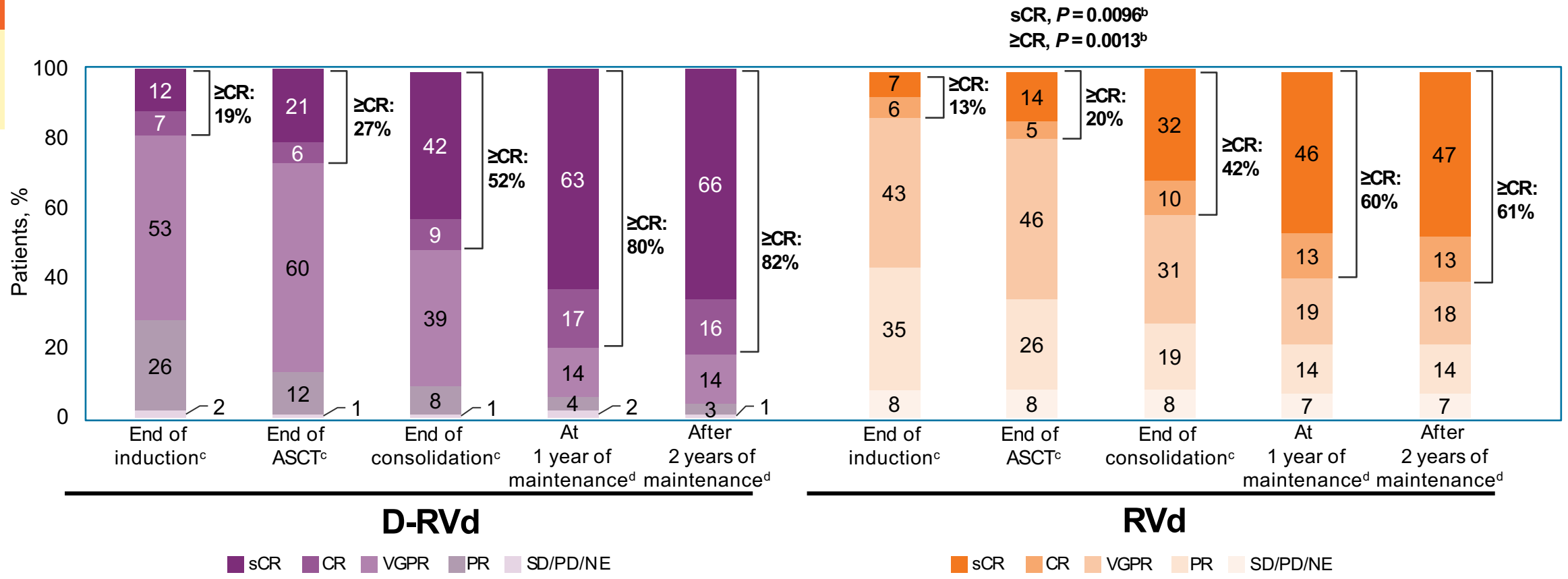
†Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide.

Primary endpoint: sCR by end of consolidation with 1-sided $\alpha = 0.1$

Key secondary endpoints: rates of MRD negativity, ORR, ≥VGPR, CR, PFS, OS

Laubach. ASH 2021. Abstr 79.

GRIFFIN: Responses Deepened Over Time



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

CR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran-Mantel-Haenszel test. [c]Response rates are from the primary analysis cutoff (median follow-up: 13.5 mo), and the response-evaluable population included 196 patients (D-RVd, n = 99; RVd, n = 97). [d]Response rates for the maintenance phase have longer follow-up (median: 36.6 mo), and the response-evaluable population included 157 patients (D-RVd, n = 100; RVd, n = 57). Percentages may not add up to 100% due to rounding.

Laubach. ASH 2021. Abstr 79.

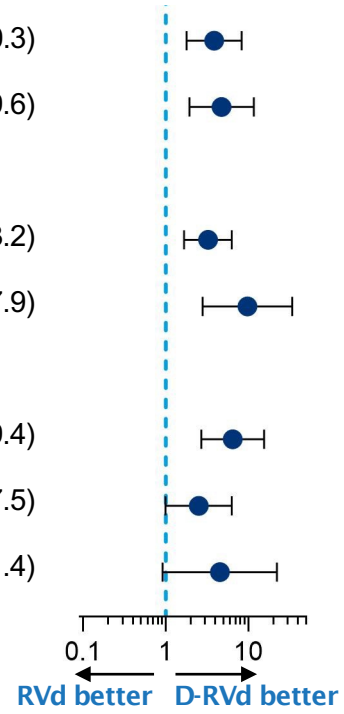
GRIFFIN 2-yr Maintenance Update

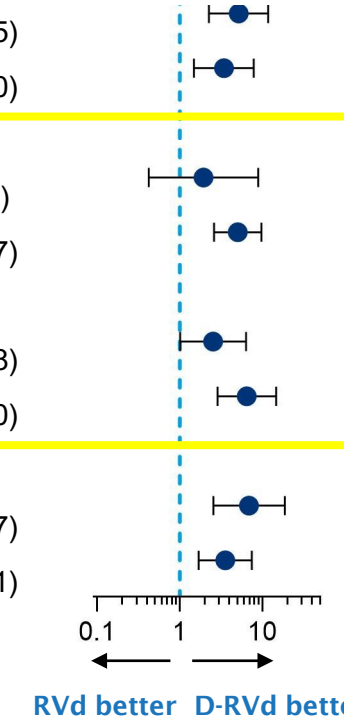
MRD Negativity After 24-Mo Maintenance, %	D-VRd (n = 104)	VRd (n = 103)	P Value
MRD at 10^{-5} threshold, % ▪ ITT population ▪ ≥CR	 64 78	 30 47	 <.0001 .0003
MRD at 10^{-6} threshold, % ▪ ITT population ▪ ≥CR	 36 43	 15 22	 .0007 .0121
Sustained MRD negativity lasting ≥12 mo, %	44.2	12.6	<.0001

Laubach. ASH 2021. Abstr 79.

GRIFFIN Update: Subgroup Analysis of MRD negativity

	RVd MRD negative, n/N (%)	D-RVd MRD negative, n/N (%)	Odds ratio (95% CI)
Sex			
Male	17/60 (28.3)	35/58 (60.3)	3.85 (1.78-8.31)
Female	14/43 (32.6)	32/46 (69.6)	4.73 (1.93-11.59)
Age			
<65 years	26/75 (34.7)	48/76 (63.2)	3.23 (1.66-6.29)
≥65 years	5/28 (17.9)	19/28 (67.9)	9.71 (2.78-33.92)
ISS disease stage			
I	13/50 (26.0)	34/49 (69.4)	6.45 (2.69-15.50)
II	13/37 (35.1)	23/40 (57.5)	2.50 (0.99-6.27)
III	5/14 (35.7)	10/14 (71.4)	4.50 (0.91-22.15)
Type of MM			
IgG	14/52 (26.9)	36/55 (65.5)	5.14 (2.25-11.76)
Non-IgG	17/51 (33.3)	29/46 (63.0)	3.41 (1.48-7.86)
Cytogenetic risk at study entry			
High risk	4/14 (28.6)	7/16 (43.8)	1.94 (0.42-8.92)
Standard risk	27/83 (32.5)	58/82 (70.7)	5.01 (2.59-9.71)
Revised cytogenetic risk			
High risk	12/37 (32.4)	23/42 (54.8)	2.52 (1.01-6.32)
Standard risk	19/60 (31.7)	42/56 (75.0)	6.47 (2.87-14.60)
ECOG PS score			
0	9/40 (22.5)	26/39 (66.7)	6.89 (2.54-18.67)
1-2	22/62 (35.5)	41/62 (66.1)	3.55 (1.69-7.44)





Laubach. ASH 2021. Abstr 79.

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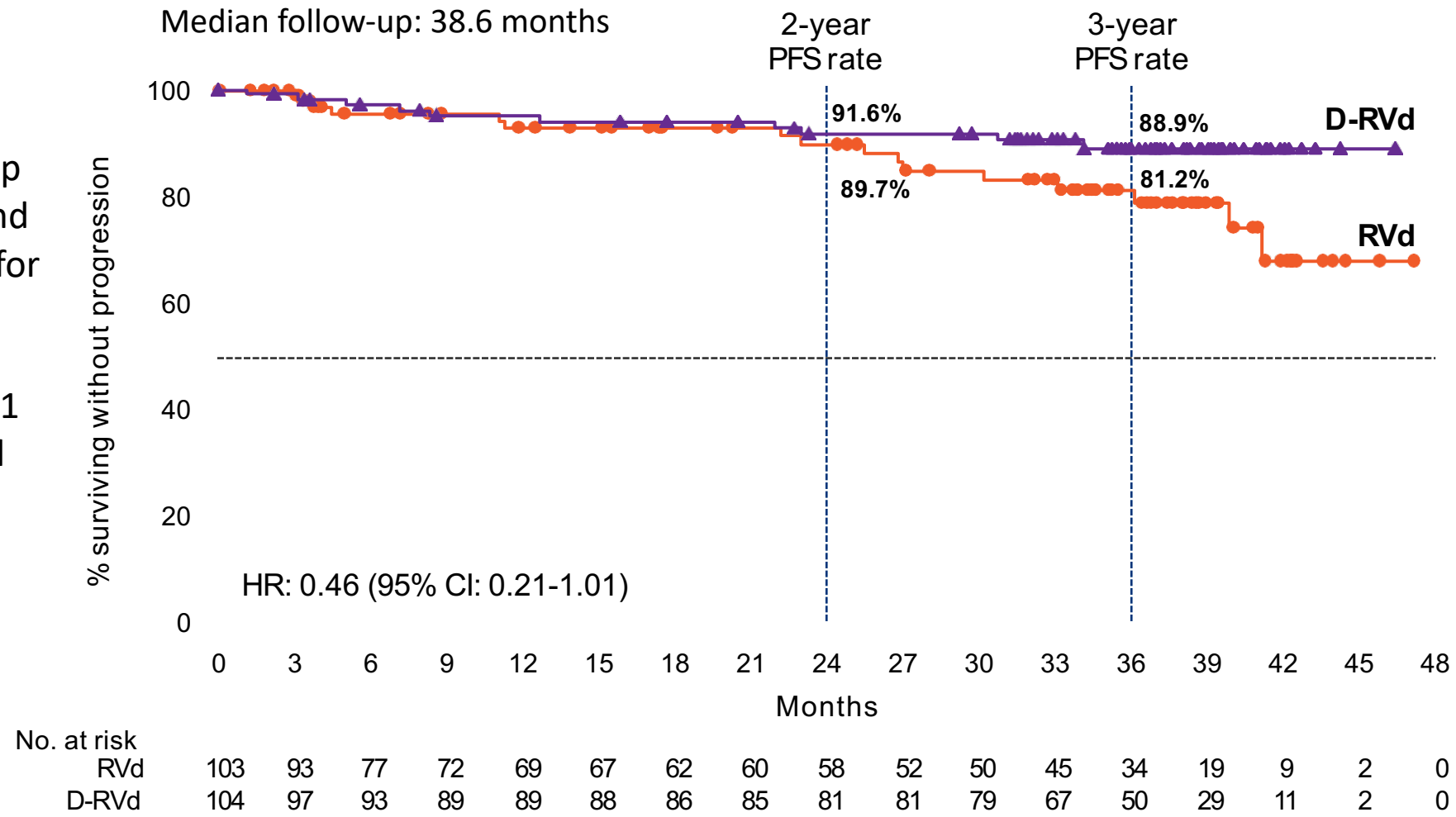
GRIFFIN 2-yr Maintenance Update: PFS in ITT Population

- Median PFS was not reached in either group
- There is a positive trend toward improved PFS for D-RVd/DR vs RVd/R
- Separation of the PFS curves begins beyond 1 yr of maintenance and suggests a benefit of prolonged DR therapy



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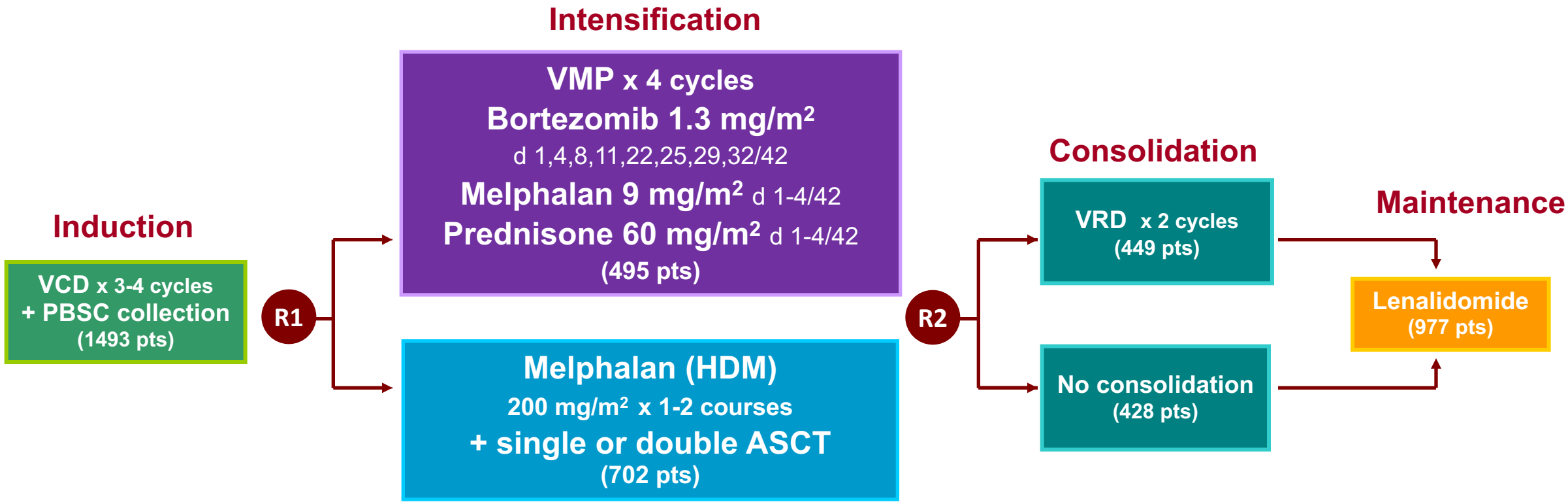
MJ

- She receives 4 cycles of RVD and has stem cells collected
- She has doubts about proceeding to high dose melphalan and autologous stem cell transplant

What is the role of high dose melphalan?

EMN02/HO95 MM study design



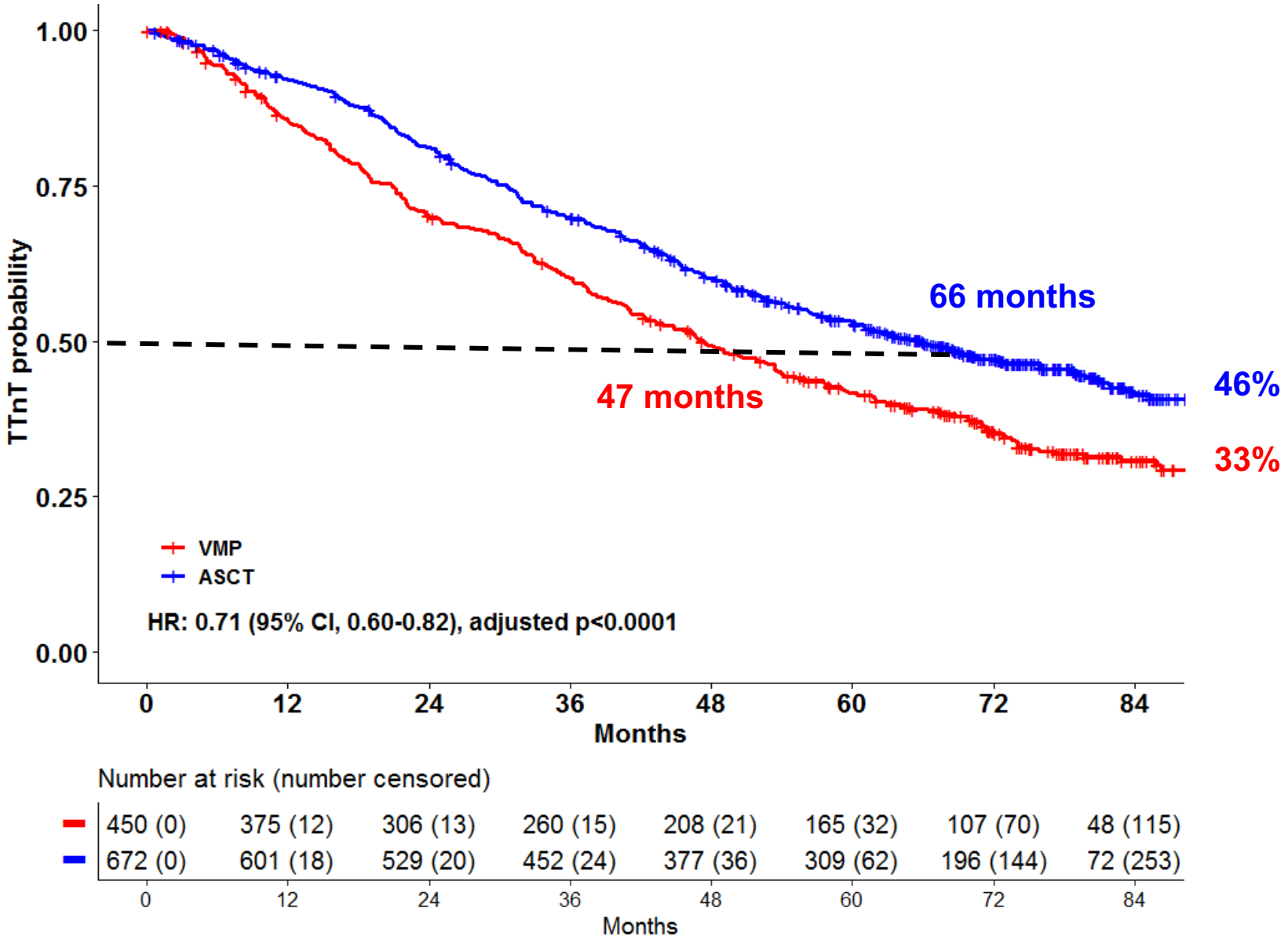
Primary endpoints:

- PFS from R1: ASCT *vs* VMP
- PFS from R2: VRD consolidation *vs* no consolidation

Secondary endpoints:

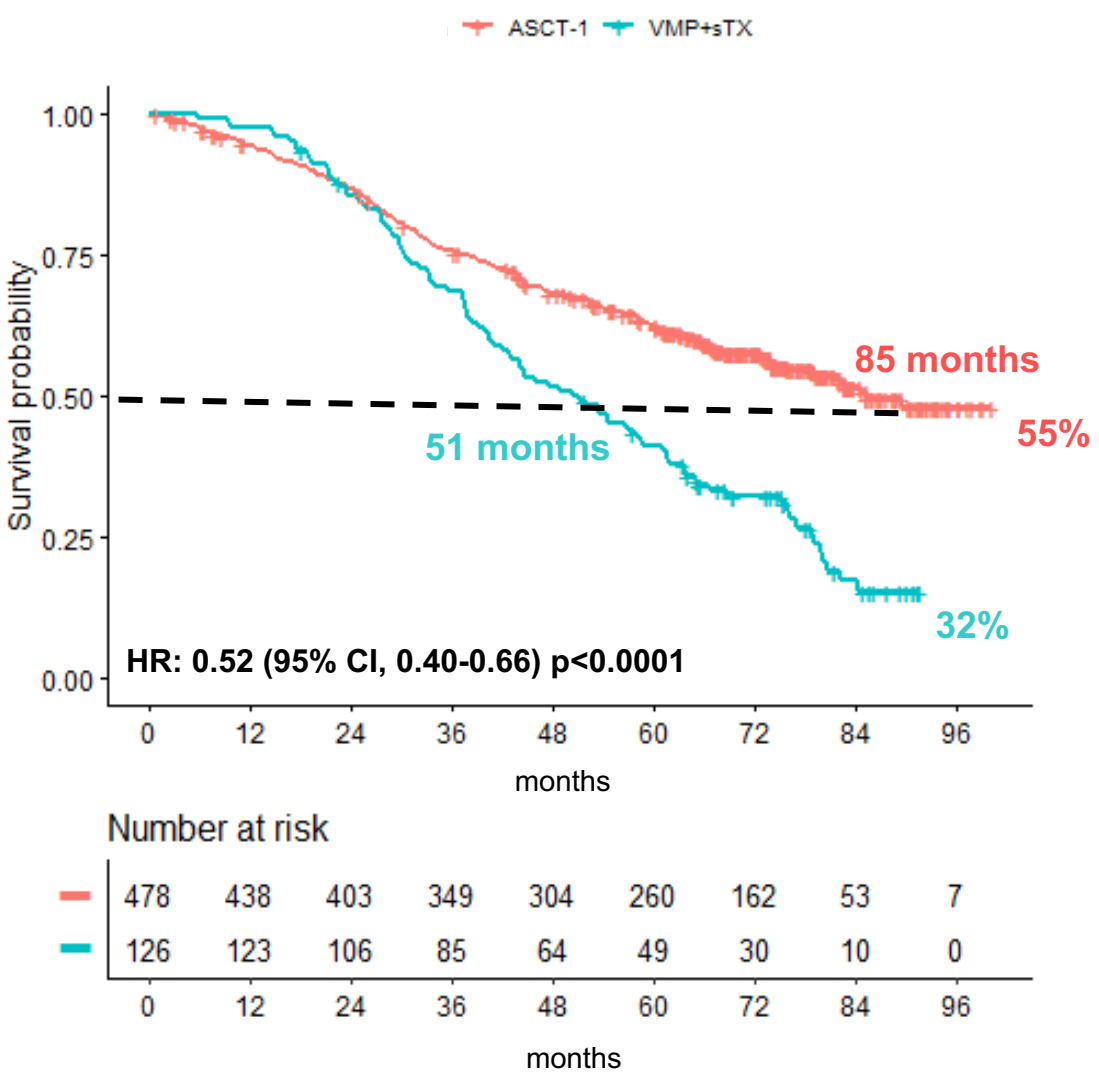
- PFS from R1: HDM-1 *vs* HDM-2
- Rates of response to ASCT or VMP
- OS from R1: ASCT *vs* VMP
- Toxicities with ASCT and VMP

Time to next treatment

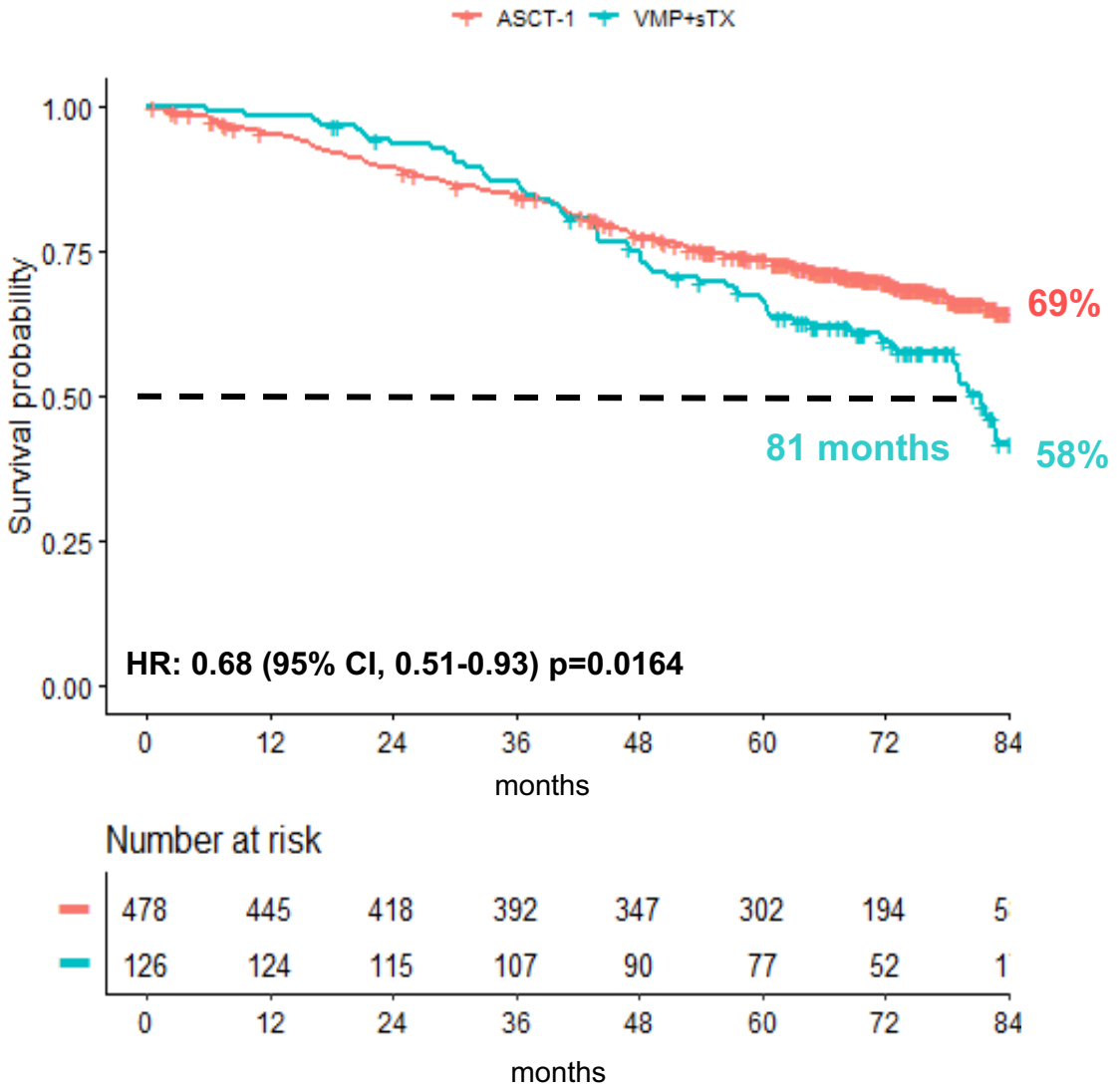


Clinical outcomes with upfront vs delayed ASCT

PFS2



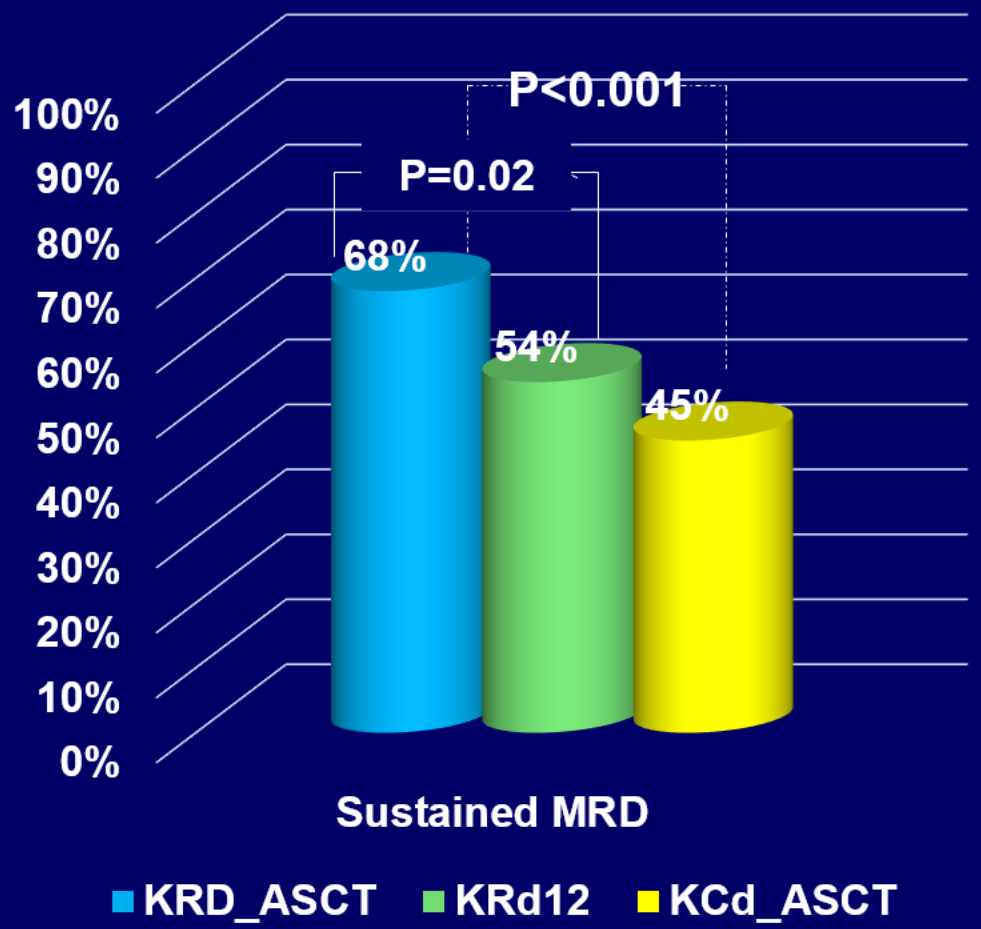
OS



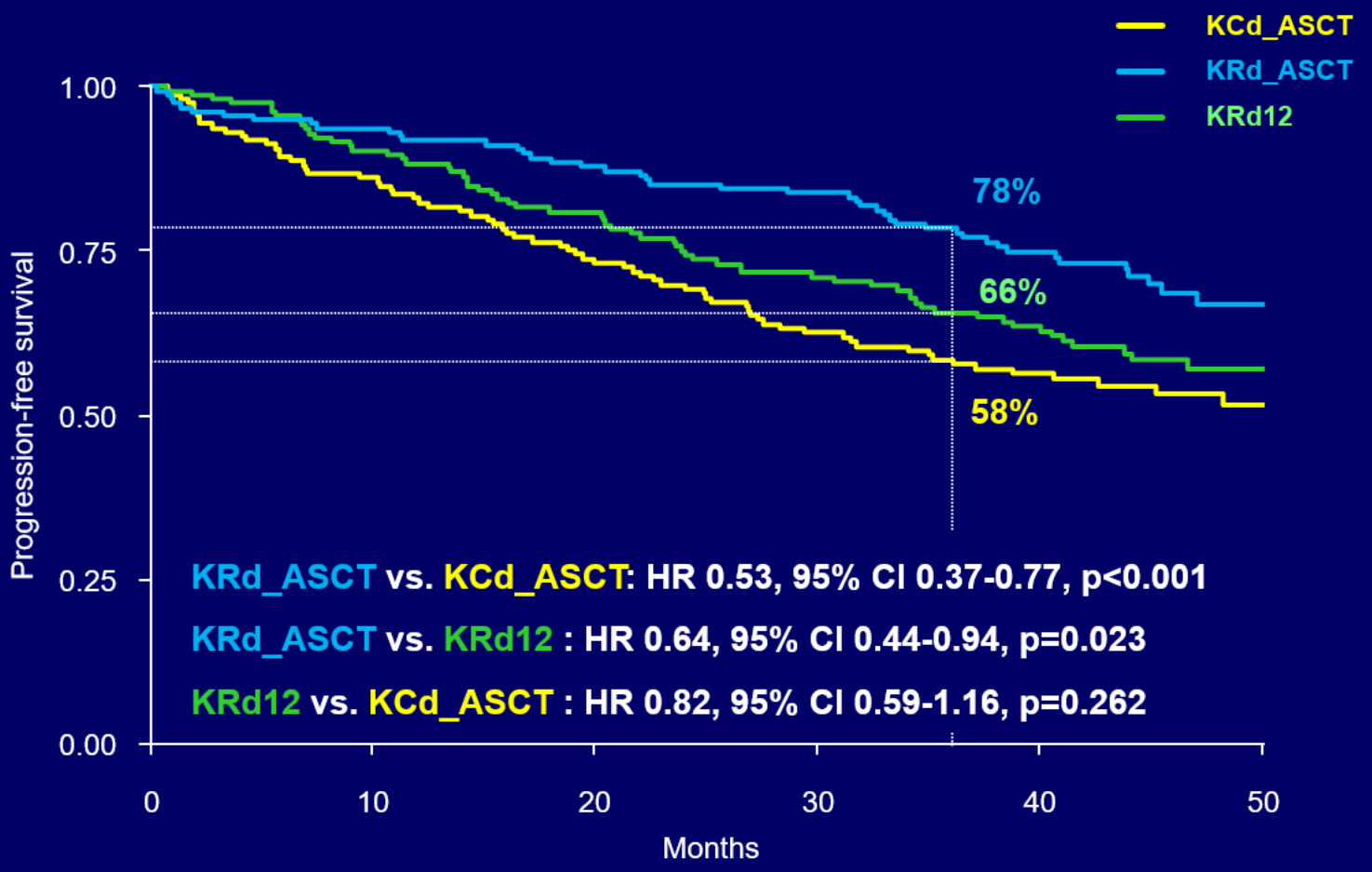
Progression-free survival: Random 1

Median follow-up from Random 1: 45 months (40-49 months)

Rate of sustained MRD MCF 10^{-5}



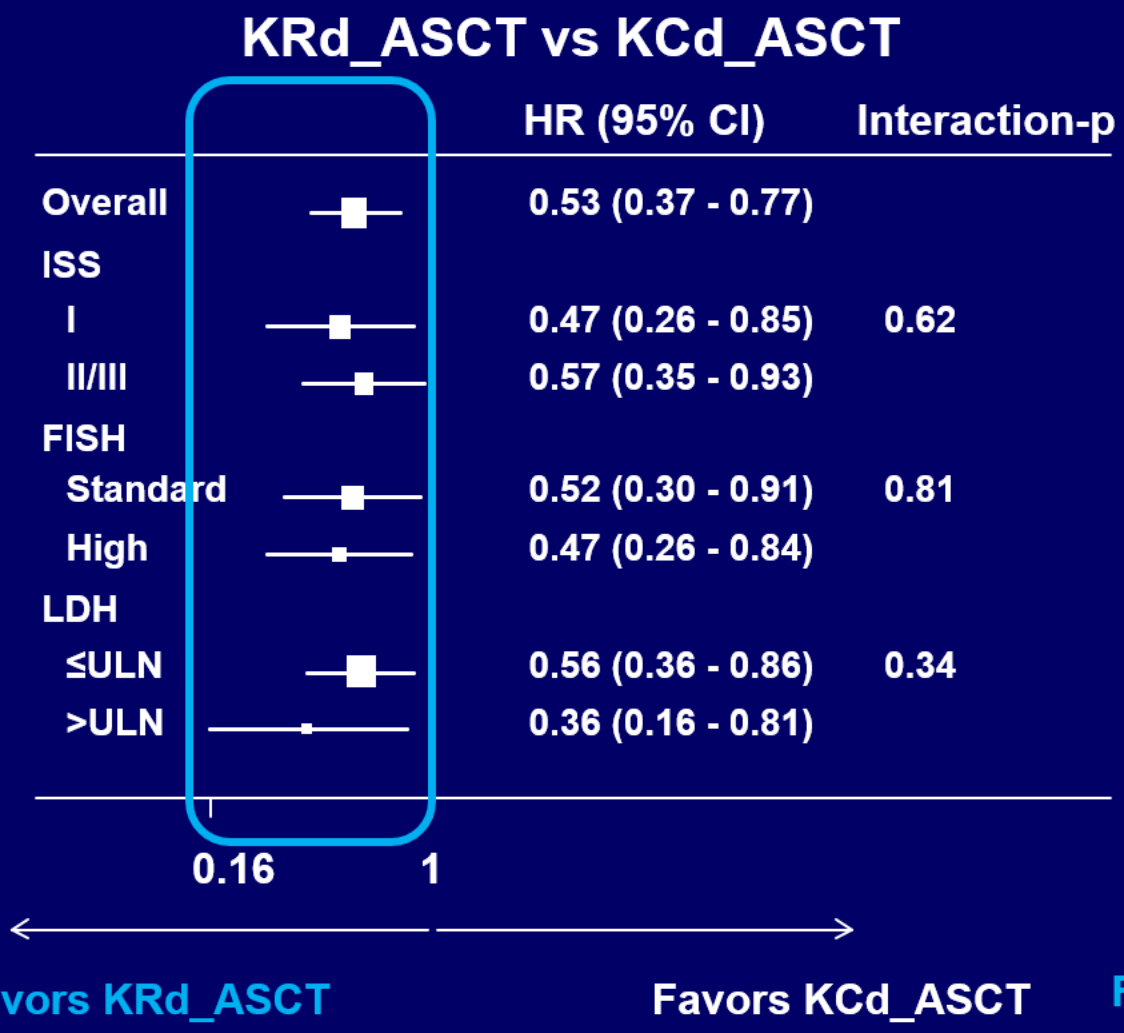
Progression-free survival

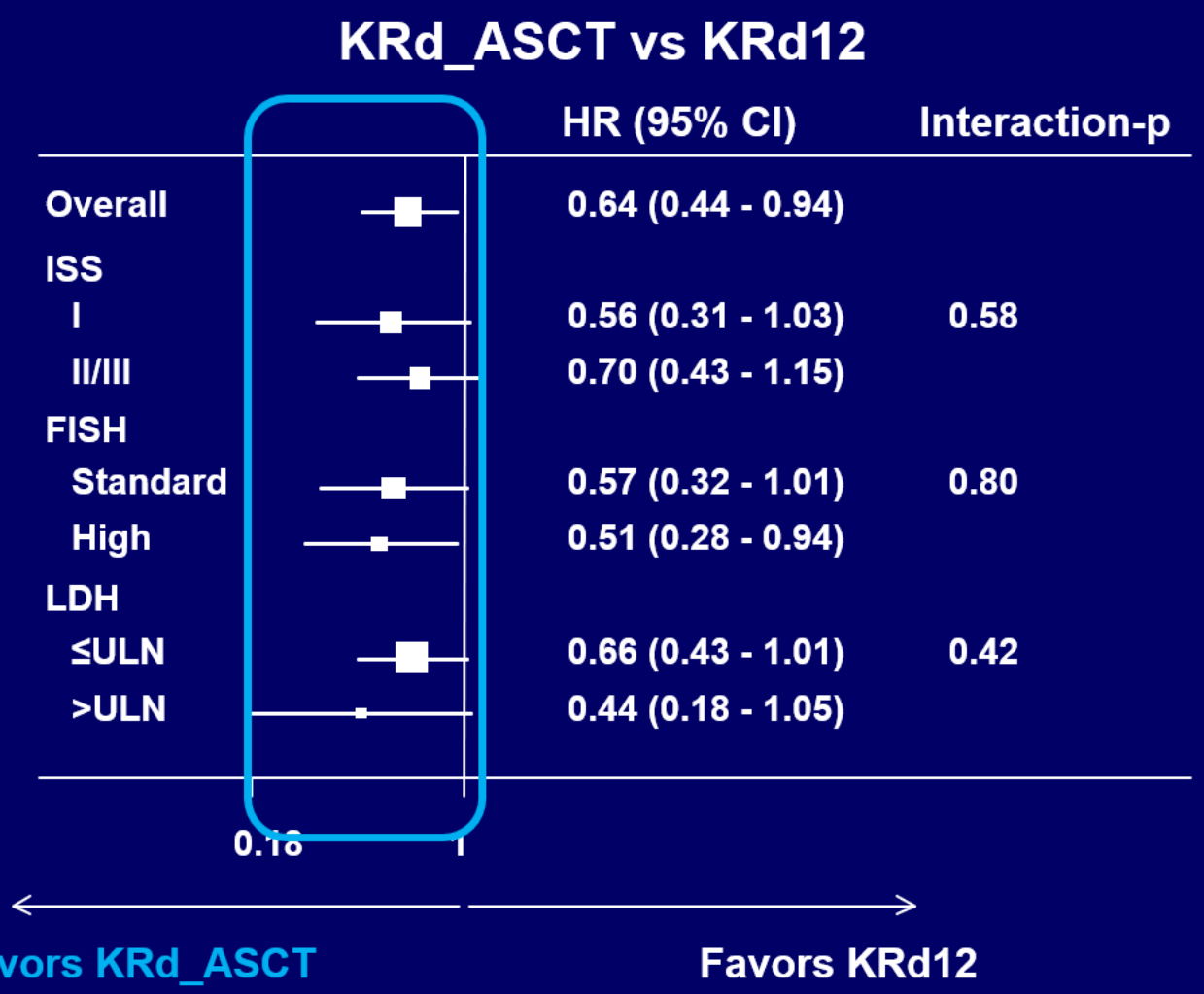


Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; p, p-value; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; MFC, multiparameter flow cytometry; 3-year PFS reported in the figure.

Progression-free survival: Random 1

Subgroup Analyses



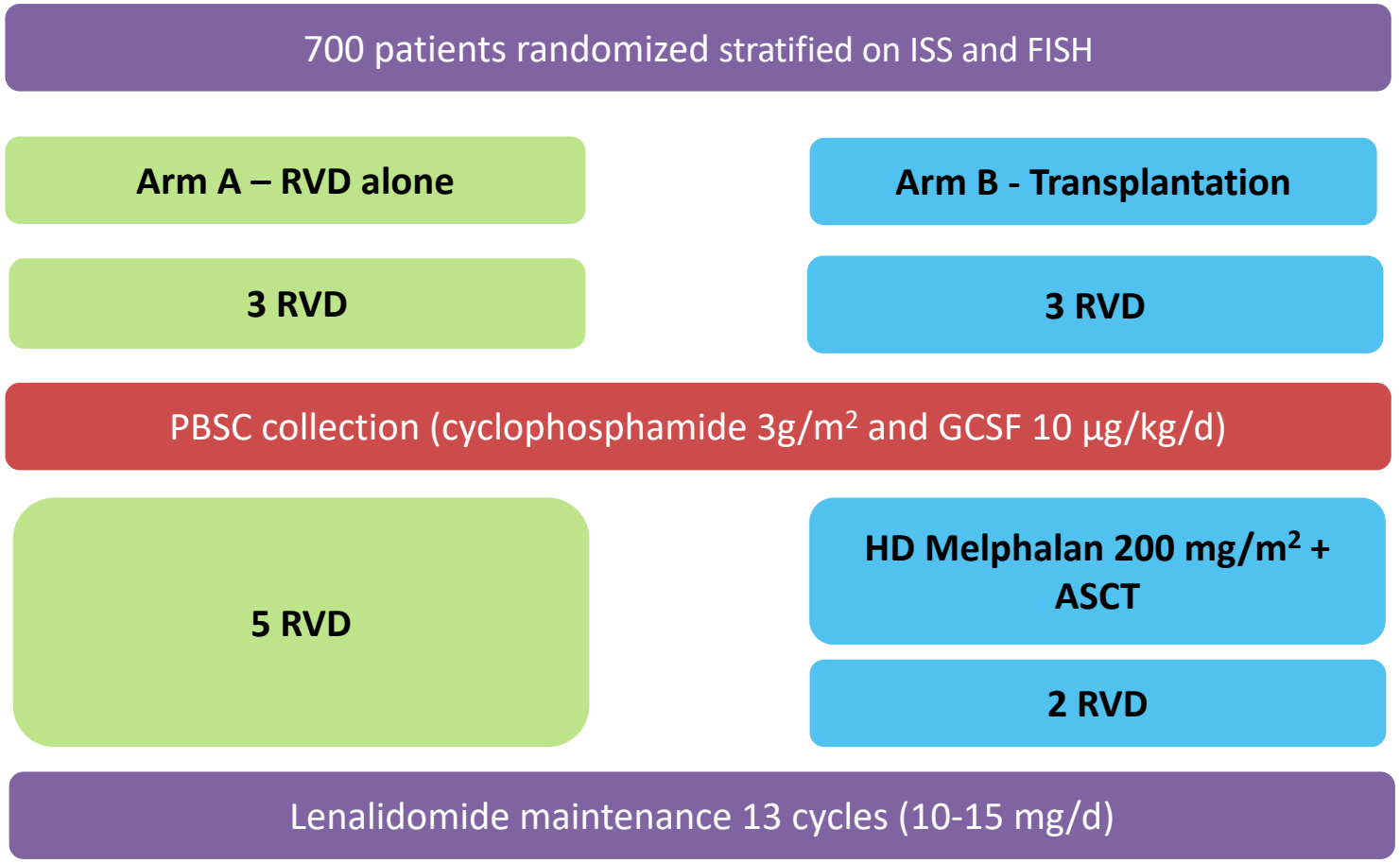


SIMILAR HR IN STANDARD AND HIGH RISK PATIENTS TREATED WITH KRD_ASCT

PFS, progression-free survival; Random 1, first randomization (induction/consolidation treatment); ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal.

What if the patient is MRD negative?

IFM 2009 Study design



Place video here

RVd 21d cycles
. Lenalidomide 25 mg/d: D1-D14
. Bortezomib 1.3 mg/m² D1, D4, D8, D11
. Dexamethasone 20 mg/d: D1, D2, D4, D5, D8, D9, D11, D12

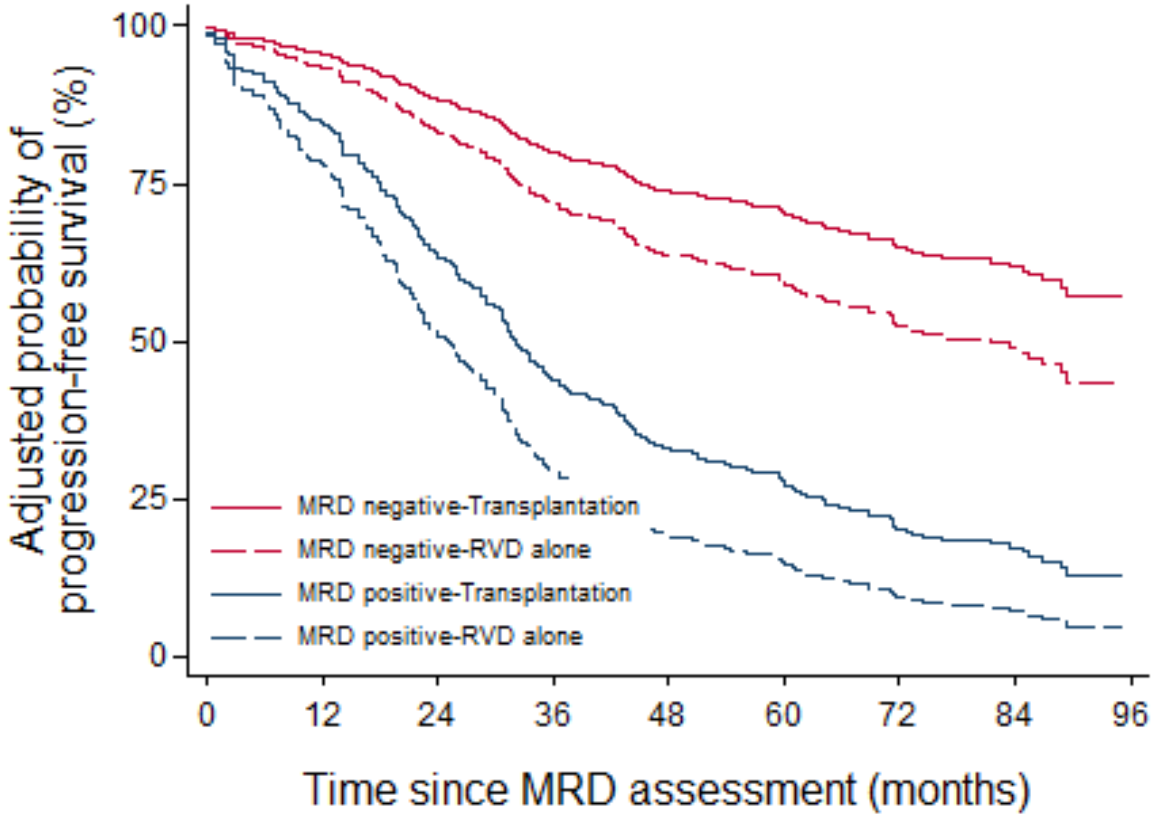
Primary endpoint = PFS

Secondary endpoints
. ORR, MRD
. TTP
. OS
. Toxicity

M Attal et al, N Engl J Med 2017

Subgroup analyses

Median follow up	89.8 months



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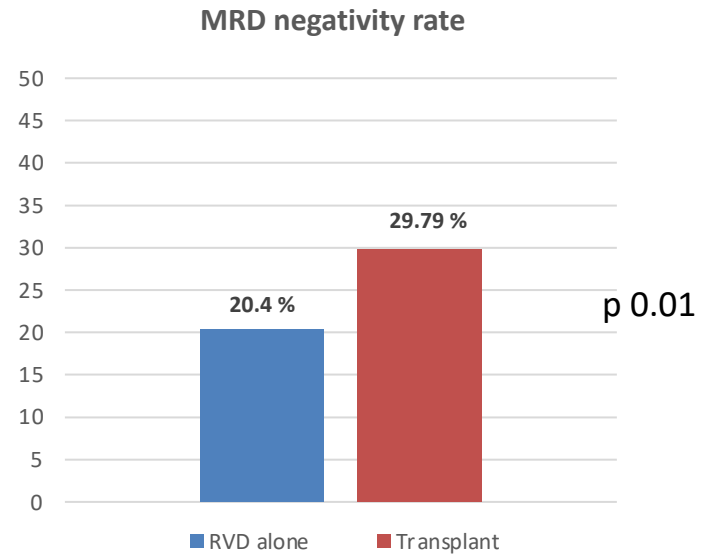


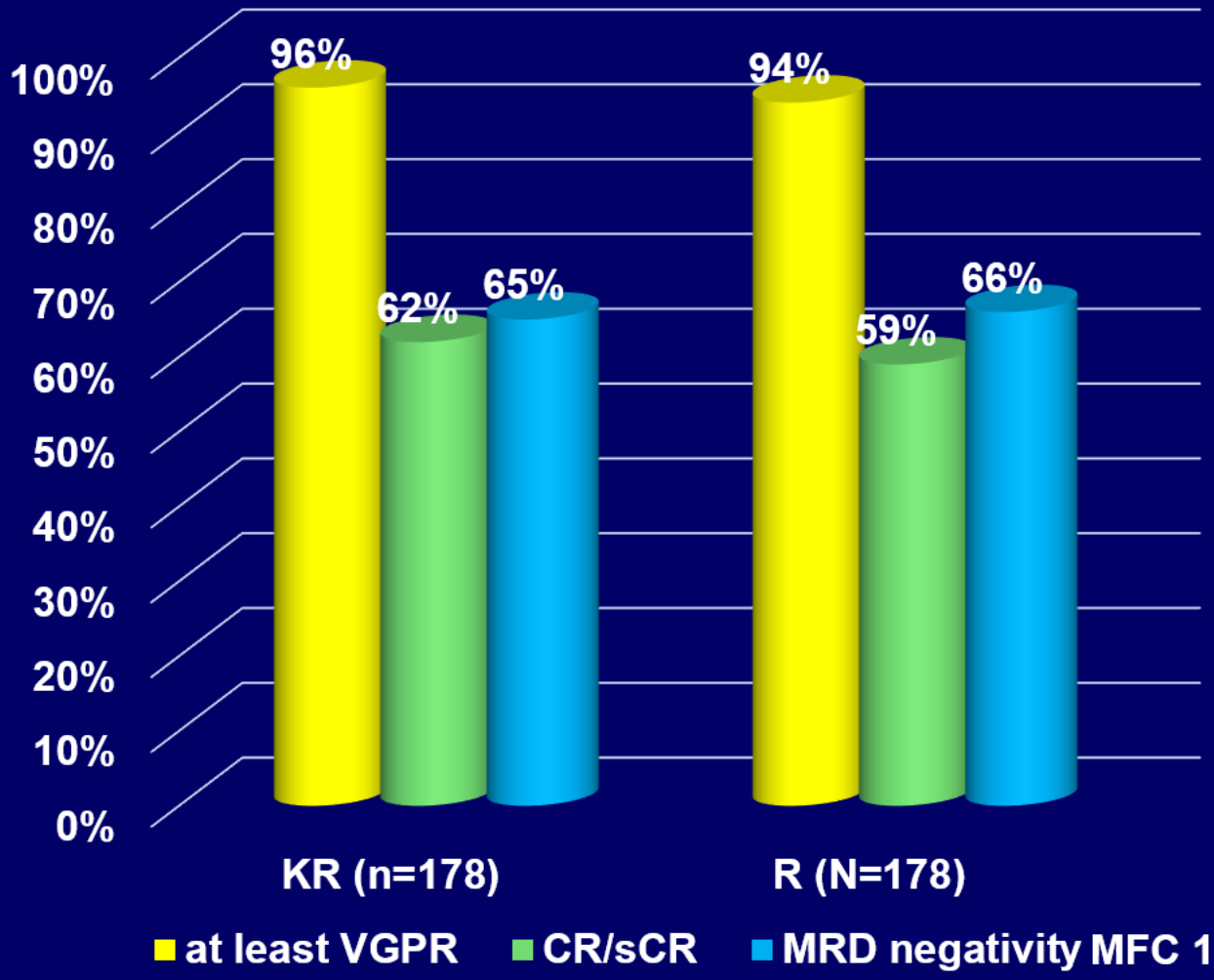
p 0.01

Transplant is superior to VRD alone, even in patients who achieved undetectable MRD at 10^{-6}

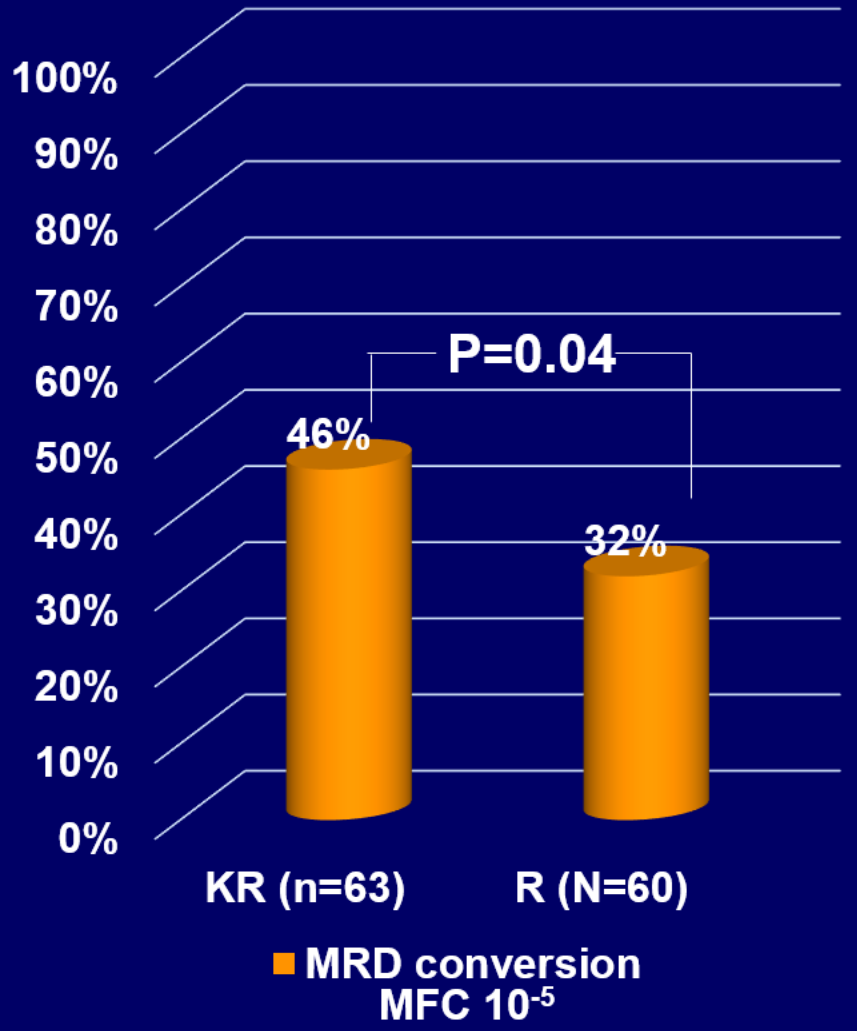
Should len maintenance be standard?

Response rate and MRD negativity: Random 2

Pre-maintenance response rate



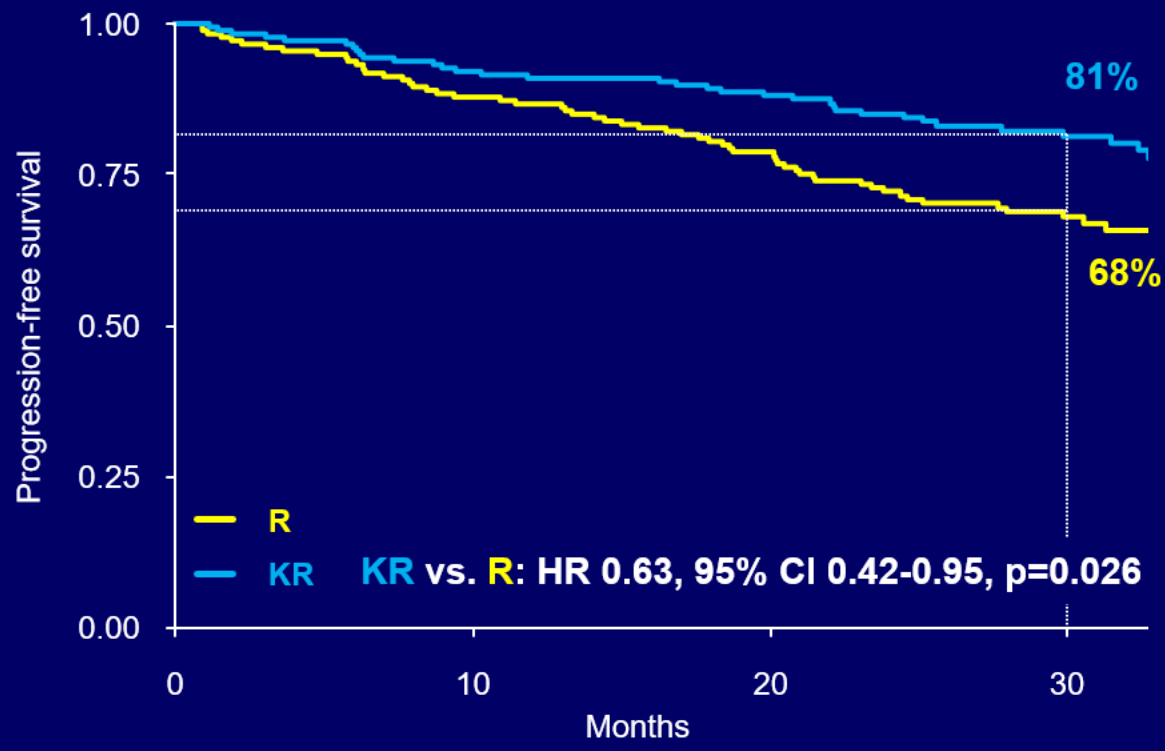
Rate of MRD conversion MRD positive → MRD negative

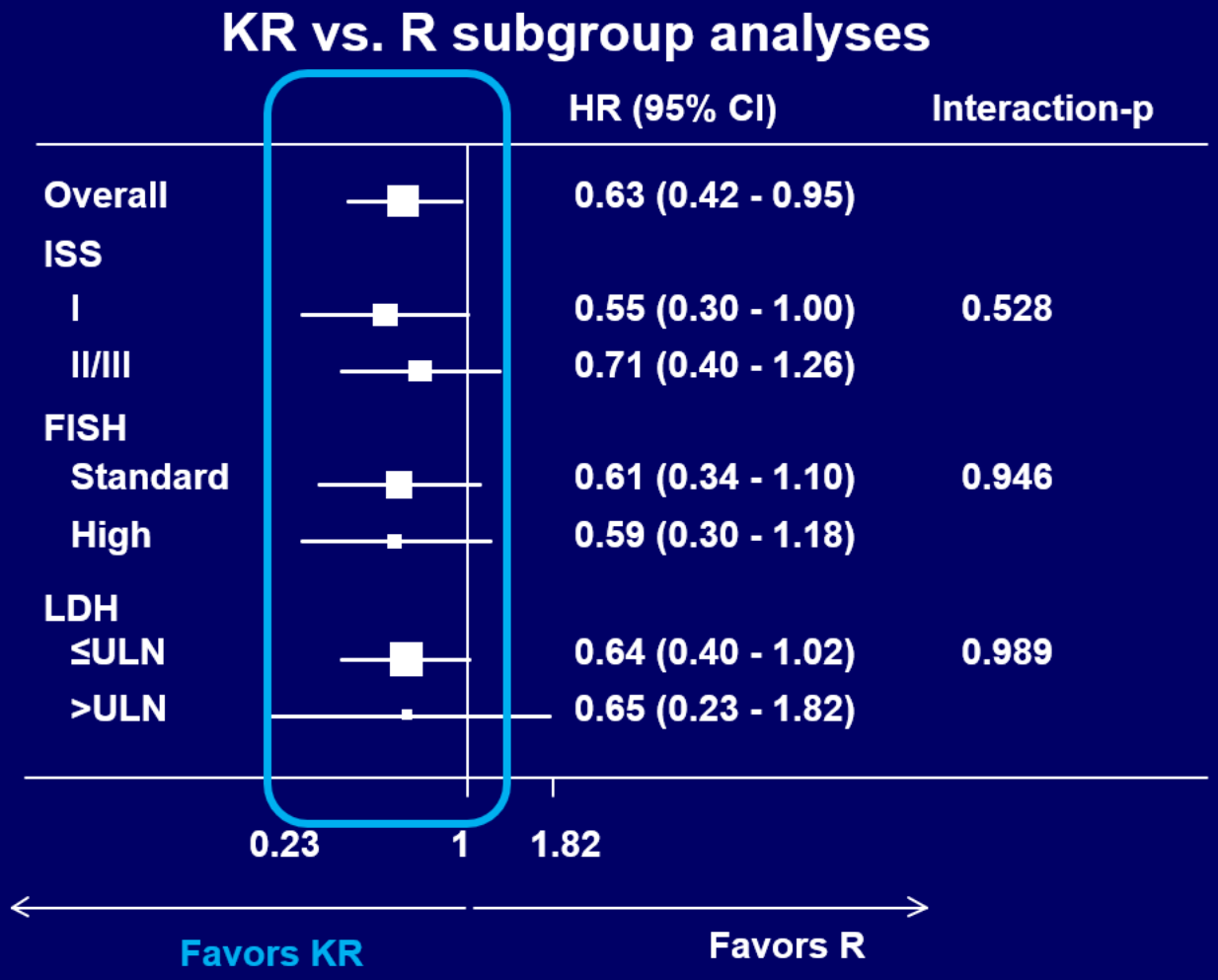


Random 2, second randomization (maintenance treatment); K, carfilzomib; R, lenalidomide; p, p-value; MRD, minimal residual disease; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; KR, carfilzomib-lenalidomide maintenance; R, lenalidomide maintenance; MFC, multiparameter flow cytometry.

Progression-Free Survival: Random 2

Median follow-up from random 2: 31 months (26-36 months)





SIMILAR HR IN STANDARD-RISK AND HIGH-RISK PATIENTS TREATED WITH KR vs. R

Random 2, second randomization (maintenance treatment); PFS, progression-free survival; K, carfilzomib; R, lenalidomide; HR, hazard ratio; CI, confidence interval; p, p-value; ISS, International Staging System stage; FISH, fluorescence *in situ* hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal; KR, carfilzomib-lenalidomide maintenance; R, lenalidomide maintenance. 30-month PFS reported in the figure.

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Role of Measurable Residual Disease

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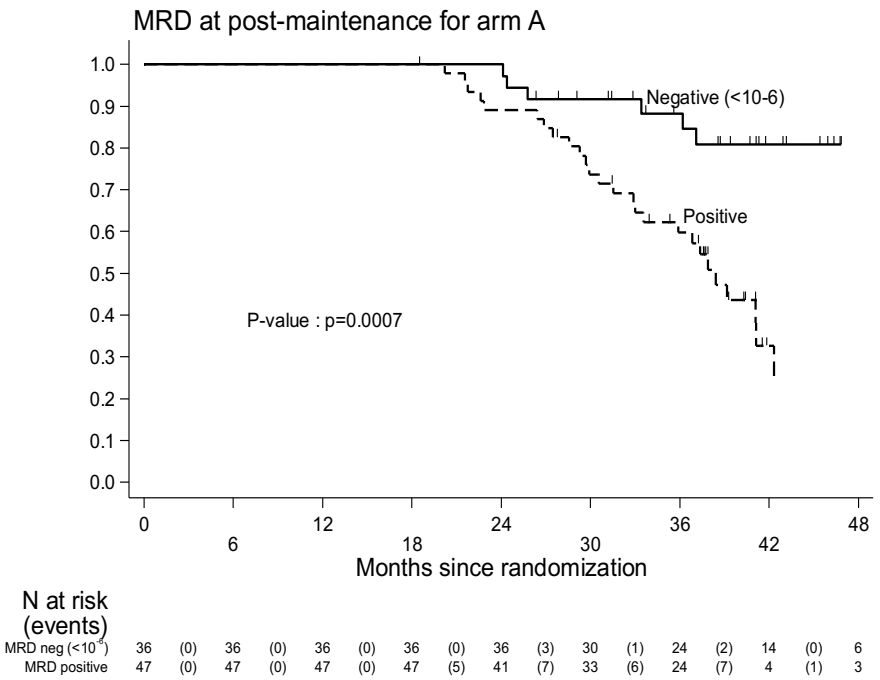
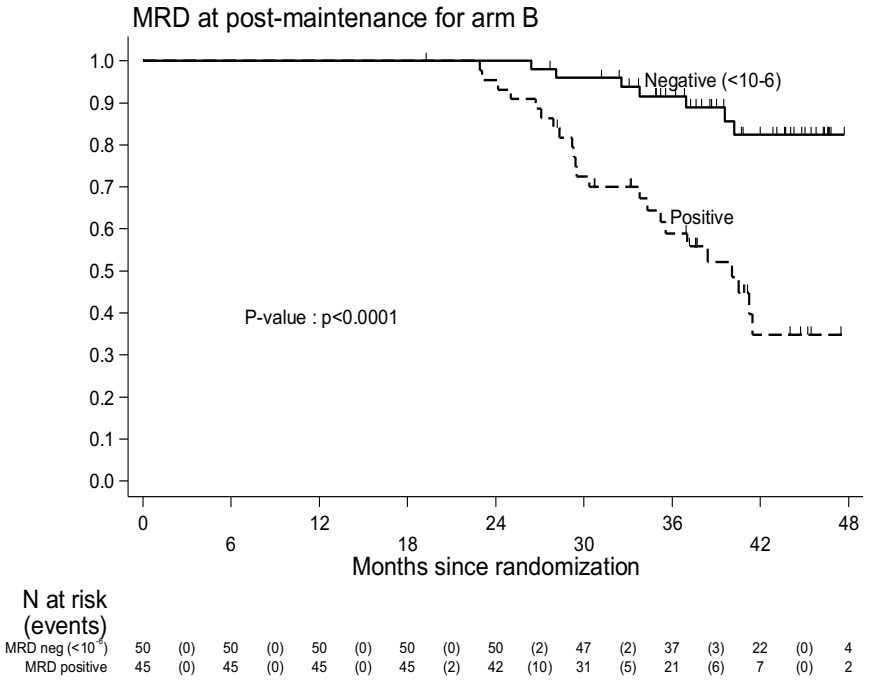
IFM/DFCI 2009 ~ PFS according to MRD Post Maintenance

RVD Arm



Transplant Arm

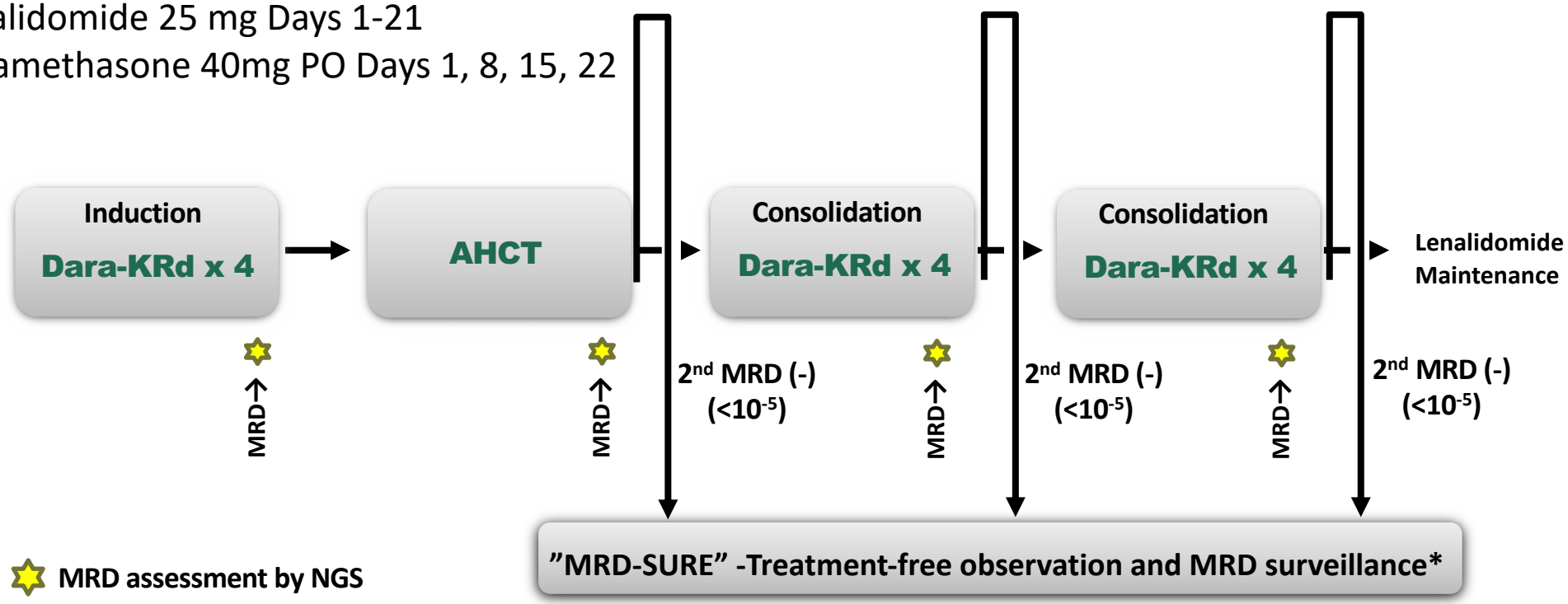


Avet-Loiseau H, et al *Blood.* 2015;126: Abstract 191.

MASTER trial

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

Costa. ASH 2021. Abstr 481.

MASTER trial: Conclusions

- **NGS-MRD response-adapted therapy is feasible in ~96% of patients in multi center setting – 72% reaching MRD-SURE.**
- **Patients with standard and high-risk NDMM have similar depth of response and low risk of MRD resurgence or progression when treated with Dara-KRd/AHCT and MRD-adapted treatment cessation.**
- **Quadruplet therapy and achievement of confirmed MRD (-) responses enables the exploration of treatment cessation and "MRD-SURE" as alternative to continuous therapy.**

Effective novel consolidative strategies should be explored to clear MRD and improve outcomes in patients with ultra-high-risk MM

Costa. ASH 2021. Abstr 481.

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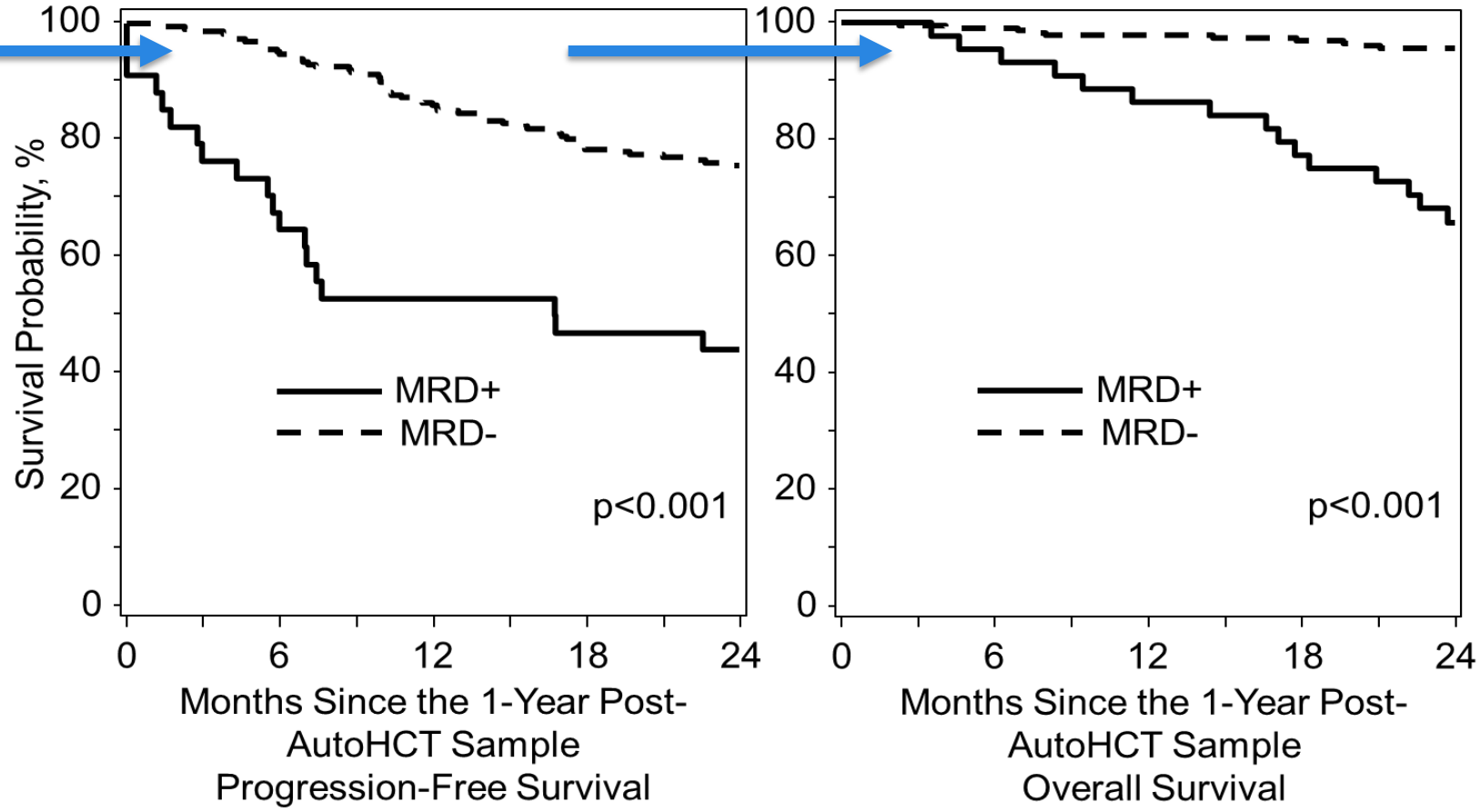
PRIMeR Results:
PFS (Left) and OS (Right) by MRD Status at 1-Year

PFS

Can pre-emptive intervention make a difference?



OS

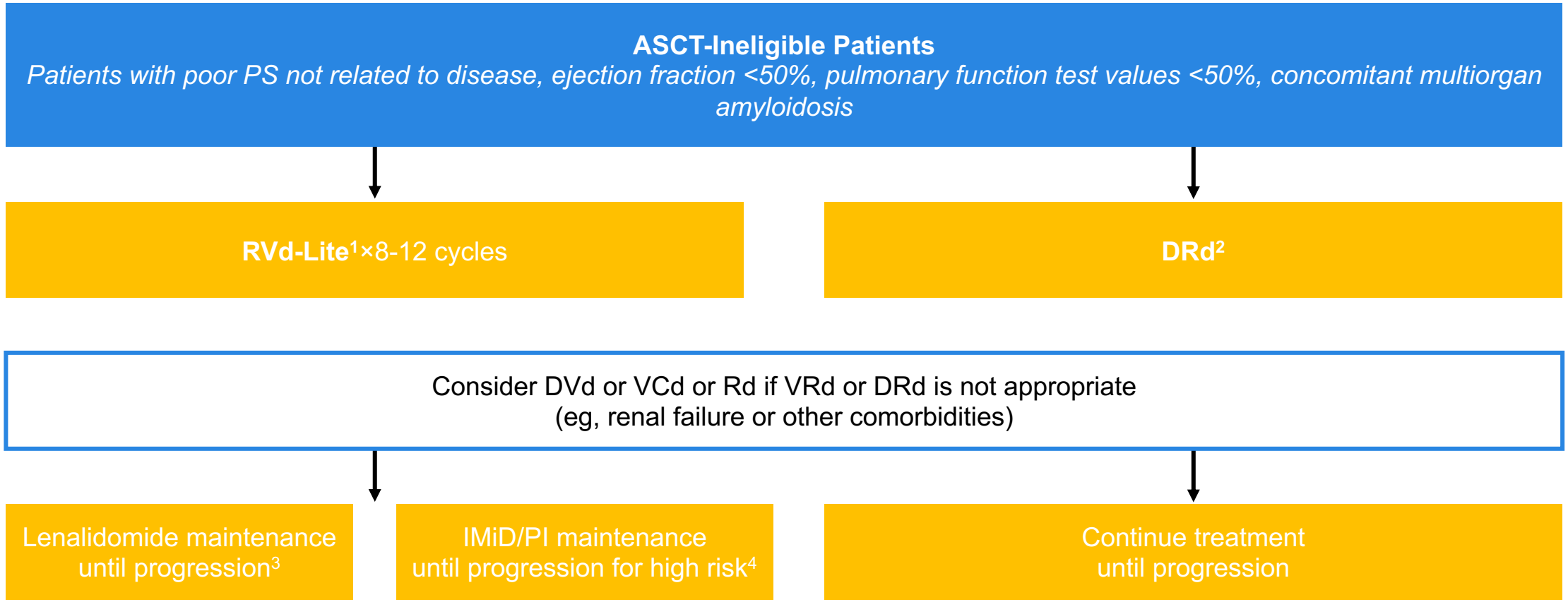
ROSWELL PARK COMPREHENSIVE CANCER CENTER

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

MEDICAL COLLEGE OF WISCONSIN

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

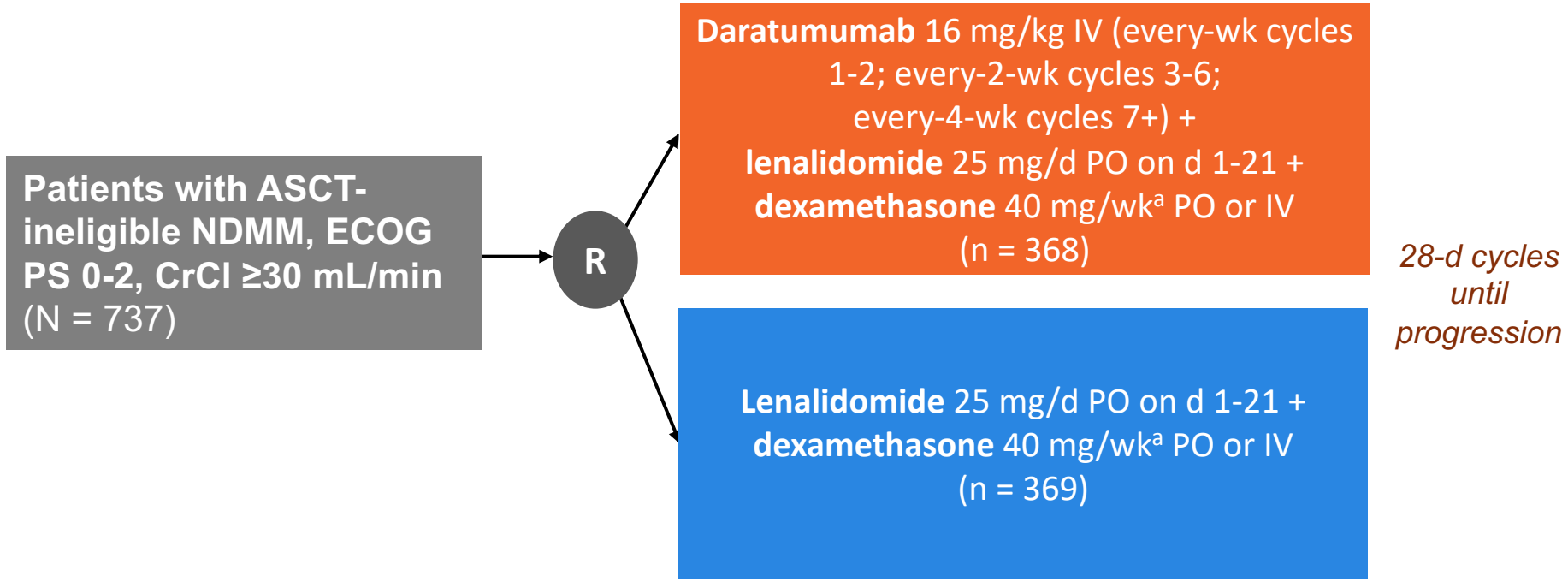
Approach to Transplant Ineligible NDMM



- DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; VRd-Lite, modified VRd regimen.
- Adjust dosing of lenalidomide based on renal function. Consider empiric age-adjusted dose reductions for all regimens, as needed.[4]
- 1. O'Donnell. Br J Haematol. 2018;182:222. 2. Facon. ASH 2018. Abstr LBA-2. 3. Larocca. ASH 2018. Abstr 305. 4.Usmani. *Lancet Haematol*. 2021 Jan;8(1):e45-e54.

Phase 3 MAIA Study: Daratumumab Plus Rd in NDMM

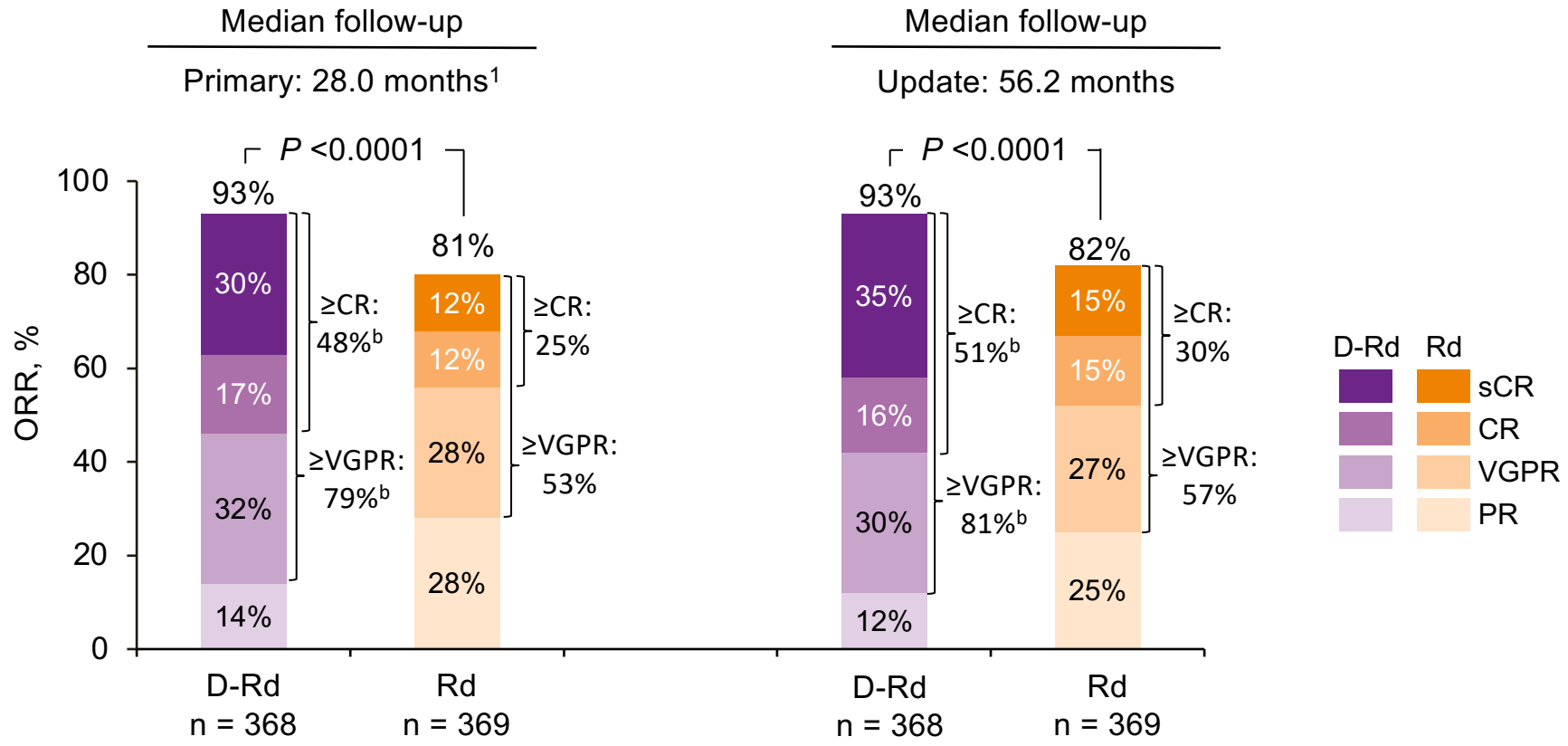
- Stratified by ISS (I vs II vs III), region (North America vs other), and age (<75 vs ≥75 y)
- **Primary endpoint:** PFS
- **Secondary endpoints:** ≥ CR rate, ≥ VGPR rate, MRD negativity, ORR, OS, and safety



[a] Reduced to 20 mg/wk if aged >75 y or BMI <18.5.

Facon T et al. *N Engl J Med*. 2019;380:2104-2115.

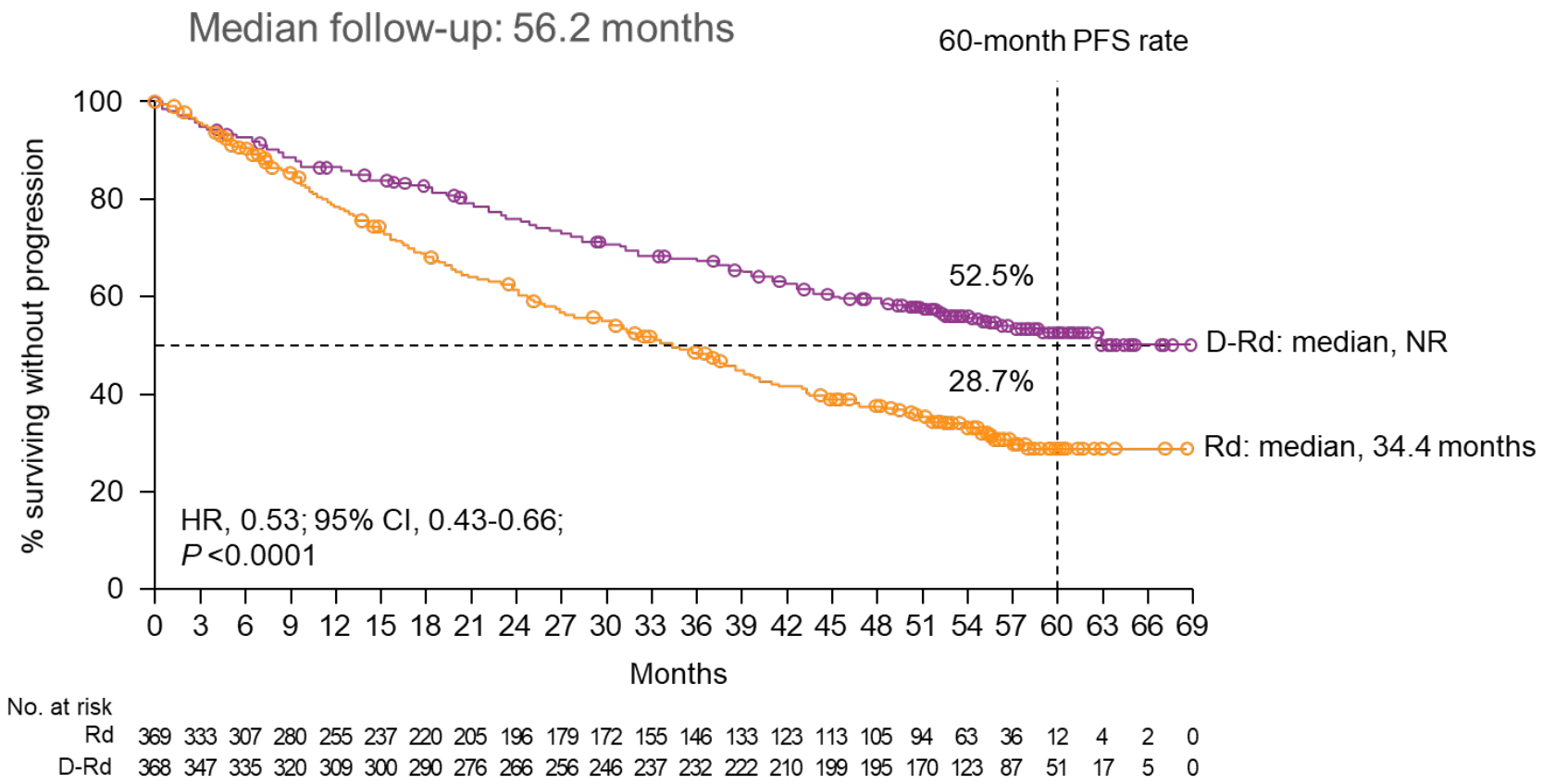
MAIA Phase III ORR[a]



- D-Rd induced deeper responses, with significantly higher rates of ≥CR and ≥VGPR, compared with Rd
- With >28 months of additional follow-up, responses deepened with continued daratumumab therapy

VGPR, very good partial response; PR, partial response; OR, odds ratio.
[a]ITT population. [b]*P* <0.0001; *P* values were calculated from the Cochran-Mantel-Haenszel Chi-Squared test.
1. Facon T, et al. *N Engl J Med*. 2019;380(22):2104-2115.
Note: percentages may not add up to the total due to rounding.

MAIA Phase III Updated PFS



- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
- These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible

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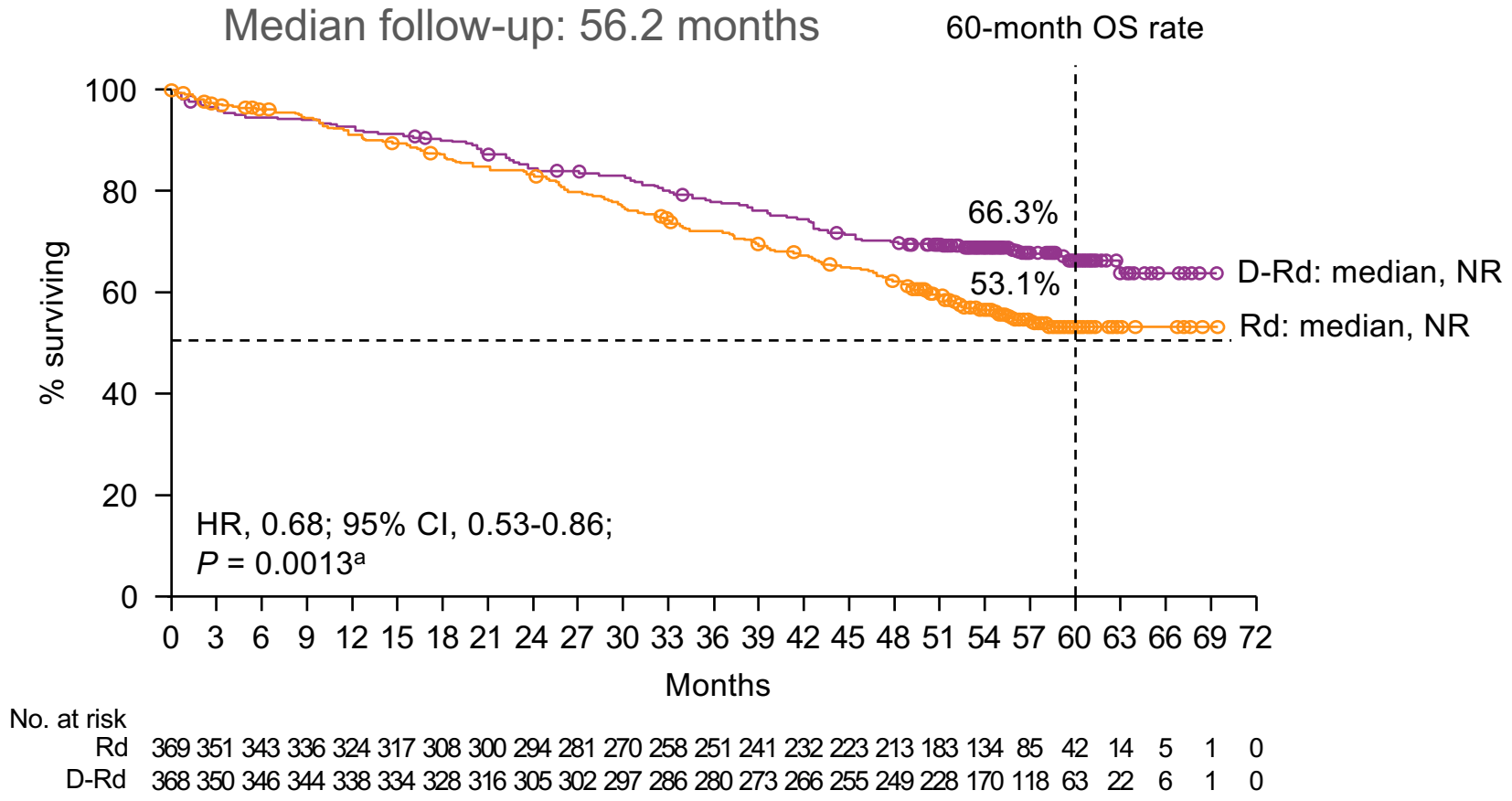
NR, not reached; CI, confidence interval.

MAIA Phase III OS

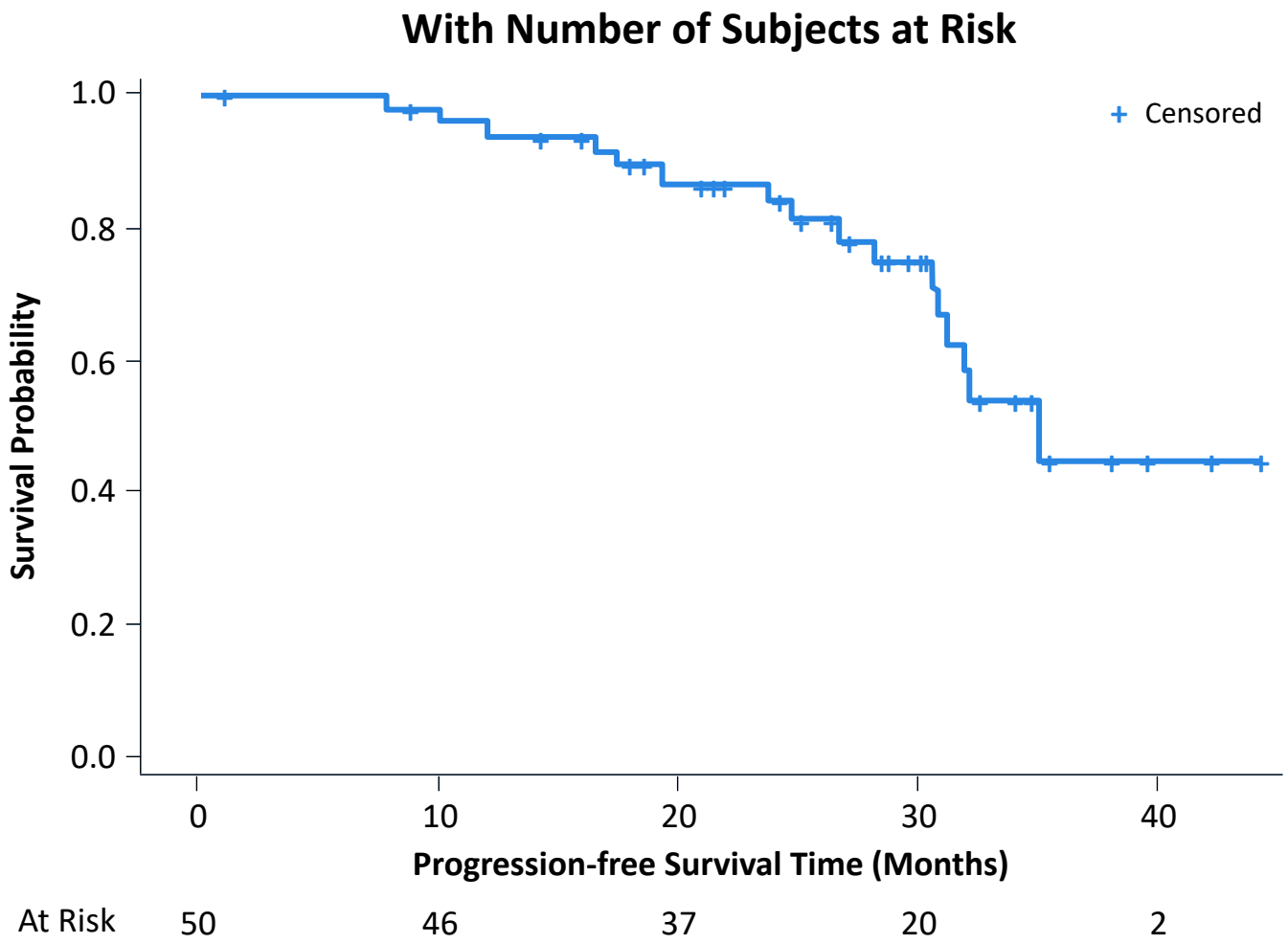


D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

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

RVd-Lite

- Regimen (N=53)
  - Lenalidomide: 15 mg po days 1 to 21
  - Bortezomib: 1.3 mg/m2 SC 1 × weekly on days 1, 8, 15, 22
  - Dexamethasone
    - If ≤75 years, 20 mg 2 × weekly
    - If >75 years, 20 mg 1 × weekly
- Results
  - 86% ORR
  - 66% ≥VGPR
  - Median PFS: 35.1 months
  - Median OS: NR
  - Median follow-up: 30 months
  - Median age: 73 years (range: 65-91)
  - PN: 62%
  - Only 1 patient had grade 3 symptoms



- PN, peripheral neuropathy.

O'Donnell et al. *Br J Haematol*. 2018;182:222-230.

Clinical Take-Homes: Induction and Maintenance

ASCT-Eligible Patients

Induction/Consolidation

- **Currently:** RVd +/- Dara, KRd
- **Other options:** CyBorD, VTd +/- Dara
- **Short-term future:** Add daratumumab to all vs risk or response adapted?
- **Long-term future:** Molecularly adapted regimens for fewer cycles?

Maintenance

- **Currently:** R for standard risk; VR ± d for high risk
- **Short-term future:** Add daratumumab in MRD-driven manner—SWOG S1803
- **Long-term future:** Post-ASCT BiTE to replace maintenance ± substitution of CAR T cells for ASCT, especially in high-risk disease?

Clinical Take-Homes: Induction Therapy

Transplant-Ineligible Patients

- VRD-lite and DRd are standards of care
- Daratumumab-based combinations are FDA approved and incorporated into treatment guidelines on the basis of phase III evidence
- **Future:** RVd-Dara (CEPHEUS Phase III), Rd-Belamaf, RVd-Belamaf
- **Long-term future:** Molecularly adapted regimens for fewer cycles?

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Case: MJ

What happens if she relapses?

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Basic Principles When Approaching the Relapsed Patient

Assessment

- Patients age and performance status
- Type of relapse (chemical vs clinical)
- Myeloma biology (high or standard risk)
- Prior history (transplant naïve or not) – Stem cells available
- Initial remission duration >12 months or <12 months

Treatment Goals

- Minimize toxicity or Maximize efficacy?
- Eligibility for clinical trials?
- Life expectancy

Guidelines

- Depth of response is important (MRD negative CRs do better)
- Response to prior agents generally good if more than 12 months from prior exposure
- Better to change class of drugs if possible (particularly true for patients on Len maintenance
- Combinations work better 3 drugs better than 2 drugs and likely 4 drugs better than 3
- Role of 2nd auto or allo consolidation being explored

Presentation number: 8502

DREAMM-6: Safety and Tolerability of Belantamab Mafodotin in Combination with Bortezomib/Dexamethasone in Relapsed/ Refractory Multiple Myeloma (RRMM)

Ajay Nooka MD[1], Keith Stockerl-Goldstein MD[2], Hang Quach, MD[3] Adam Forbes[4], Maria Victoria Mateos MD[5], Amit Khot MD[6], Alan Tan MD[7], Rafat Abonour MD[8], Bikramjit Chopra PhD[9], Rachel Rogers MS[10], Geraldine Ferron-Brady PhD[10], Jacqueline Davidge PhD[9], Steve Frey MS[10], Anne Yeakey MD[10], Mala Talekar MD[10], Katarina Luptakova MD[10], Ira Gupta MD[10], Rakesh Popat MD[11]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Washington University Medical School, St. Louis, MO, USA; [3]University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [4]Royal Cornwall Hospital, Truro, UK; [5]University Hospital of Salamanca-Instituto de Investigación Biomédica de Salamanca, Cancer Research Center-IBMCC (USAL-CSIC), Salamanca, Spain; [6]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, VIC, Australia; [7]Cancer Treatment Centers of America, University of Arizona College of Medicine, Phoenix, AZ, USA; [8]Queen Elizabeth Hospital, Adelaide, South Australia, Australia; [9]GlaxoSmithKline, Uxbridge, Middlesex, UK; [10]GlaxoSmithKline, Upper Providence, PA, USA; [11]University College London Hospitals, NHS Foundation Trust, London, UK.

http://tago.ca/ASCO_18

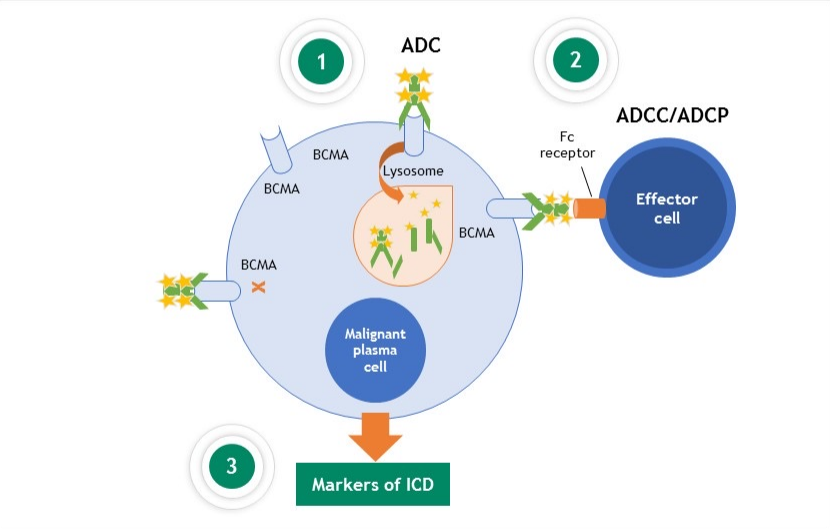
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Ajay Nooka

Presented By Ajay Nooka at TBD

Belamaf Is An Ideal Candidate For Use In Combination With Other Treatments

Belantamab Mafodotin (belamaf; GSK2857916) is a first-in-class anti-BCMA antibody-drug conjugate with a **multimodal MoA**[1,2]



In the Phase II DREAMM-2 study, **single-agent belamaf demonstrated deep and durable responses** in patients with heavily pre-treated RRMM[3,4*]

Outcome at 13-month follow-up	Belamaf 2.5 mg/kg (n=97)	Belamaf 3.4 mg/kg (n=99)
ORR†, n (%) (97.5% CI)	31 (32) (21.7-43.6)	35 (35) (24.8-47.0)
Median DoR, months (95% CI)	11.0 (4.2-NR)	6.2 (4.8-NR)
Median PFS, months (95% CI)	2.8 (1.6-3.6)	3.9 (2.0-5.8)
Median OS, months (95% CI)	14.9 (9.9-NR)	14.0 (10.0-NR)

In DREAMM-2, belamaf showed an **acceptable safety profile**[3,4]

*Refractory to an immunomodulatory agent, a proteasome inhibitor, and refractory and/or intolerant to an anti-CD38 monoclonal antibody †Defined as partial response or better.
ADC, antibody-drug conjugate; ADCC/P, antibody-dependent cellular cytotoxicity/phagocytosis; BCMA, B-cell maturation antigen; Belamaf, belantamab mafodotin; CI, confidence interval; DoR, duration of response; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; ICD, immunogenic cell death; MoA, mode of action; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RRMM, relapsed or refractory multiple myeloma
1. Tai YT et al. Blood. 2014;123:3128-38; 2. Tai YT & Anderson KC. Immunotherapy 2015; 7:1187-99; 3. Lonial S et al. Lancet Oncol 2020;21:207-21; 4. Lonial S et al. ASCO 2020 poster 436.

Presented By Ajay Nooka at TBD

Bispecific Antibodies Summary (BCMA)

	Teclistamab[1]	Elranatamab[2]	ABBV-383[3]	REGN5458[4]
Schedule	Weekly SC	Weekly SC or Q2W SC	IV q3W	Weekly IV
Patients, N	165	55	118	73
Median prior lines	5	6	5	5
Triple Class and Penta Refractory	78% and 30%	91% and NA	61% and NA	89% and 38%
Prior BCMA	No	22%	No	No
CRS, All (Gr 3/4)	72% (0.6%)	87% (0%)	54% (3%)	38% (0%)
ICANS, All (Gr 3/4)	3% (0%)	NA	2% (NA)	4% (0%)
ORR at higher doses	62%	69% 70% in prior BCMA	60%	75%
CR at higher doses	29%	Not reported	20%	16%

1. Moreau et al. Abstract #896; 2.Sebag et al. Abstract#895; 3. Kumar et al. Abstract #900; 4. Zonder et al. Abstract #160 (ASH 2021)

Bispecific Antibodies Summary (non-BCMA)

	Talquetamab[1]	Cevostamab[2]
Target	GPRC5D	FcRH5
Schedule	Weekly & Q2W SC	Q3 week IV
Patients	55	161
Median prior lines	5-6	6
Prior BCMA	**22%**	**34%**
Triple Class and Penta Refractory	76% and 21%	85% and 68%
CRS, All (Gr 3/4)	75% (2%)	81% (1%)
ICANS, All (Gr 3/4)	NA	14% (0.6%)
ORR at higher doses	**69%**	**57%**
CR at higher doses	**16%**	**8%**
Other notable AEs	**Skin, nail, taste changes**	

1. Krishnan et al. Abstract # 158; 2. Trudel et al. Abstract #157 (ASH 2021)

Bispecific Antibodies Summary (Combinations)

	Talquetamab+ Daratumumab[1]	Teclistamab + Daratumumab[2]
Target	GPRC5D + CD38	BCMA + CD38
Schedule	Weekly & Q2W SC	Weekly & Q2W SC
Patients	29	37
Median prior lines	6	5
Prior BCMA	**55%**	**19%**
CD38 refractory	**66%**	**60%**
Triple Class and Penta Refractory	52% and 31%	54% and 19%
CRS, All (Gr 3/4)	55% (0%)	65% (0%)
ICANS, All (Gr 3/4)	3% (3%)	3% (0%)
ORR	**81%**	**82%**
CR	**19%**	**27%**

1. Chari et al. Abstract #161; 2. Rodriguez-Otero et al. Abstract #1647.

BCMA CAR T: Summary

	CARTITUDE-1[1] Cilta-cel Phase 1/2	CRB-401[2] Ide-cel Phase 1	KarMMa[3] Ide-cel Phase 2	LUMMICAR-2[4] Zivo-Cel Phase 1b	PRIME[5] P-BCMA-101 Phase 1/2	GC012F[6] Dual CAR-T BCMA+CD19
Patients	97	62	128	20	55	19
Median prior regimens	6	6	6	5	8	5
Triple refractory, %	87.6%	69.4%	84.0%	85%	60%	95%
CAR-T dose	0.71×10^6 (range 0.5–0.95×10^6)	50, 150, 450 and 800 x 10^6	150, 300, 450 x10^6	1.5-1.8/2.5-3.0 x10^8	0.75-15 x10^6	1.0-3.0 x10^5
ORR	97.9%	75.8%	50%/69%/82.0%	94.0%	67%[b]	94.7%
CR/sCR	82.5%	38.7%	25%/29%/39%	28%	NR	84.2%
PFS	61% at 2 yrs Median PFS NR	Median PFS 8.8m	12m @450mil			
CRS, all grades	94.8%	75.8%	50%/76%/96%	77%/83%[a]	17%	95%
CRS, grade 3/4	4%	6.5%	0/7%/6%	0%	0%	11%
Neurotoxicity, all grades	20.6%	35.5%	0/17%/20%	15%/17%[a]	3.8%	0%
Neurotoxicity, grade 3/4	10.3%	1.6%	0/1%/6%	8%/0[a]	3.8%	0%

1. Martin et al., ASH 2021: Abstract 549; 2. Lin et al., ASH 2020: Abstract 131;
3. Anderson et al., ASCO 2021: Abstract 130; 4. Kumar et al., ASH 2020: Abstract 133;
5. Costello et al., ASH 2020: Abstract 134; 6. Jiang et al., ASCO 2021: Abstract 8014

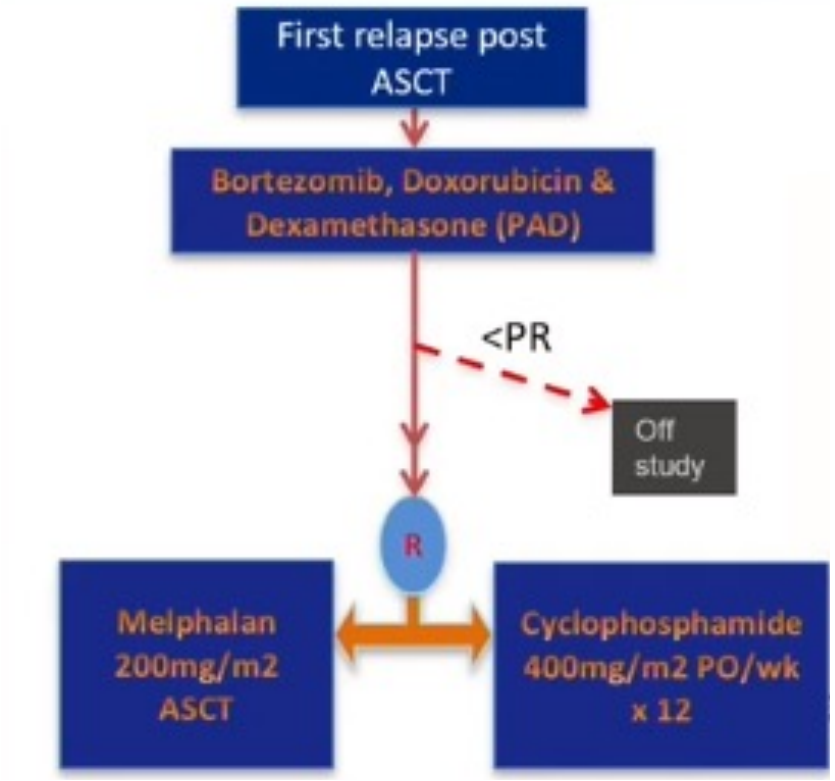
BCMA CAR T: Summary

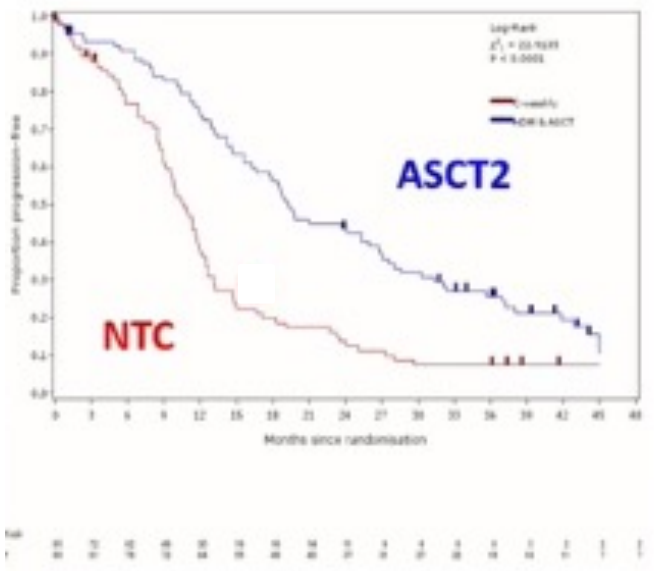
	ALLO-715[1]	BB21217[2]	Fred-Hutch[3]
Key feature	Allogeneic CAR-T	Co-culture with PI3 Kinase inhibitor	BCMA CAR-T + Gamma Secretase Inhibitor
Patients	43	72	18
Median prior lines	5	6	10
CRS, All (Gr 3/4/5)	56% (2%)	75% (4%)	94% (28%)
ICANS, All (Gr 3/4)	14% (0%)	15% (4%)	Not reported
ORR at higher doses	**71%**	**74%**	**89%**
CR at higher doses	25%	39%	44%
PFS	Not reported, DoR: 8.3 m	Not reported, DoR: 23.8m	11 months (2 m with prior BCMA)

1. Mailankody et al. Abstract #651; 2. Raje et al. Abstract #548; 3. Cowan et al. Abstract #551 (ASH 2021)

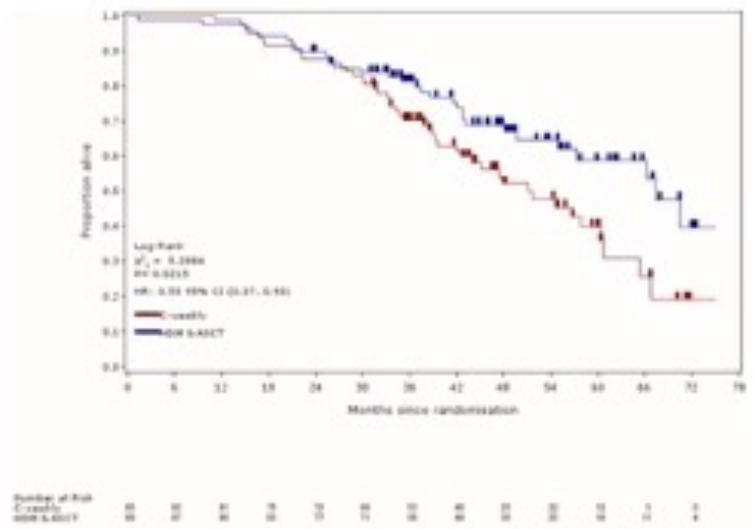
Role of Salvage Auto and Allo HCT in Myeloma

Salvage ASCT for first relapse: Myeloma X





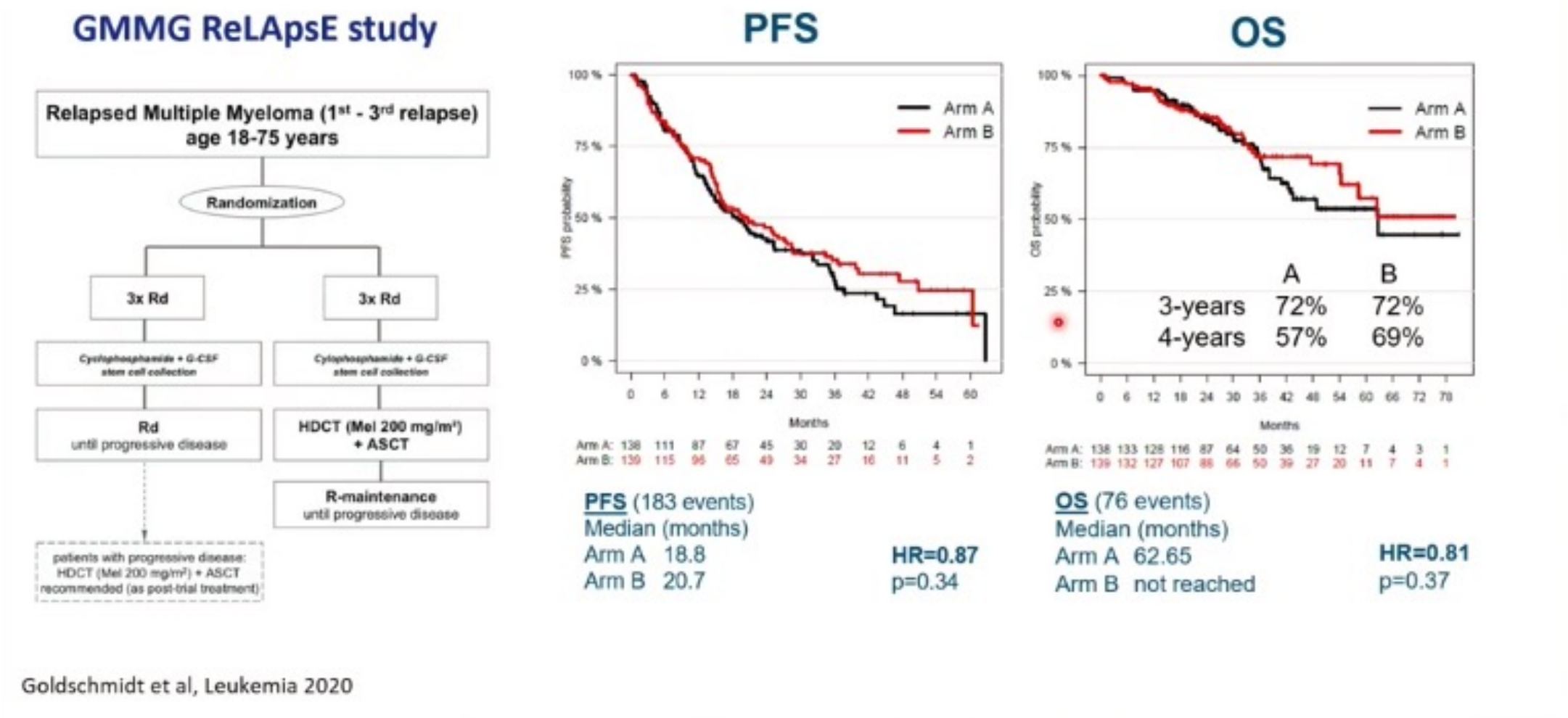
Median TTP:
ASCT2 19 months [95% CI 16,26] NTC 11 months [95% CI 9,12]



Median overall survival:
ASCT2 67 months (95% CI 55, ∞)
NTC 52 months (95% CI 42,60)

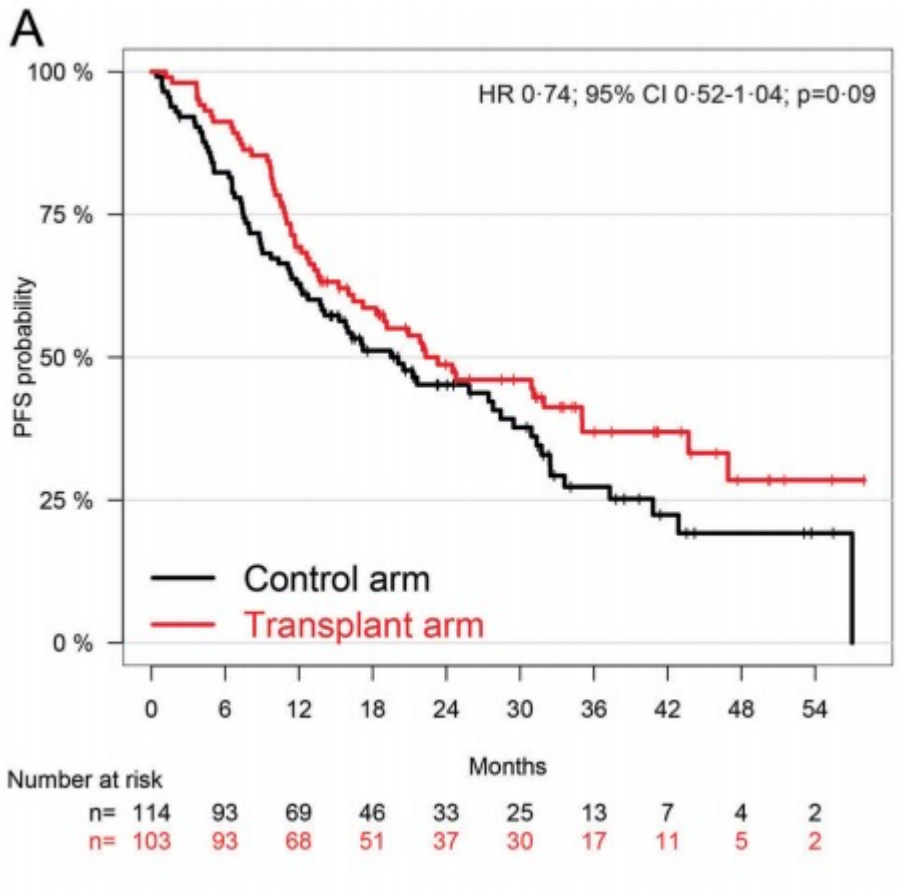
Cook G et al Lancet Oncology 2014
Cook G et al Lancet Haematology 2016

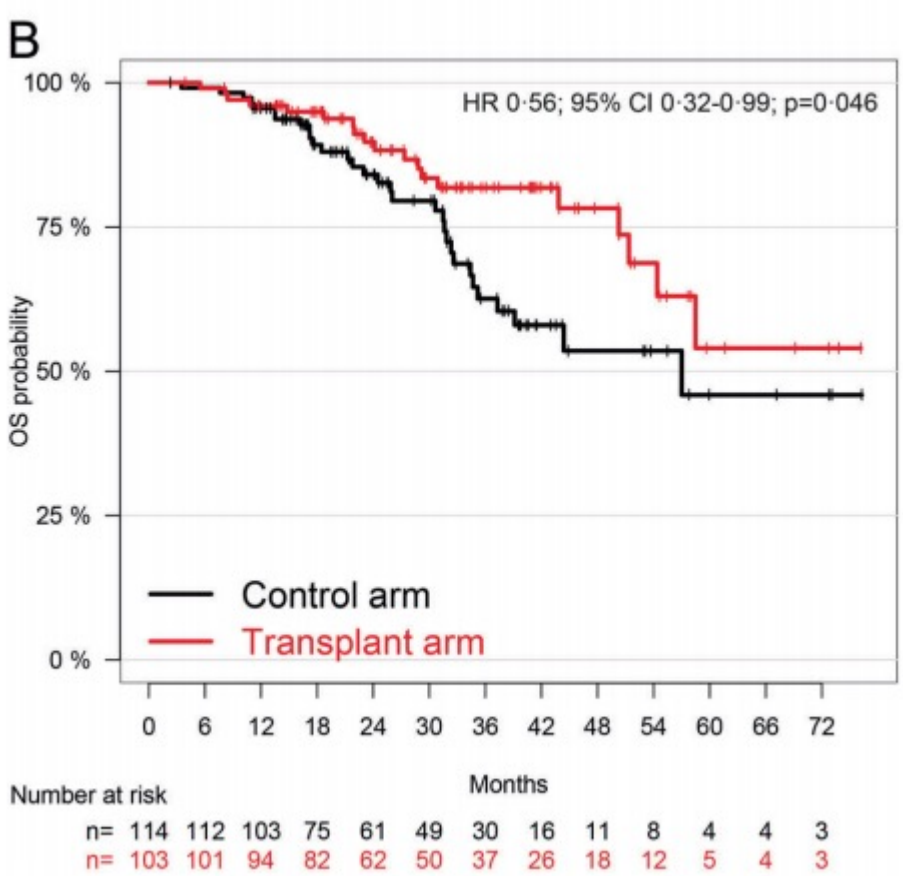
Salvage ASCT for relapse: GMMG study



Goldschmidt et al, Leukemia 2020

Progression-free (PFS) and overall survival (OS) landmark analysis from high-dose chemotherapy (HDCT; transplant arm) and Rd cycle 5 (control arm)

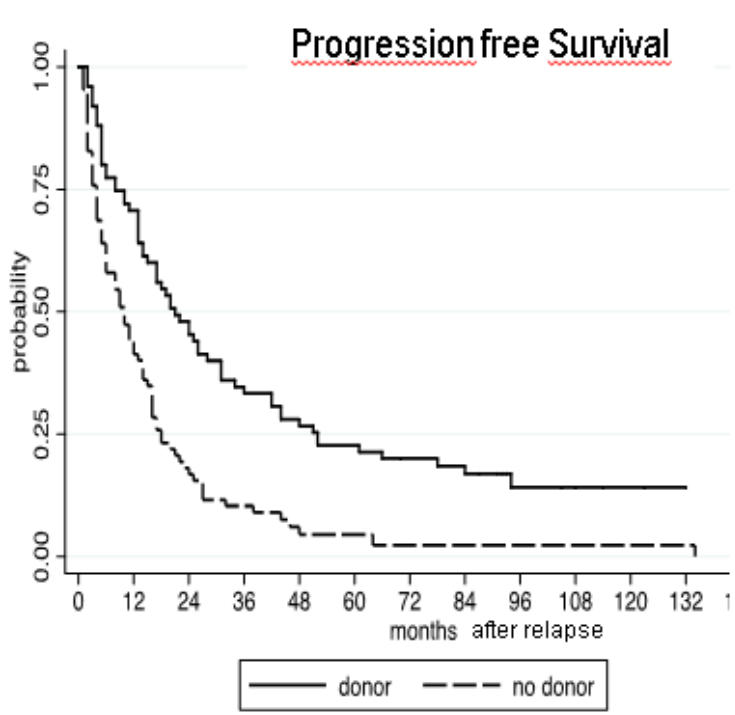


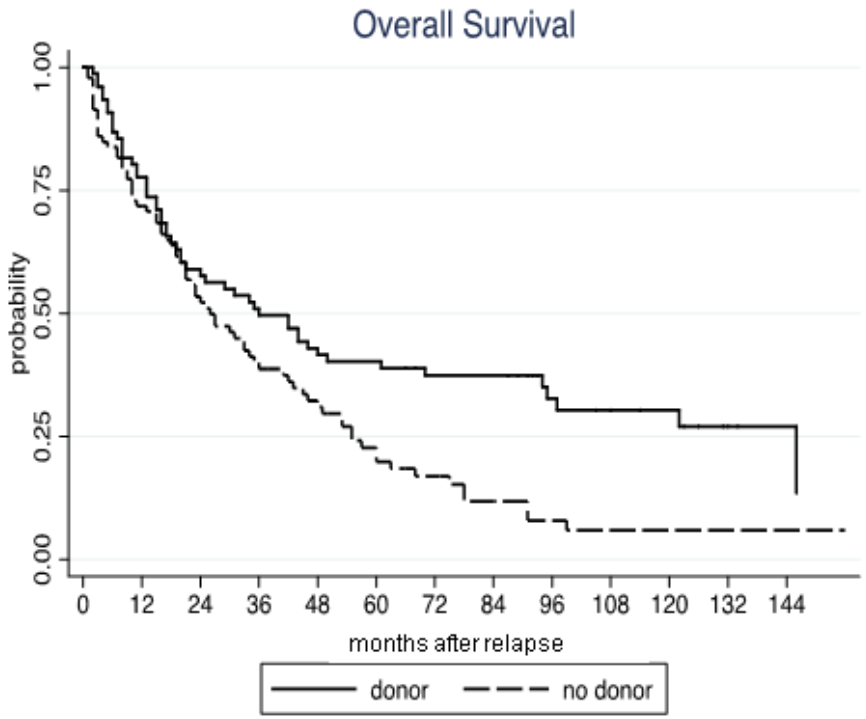


Kaplan–Meier curves are shown for a PFS (log-rank p = 0.09) and b OS (log-rank p = 0.046)

Goldschmidt H et al, Leukemia 2021

LONG TERM FOLLOW-UP OF A DONOR VERSUS NO DONOR COMPARISON IN MULTIPLE MYELOMA PATIENTS AT FIRST RELAPSE AFTER PREVIOUS AUTOTRANSPLANT





Patriarca F. et al,
15th international myeloma workshop
abstract N. 0002

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Salvage AutoSCT/ Salvage AlloSCT

T Cell Redirection Strategies for relapsed MM

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Myeloma Spaces and Therapeutic Options

Newly Diagnosed			NOT Triple Refractory Penta Exposed	Triple Refractory Penta Exposed
Non Transplant Eligible Frail	Dara based (DVd; DRd) RVD lite Goal Disease Control with minimum toxicity		Depending on prior exposure or response Pomalyst/Elotuzimab Repeat prior combos	Clinical Trials BCMA Targeted Therapy Belantemab CAR T cells IdeCel / Siltacel
Transplant Eligible Standard Risk	Dara based (DVd; DRd) RVD/KRD CyBOR D if CKI Dara KRD / Dara RVD	HCT	Depending on prior exposure or response Pomalyst/Elotuzimab Repeat prior combos Major response desired 2nd Auto Allo in younger patients with short remissions Clinical Trials	
Transplant Eligible High Risk*	KRD CyBOR D if CKI Dara KRD / Dara RVD			

* ISS 3 ; del17; 4,14; 14,16, gain 1q

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Conclusions

- The diagnosis, work up and treatment of myeloma has changed dramatically over the last 10 years.
- The therapeutic goal is to obtain deep remissions that translate into improved PFS and OS
- With combination therapy of IMIDS, Pis, MoAbs, BITES, autologous and allogeneic HCT as well as CAR T cells long term disease control and cures will be achievable in a substantial proportion of patients with MM.

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Questions?

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Q&A Session

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