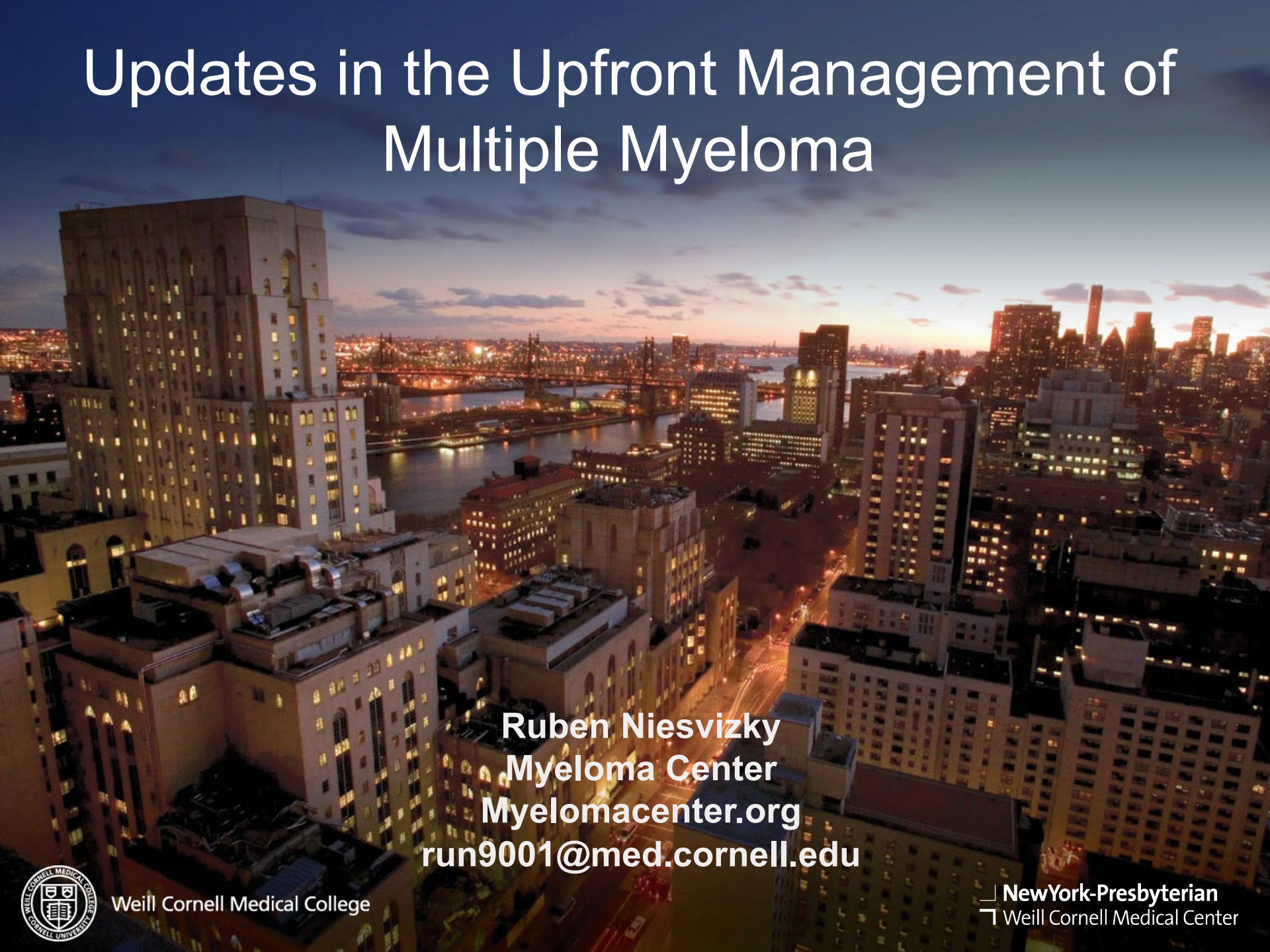
Updates in the Upfront Management of Multiple Myeloma



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Disclosures for Ruben Niesvizky

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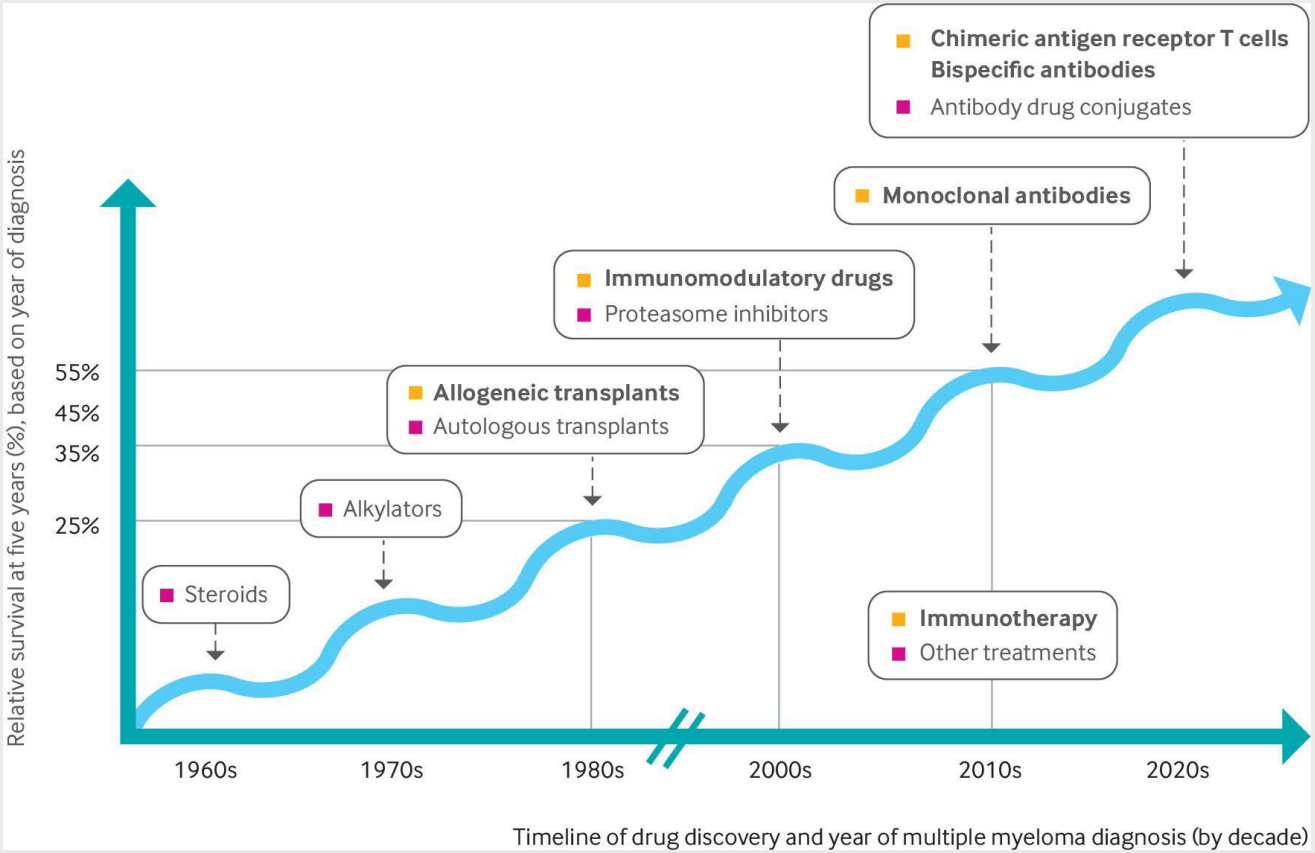
Research Support/P.I.	**Takeda, Amgen, Janssen, BMS, Karyopharm, GSK**
Employee	**N/A**
Consultant	**Celgene, Takeda, Amgen, Janssen, BMS, GSK**
Major Stockholder	**N/A**
Honoraria	**N/A**
Speakers Bureau/Scientific Advisory Board	**N/A**

Outline

- Should we aim to CR MRD negative?
- Induction: 2 vs 3 vs 4 drugs
- Is transplant still necessary?
- The ASCT-ineligible patient
- Summary and future directions

The Evolution of Multiple Myeloma Treatment



Shah et al, *BMJ*, 2020

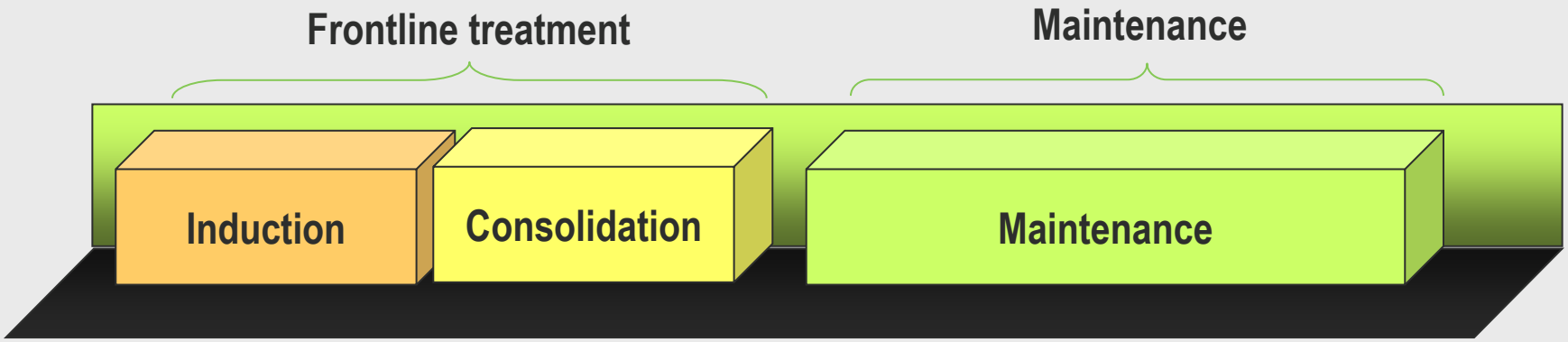
Goals of Initial Treatment[1,2]

- Alleviate disease-related complications
- Achieve effective disease control
- Extend disease control
- Improve overall survival
- Use a regimen that is well tolerated
- Maintain QoL
- Facilitate stem cell collection

Mounting evidence correlates depth and duration of initial response with clinical outcomes[3-6]

References: 1. Kumar S. *Cancer Treat Rev*. 2010;36(suppl 2):S3-S11. **2.** Lonial S et al. *Leukemia*. 2014;28(2):258-268. **3.** Lahuerta JJ et al. *J Clin Oncol*. 2008;26(35):5775-5782. **4.** Wang M et al. *Bone Marrow Transplant*. 2010;45(3):498-504. **5.** Barlogie B et al. *Cancer*. 2008;113(2):355-359. **6.** Chanan-Khan A et al. *J Clin Oncol*. 2010;28(15):2612-2624.

Younger or Fit

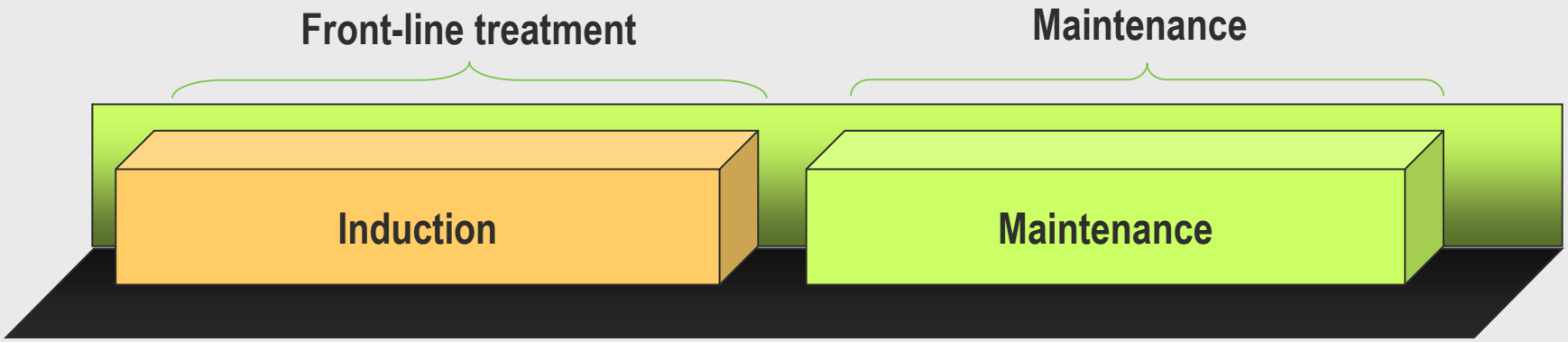


IMID: Thal-Len
Proteasome Inhibitor: Bor-Car-ixa
MoAb: aCD38
Steroids: Dex-MPred
Alkylator: Cyclo-Mel
Anthracycline: LipoDox-Dox

SCT

Observation
IMID: Thal, Len
Proteasome Inh: Bor
Steroids: Dex-Pred

Elderly or Unfit



IMID:Thal-Len
Proteasome Inhibitor: Bor-Car-Ixa
Steroids: Dex-Pred
Alkylator: Cyclo-Mel
Mo Abs: Dara
Anthracycline: LipoDox-Dox

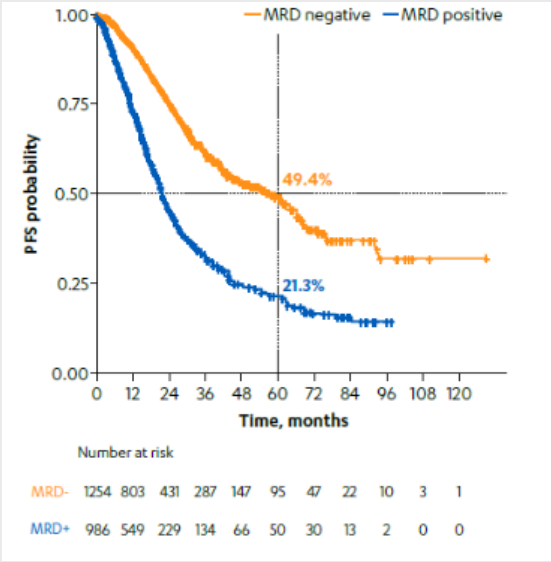
Observation
IMID: Thal, Len
Proteasome Inh: Bor-Ixa
MoAb: aCD38
Steroids: Dex-Pred

Should We Aim to MRD Neg?

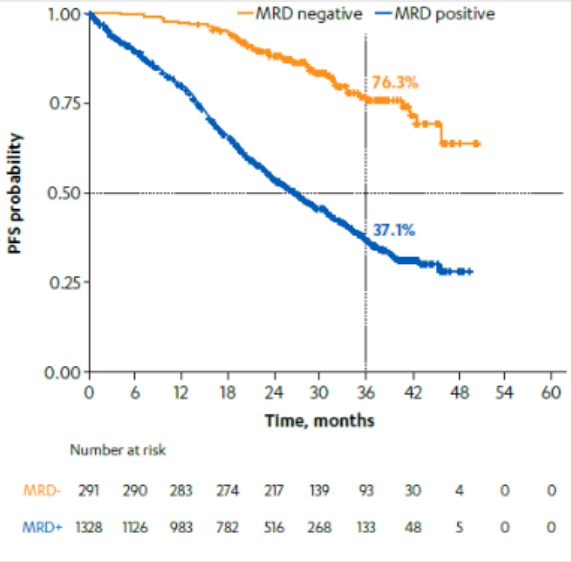
Positive vs Negative MRD: Two Different Myelomas

Results from an expanded meta-analysis (8,114 patients)

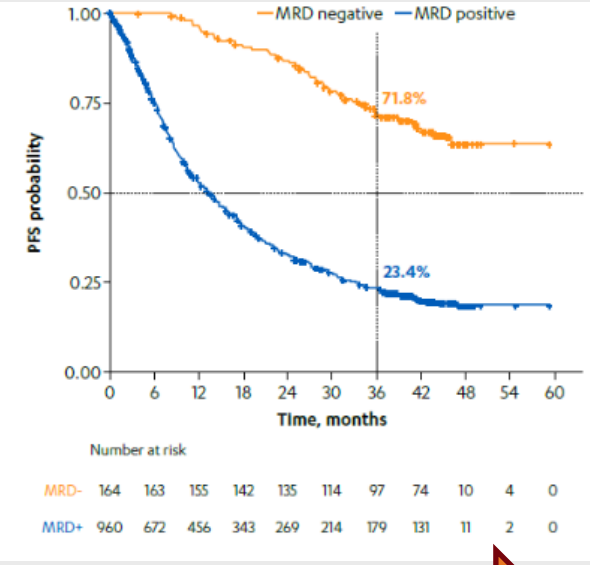
NDMM (transplant-eligible)



NDMM (transplant-ineligible)



RR MM

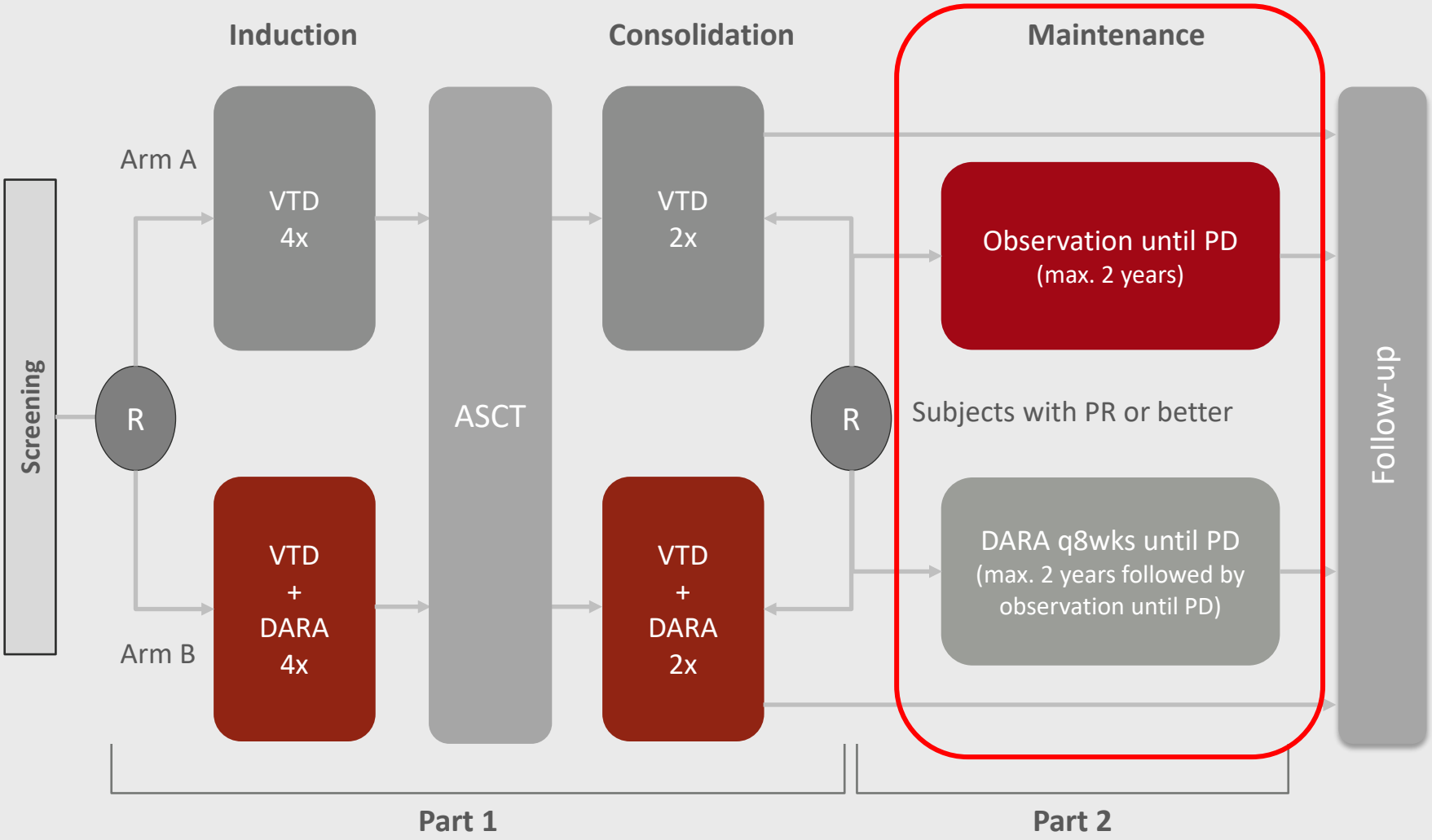


Progressive improvement in MRD technologies

Munshi. ASH 2019. Abstr 4742.

Daratumumab in the Setting of ASCT

CASSIOPEIA phase 3 trial



DARA, daratumumab.

www.clinicaltrials.gov; NCT02541383.

Phase 3 CASSIOPEIA Trial: VTD ± Daratumumab in Newly Diagnosed Myeloma

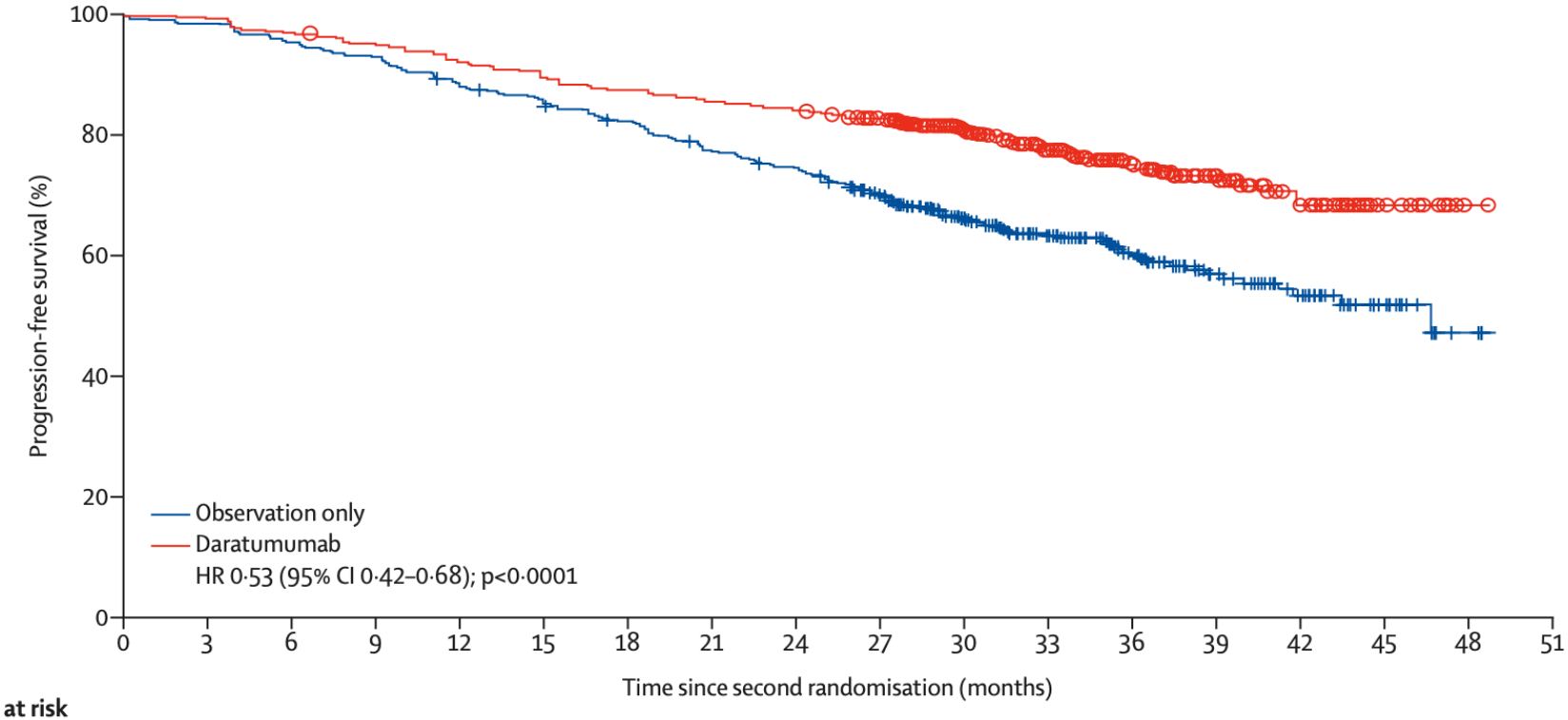
- Patients with newly diagnosed, previously untreated symptomatic myeloma who are eligible for ASCT (N = 1085)
  - **Part 1: randomized to receive induction and consolidation treatment with daratumumab + VTD or VTD alone (primary endpoint: sCR)**
  - **Part 2: second randomization of patients achieving response to either maintenance daratumumab or observation (primary endpoint: PFS)**
- Primary endpoint met: improved sCR with daratumumab + VTD vs VTD alone (press release)

Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial.

Philippe Moreau;Cyrille Hulin;Aurore Perrot;Bertrand Arnulf;Karim Belhadj;Lotfi Benboubker;Marie C Béné;Sonja Zweegman;Hélène Caillon;Denis Caillot;Jill Corre;Michel Delforge;Thomas Dejoie;Chantal Doyen;Thierry Facon;Cécile Sonntag;Jean Fontan;Mohamad Mohty;Kon-Siong Jie;Lionel Karlin;Frédérique Kuhnowski

ISSN: 1470-2045 , 1474-5488; **DOI:** 10.1016/S1470-2045(21)00428-9; **PMID:** 34529931
The Lancet oncology. , 2021, Vol.22(10), p.1378-1390

Phase 3 CASSIOPEIA Trial: VTD ± Daratumumab in Newly Diagnosed Myeloma

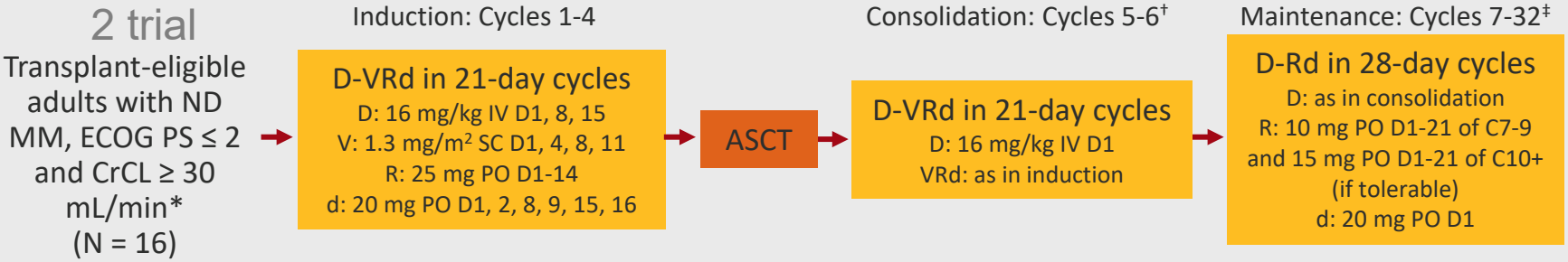


Number at risk (number censored)																	
Observation only	444	438	424	413	392	377	362	339	326	294	227	178	118	76	53	21	3	0
	(0)	(0)	(0)	(0)	(1)	(2)	(4)	(5)	(6)	(20)	(71)	(112)	(164)	(201)	(220)	(251)	(268)	(271)
Daratumumab	442	439	429	420	406	396	386	377	372	354	283	215	155	102	64	25	1	0
	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(12)	(76)	(133)	(188)	(237)	(270)	(309)	(333)	(334)

Figure 2: **Kaplan-Meier estimates of progression-free survival in patients in the maintenance-specific intention-to-treat population**
HR=hazard ratio.

GRIFFIN: Study Design

- Preliminary efficacy in safety run-in phase of open-label, randomized phase 2 trial



Response, %	End of Induction	End of Consolidation	During Maintenance
ORR	**94**	**100**	**100**
▪ sCR	0	25	63
▪ CR	6	38	31
▪ VGPR	50	38	6
▪ PR	38	0	0

Voorhees. ASH 2018. Abstr 151.

*Len dose adjusted in patients with CrCl ≤ 50 mL/min. †Consolidation began 60-100 days after ASCT. ‡Patients completing maintenance were permitted to continue single-agent len.

GRIFFIN 2-Yr Maintenance Phase Update: Response

Response, %	D-VRd (n = 100)					VRd (n = 97)				
	Induction	ASCT	Consol	1-Yr Maint	2-Yr Maint	Induction	ASCT	Consol	1-Yr Maint	2-Yr Maint
sCR	12	21	42	63	66*	7	14	32	46	47*
CR	7	6	9	17	16†	6	5	10	13	13†
≥CR	19	27	52	80	82	13	19	42	60	61
VGPR	53	60	39	14	14	43	46	31	19	18
PR	26	12	8	4	3	35	26	19	14	14
SD/PD/NE	2	1	1	2	1	8	8	8	7	7

*P = .0096 for comparison of sCR for D-VRd vs VRd. †P = .0013 for comparison of CR for D-VRd vs VRd.

- Median follow-up 38.6 mo

Laubach. ASH 2021. Abstr 79.

GRIFFIN 2-Yr Maintenance Phase Update: MRD Status

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

MRD Neg (10^{-5}) After 24-Mo Maintenance, n/N (%)		D-VRd (n = 104)	VRd (n = 103)	OR (95% CI)
Cytogenetic risk	▪ 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)

Laubach. ASH 2021. Abstr 79.

GRIFFIN 2-Yr Maintenance Phase Update: PFS and OS

PFS*	D-VRd (n = 104)	VRd (n = 103)	HR (95% CI)
24-mo PFS, %	91.6	88.9	0.46 (0.21-1.01)
36-mo PFS, %	89.7	81.2	
OS	**D-VRd (n = 104)**	**VRd (n = 103)**	**HR (95% CI)**
24-mo OS, %	94.8	93.3	0.90 (0.32-2.57)
36-mo OS, %	92.6	92.2	

*Study not powered for PFS analysis.

- Median PFS and OS were not reached in either treatment arm
- Data suggest PFS benefit to prolonged D-R therapy

GRIFFIN 2-Yr Maintenance Phase Update: Conclusions

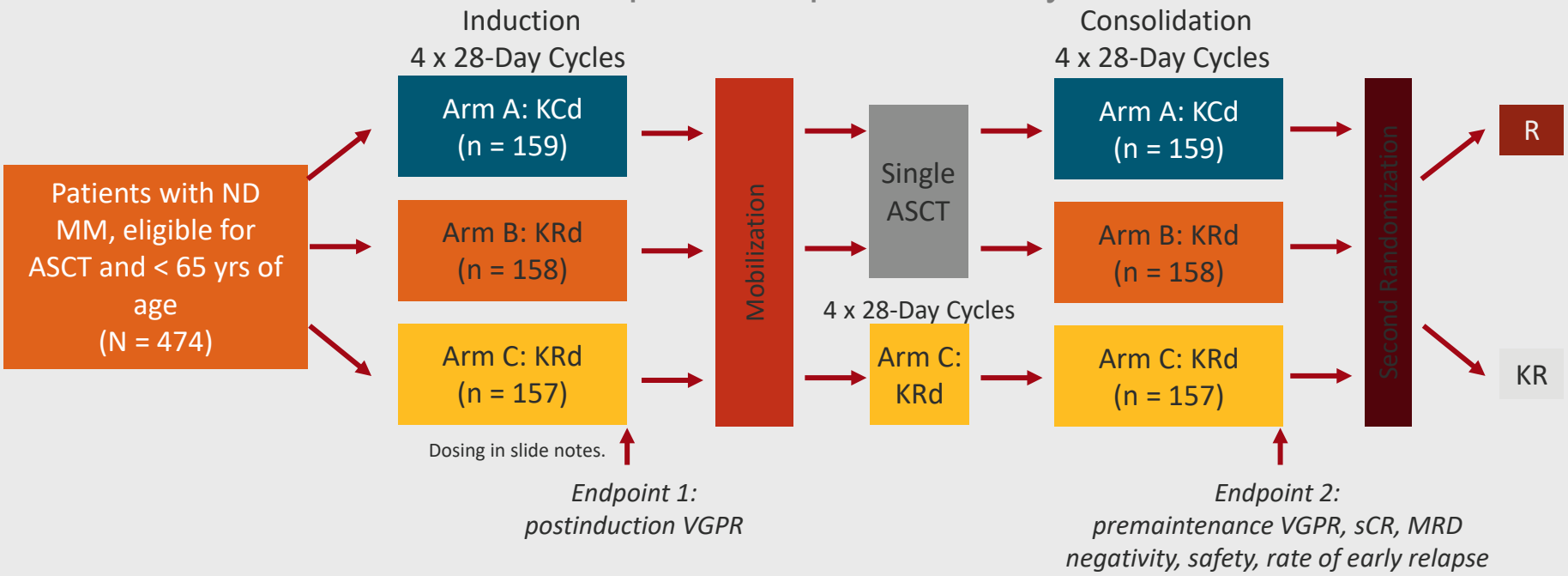
- After 24 mo of maintenance therapy in the phase 2 GRIFFIN trial of ASCT-eligible patients with ND MM, D-VRd followed by D-R maintenance continued to show significant improvement in sCR and depth of response vs VRd followed by R maintenance[1]
  - **Patients with sCR after 24-mo maintenance: 66.0% vs 47.4% (*P* = .0096)**
  - **Patients with MRD negativity after 24-mo maintenance at 10^{-5} threshold: 64.4% vs 30.1% (*P* <.0001); at 10^{-6} threshold: 35.6% vs 14.6% (*P* = .0007)**
- Safety at 24 mo of maintenance cutoff was consistent with earlier analyses with no new safety concerns identified[2,3]
- Investigators conclude results support use of D-VRd induction and consolidation with D-R maintenance in transplant-eligible patients with ND MM
  - **Phase 3 PERSEUS trial ongoing (NCT03710603)**

1. Laubach. ASH 2021. Abstr 79. 2. Voorhees. *Blood.* 2020;136:936. 3. Kaufman. ASH 2020. Abstr 549.

Is Transplant Still Needed?

FORTE: Study Design

- Multicenter, randomized, open-label phase 2 study



Gay. ASCO 2021. Abstr 8002.

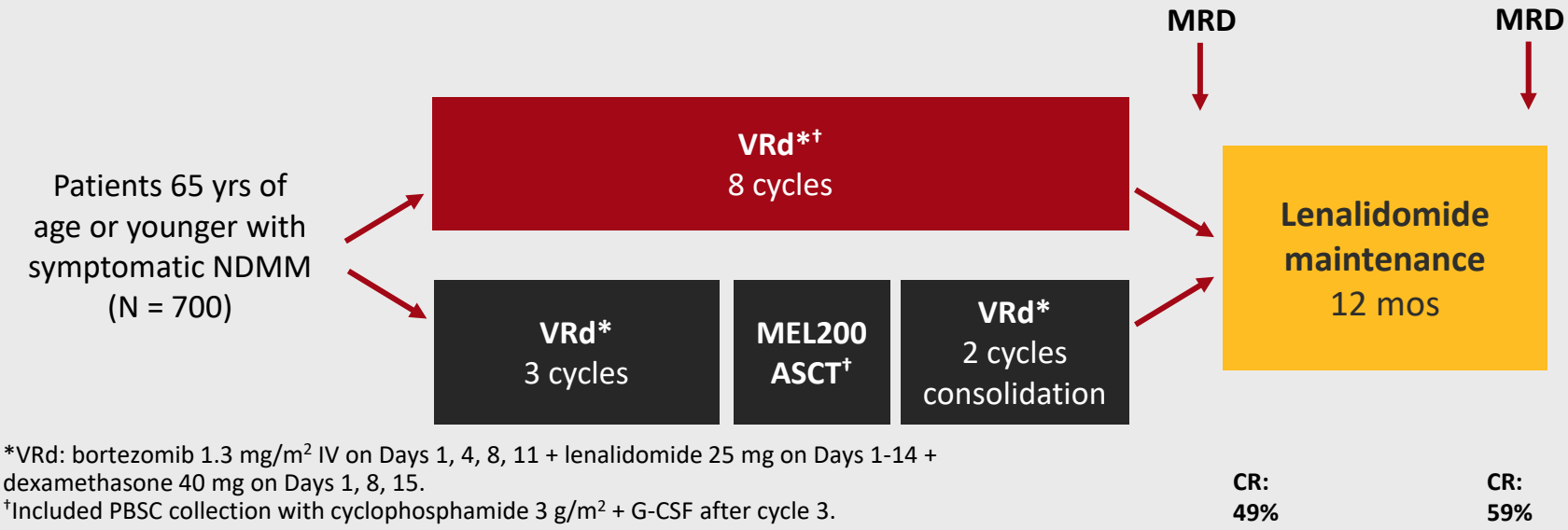
FORTE Efficacy by Cytogenetic Risk: MRD in High-Risk Patients

MRD, %	KCd-ASCT (n = 138)	KRd-ASCT (n = 132)	KRd12 (n = 126)
Premaintenance MRD negativity			
▪ High risk	47	59	62
▪ Double hit	39	44	50
Sustained 1-yr MRD negativity			
▪ High risk	29	50	39
▪ Double hit	17	47	25

- Among patients with 1-yr sustained MRD negativity, 4-yr PFS was:
  - **87% in patients with high-risk cytogenetics**
  - **84% in patients with double-hit cytogenetics**

Gay. ASCO 2021. Abstr 8002.

Phase 3 IFM/DFCI 2009: VRd ± ASCT in Newly Diagnosed MM

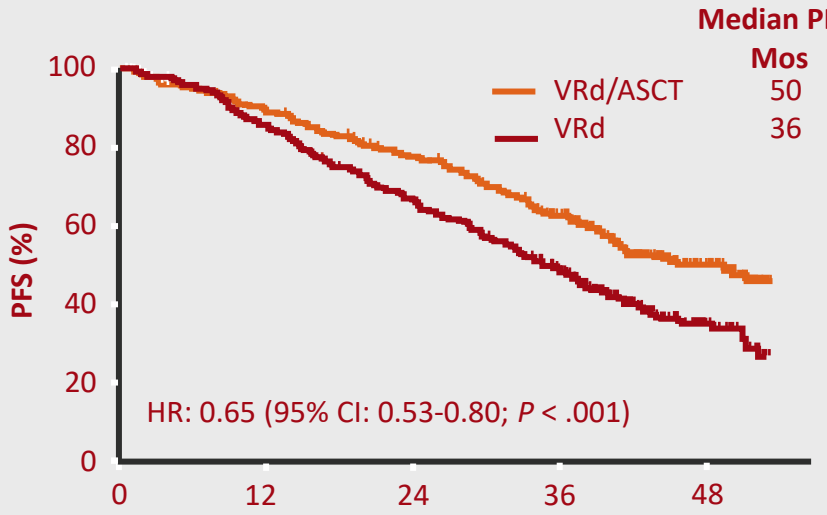


*VRd: bortezomib 1.3 mg/m^2 IV on Days 1, 4, 8, 11 + lenalidomide 25 mg on Days 1-14 + dexamethasone 40 mg on Days 1, 8, 15.
†Included PBSC collection with cyclophosphamide 3 g/m^2 + G-CSF after cycle 3.

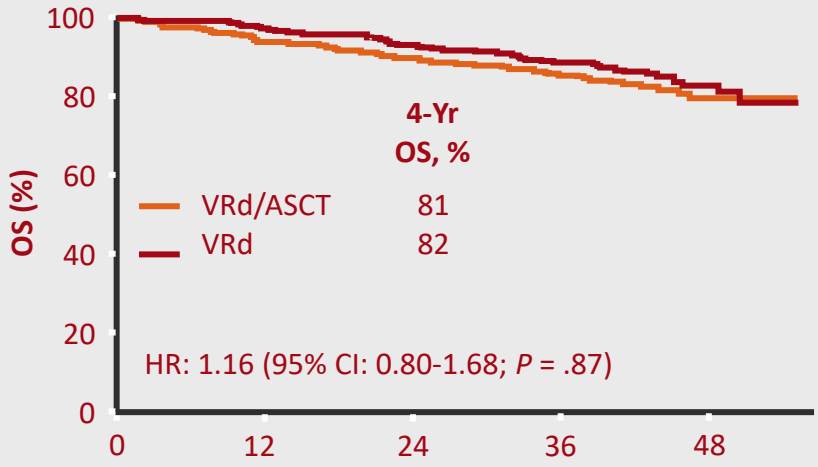
- Primary objective: PFS
- Secondary objectives: ORR, MRD, TTP, OS, safety

Attal. *N Engl J Med*. 2017;376:1311.

IFM 2009: Efficacy



Patients Risk, n					
VRd/ASCT	350	308	264	157	50
VRd	350	294	228	196	32



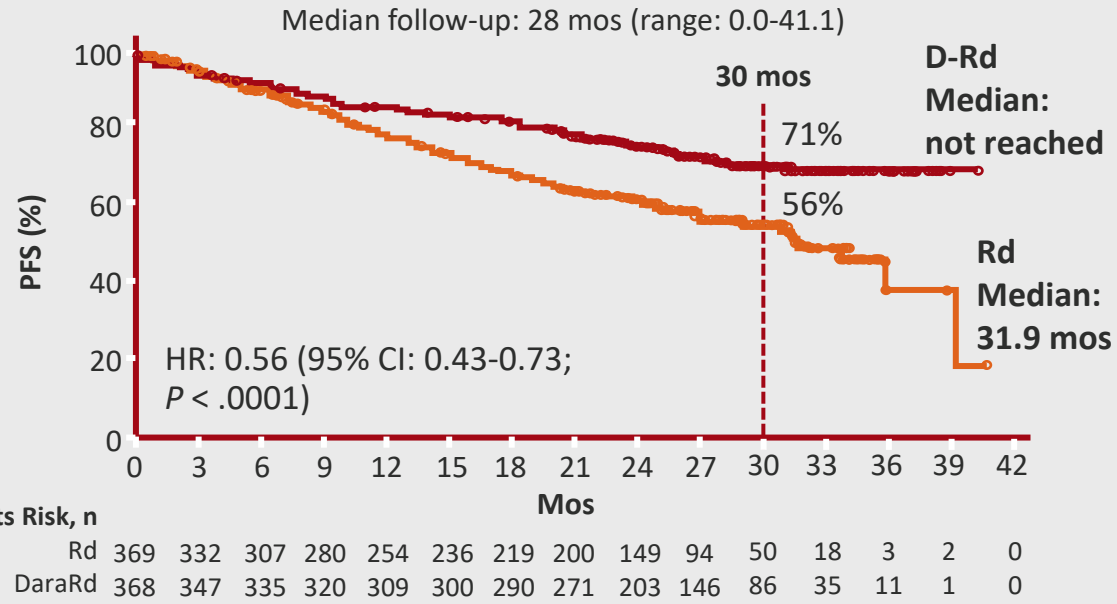
Patients Risk, n					
VRd/ASCT	35	33	31	28	89
VRd	0	0	3	1	95
	35	33	32	29	
	0	9	5	3	

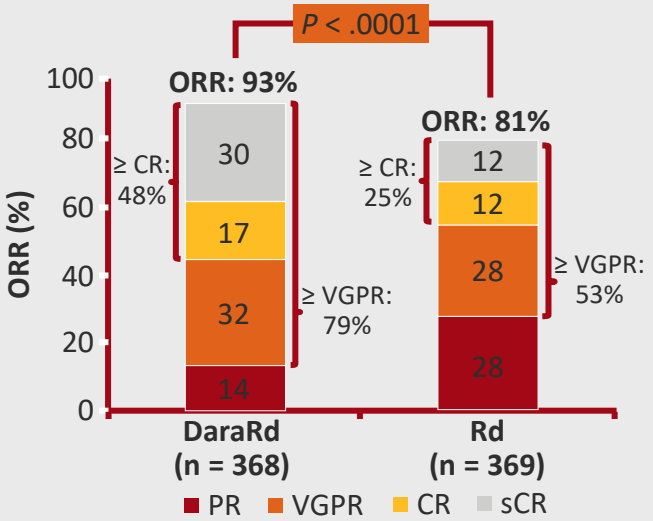
Median follow-up: 43 mos with VRd/ASCT, 44 mos with VRd

Attal. *N Engl J Med*. 2017;376:1311.

ASCT-Ineligible

Phase 3 MAIA Trial: Survival With DaraRd vs Rd in Older or ASCT-Ineligible Patients

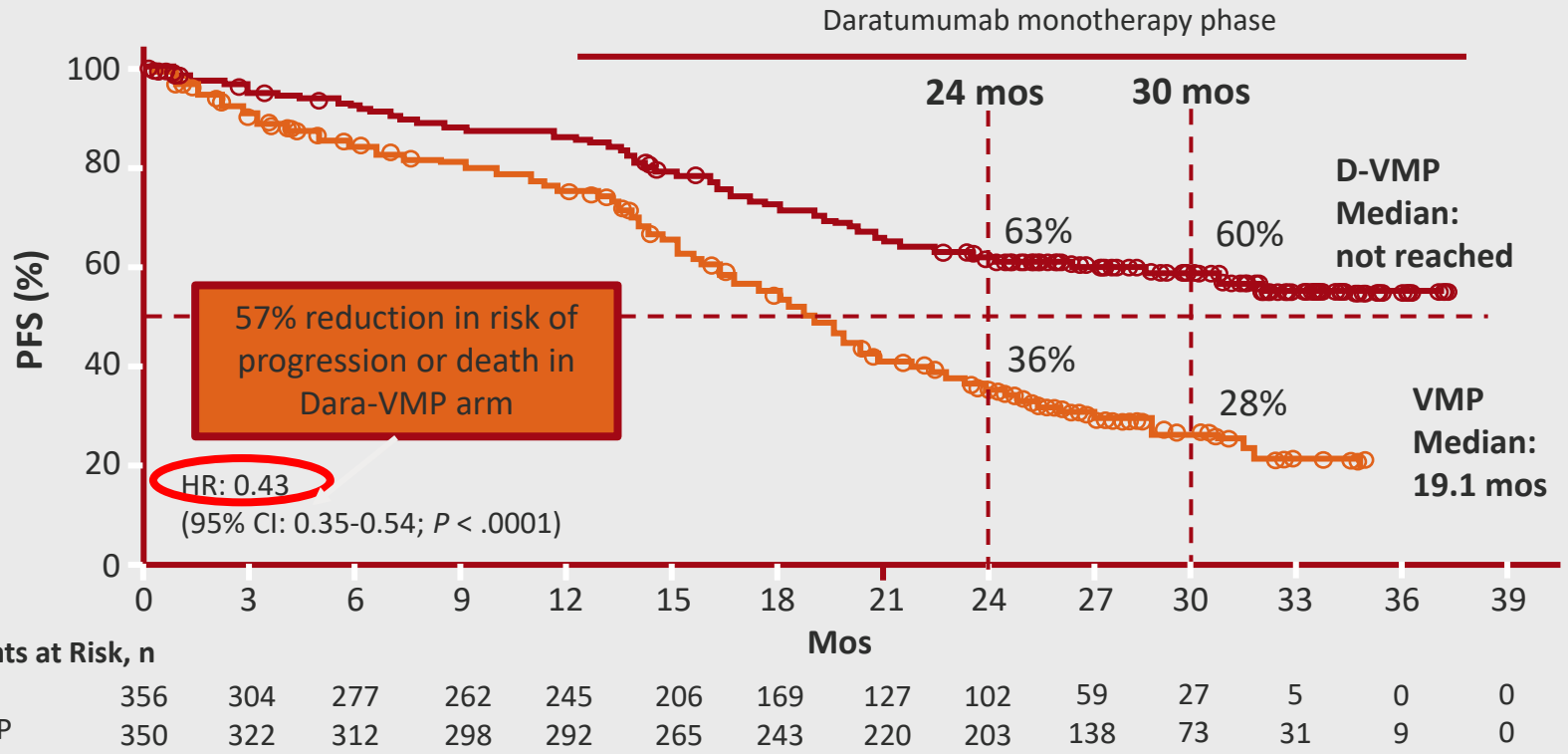




- Daratumumab treatment favored in most subgroups analyzed, including age, race, ISS stages, ECOG PS scores
- Reduced risk of progression or death with MRD negativity in both arms
- MRD negativity increased with addition of daratumumab
  - DaraRD: 24% MRD negative
  - Rd: 7% MRD negative

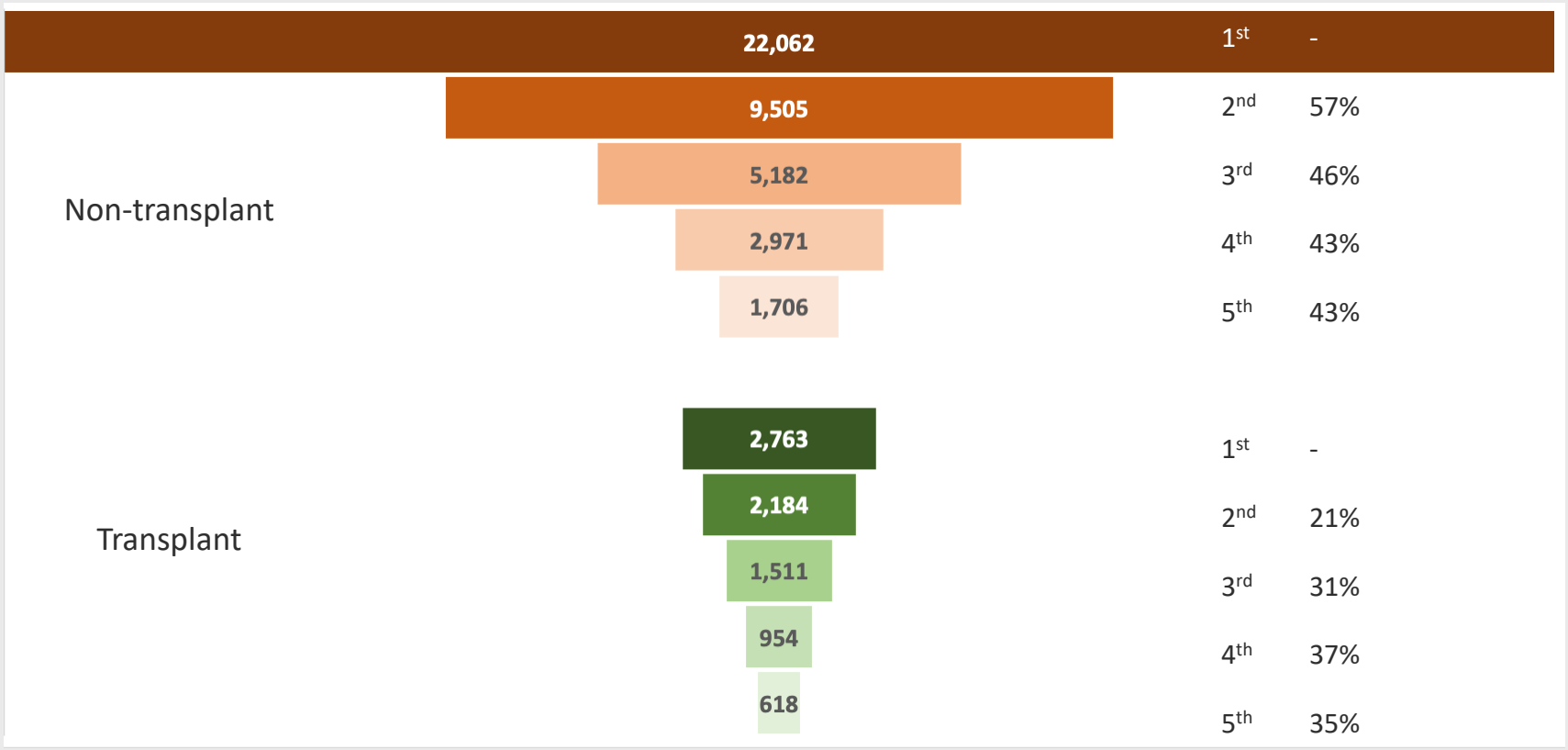
Facon. ASH 2018. Abstr LBA-2.

Phase 3 ALCYONE Trial: VMP ± Daratumumab in ASCT-Ineligible Patients With Newly Diagnosed Myeloma



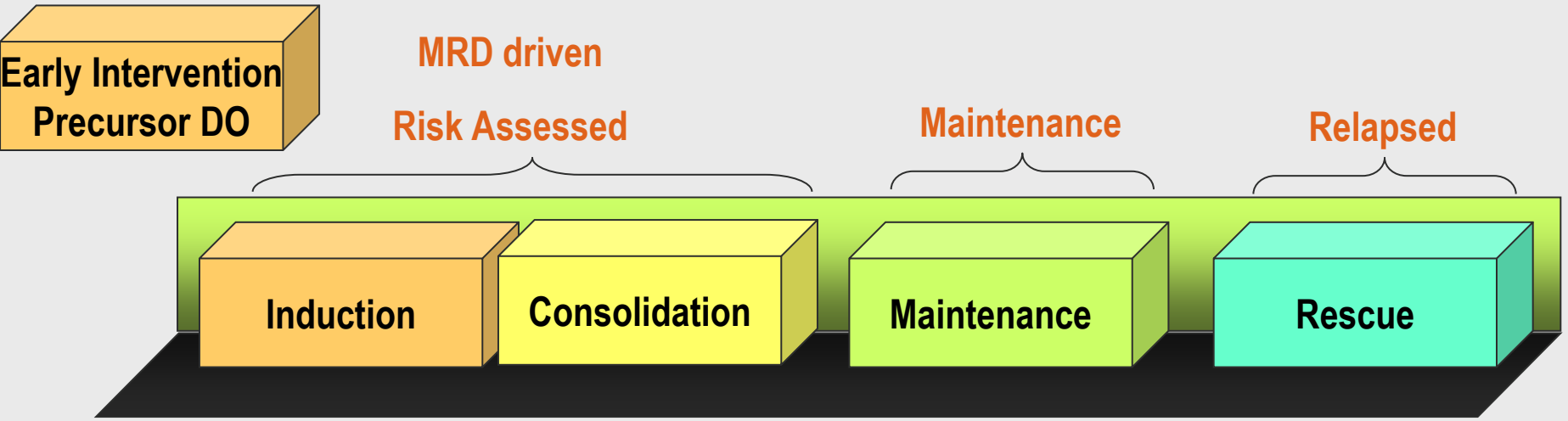
Dimopoulos. ASH 2018. Abstr 156.

Attrition with Subsequent Treatment



Fonseca et al BMC 20: 1087 (2020)

Multiple Myeloma: Future



IMiD: Len-Cell mods
Proteasome Inhibitor: Bor-Car
Steroids: Dex-Pred
a CD38
Molecular Targets
Ven for 11;14
BRAF, others

SCT
CAR T/T cell eng

Sustained MRD neg:
Observation
IMiD: Len
Proteasome Inh:
Bor/Ixa

Alkylators: Mel-Cy-Benda
Investigational
ADC BCMA

[a] Transplant-eligible patients.

Bor = bortezomib; Dex = dexamethasone; Dox = doxorubicin; Thal = thalidomide; Len = lenalidomide; SCT = stem-cell transplant; Pred = prednsione; Lipo/Dox = liposomal doxorubicin.

NCCN, 2013.

Thank you

Collaborators

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