Optimizing Induction Therapy for Transplant-Eligible and Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Robert Z. Orlowski, Ph.D., M.D.

Florence Maude Thomas Cancer Research Professor

Director, Myeloma Section, Department of Lymphoma/Myeloma

Principal Investigator, LLS SCOR in High Risk Plasma Cell Dyscrasias

Chair, SWOG Myeloma Committee

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Smoldering vs. Symptomatic Myeloma

Clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features and myeloma-defining events:

- Any one or more of the following biomarkers of malignancy (MDEs):
  - 60% or greater clonal plasma cells on bone marrow examination
  - Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L (a patient's involved free light chain either kappa or lambda is the one that is above the normal reference range; the uninvolved free light chain is the one that is typically in, or below, the normal range)
  - More than one focal lesion on MRI that is at least 5mm or greater in size.

clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

https://www.myeloma.org/international-myeloma-working-group-imwg-criteria-diagnosis-multiple-myeloma

Courtesy of Robert Z Orlowski, MD, PhD

Transplant Eligible Patients

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[e]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Daratumumab[f]/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[g] • Ixazomib/cyclophosphamide/dexamethasone[g] • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone • Daratumumab[f]/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[h] (VTD-PACE)

https://www.nccn.org/ Version 3.2021 – October 19, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Clinical & Biologic Considerations

- Clinical
  - Disease burden
  - Aggressiveness
  - Comorbid medical features
  - Eligibility for high-dose therapy
  - Patient and family preferences
- Biologic
  - ISS/R-ISS stage
  - Molecular risk status
  - Extramedullary disease
  - ? Drug sensitivity/resistance
  - ? Immune effector cell competence

http://www.nccn.org/ Version 4.2020.

Courtesy of Robert Z Orlowski, MD, PhD

SWOG-S0777: Updated VRd Data

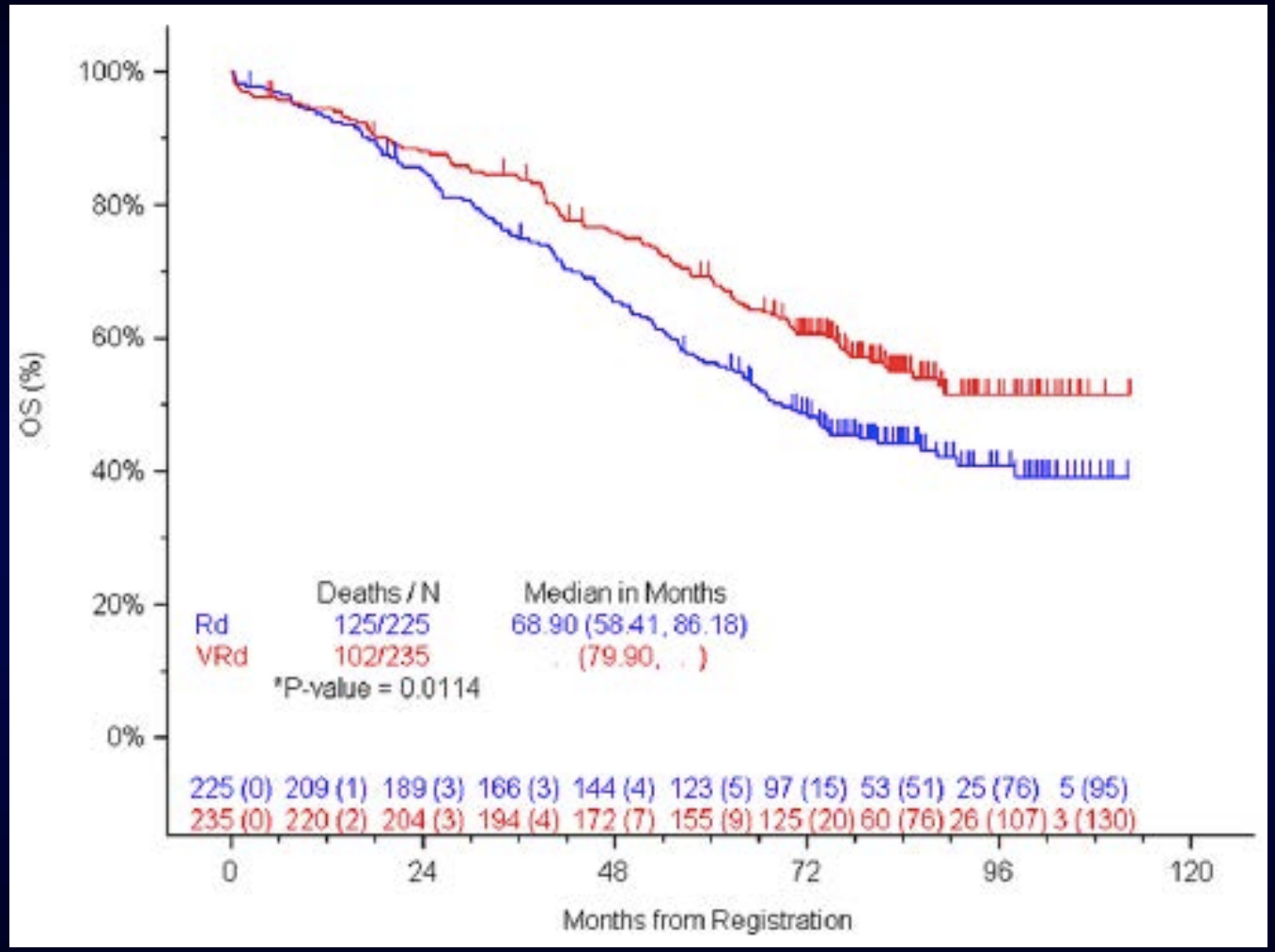
	VRd[a] (*n* = 215)	Rd[a] (*n* = 207)
Complete response (CR)	24.2% (52)	12.1% (25)
Very good partial response (VGPR)	50.7% (109)	41.1% (85)
VGPR or better	**74.9% (161)**	**53.2% (110)**
Partial response (PR)	15.3% (33)	25.6% (53)
Overall response rate (ORR)	**90.2% (194)**	**78.8% (163)**
Stable disease (SD)	7.0% (15)	16.4% (34)
PD or Death	2.8% (6)	4.8% (10)

- Confirmed best responses

Durie, BGM et al. Blood Cancer J. 10(5):53. doi: 10.1038/s41408-020-0311-8.

Courtesy of Robert Z Orlowski, MD, PhD

SWOG-S0777: OS Data



Durie, BGM et al. Blood Cancer J. 10(5):53. doi: 10.1038/s41408-020-0311-8.

Courtesy of Robert Z Orlowski, MD, PhD

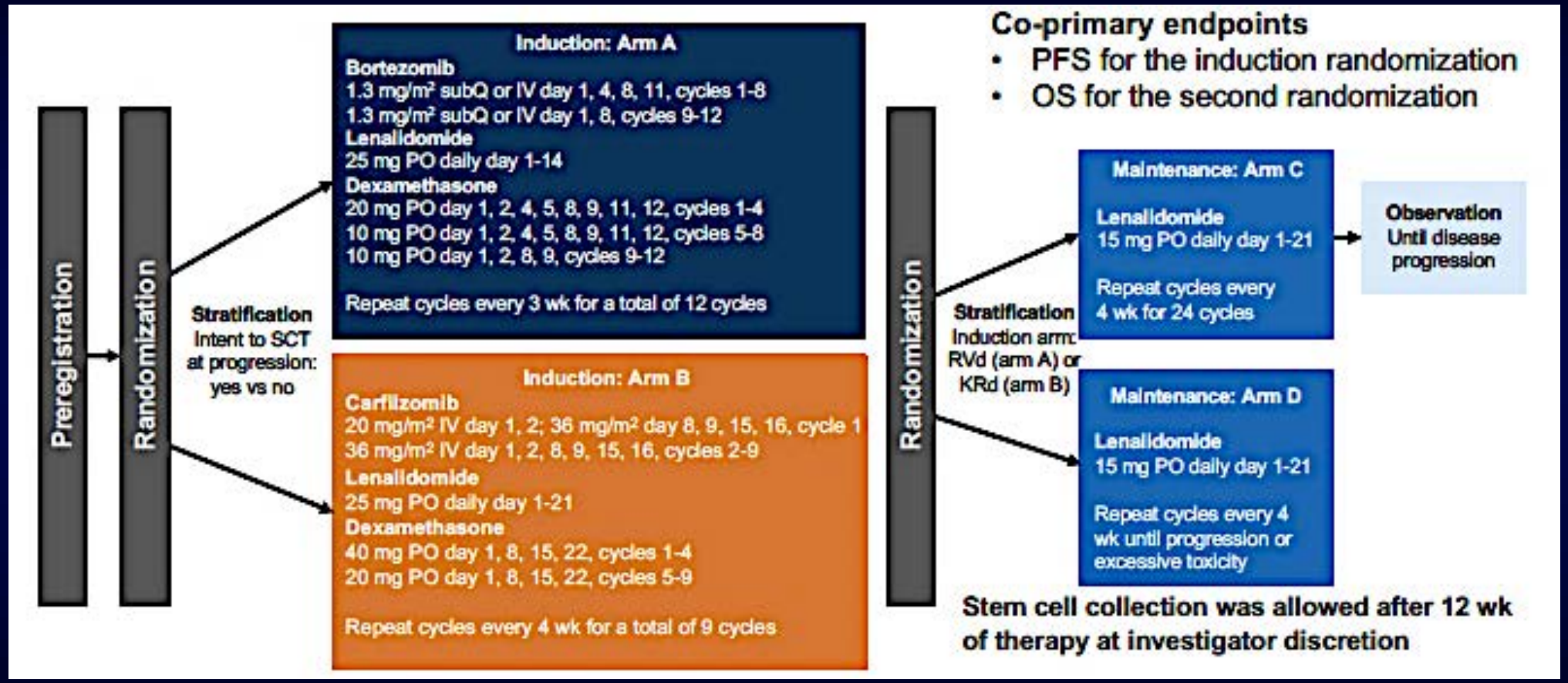
SWOG-S0777: High Risk Patients

Follow-up analyses of outcomes linked to presence or absence of high-risk FiSH abnormalities were conducted (results not shown). Although there were trends towards better PFS and OS with VRd for patients with *t*(4;14) and/or chromosome 17p deletion, differences were not statistically significant primarily because of the limited number of patients with available data. The median duration of lenalidomide plus dexamethasone maintenance was 17.1 months for both arms of the trial. Unfortunately, Time to Next Treatment (TN) was not captured as part of this study.

Durie, BGM et al. Blood Cancer J. 10(5):53. doi: 10.1038/s41408-020-0311-8.

Courtesy of Robert Z Orlowski, MD, PhD

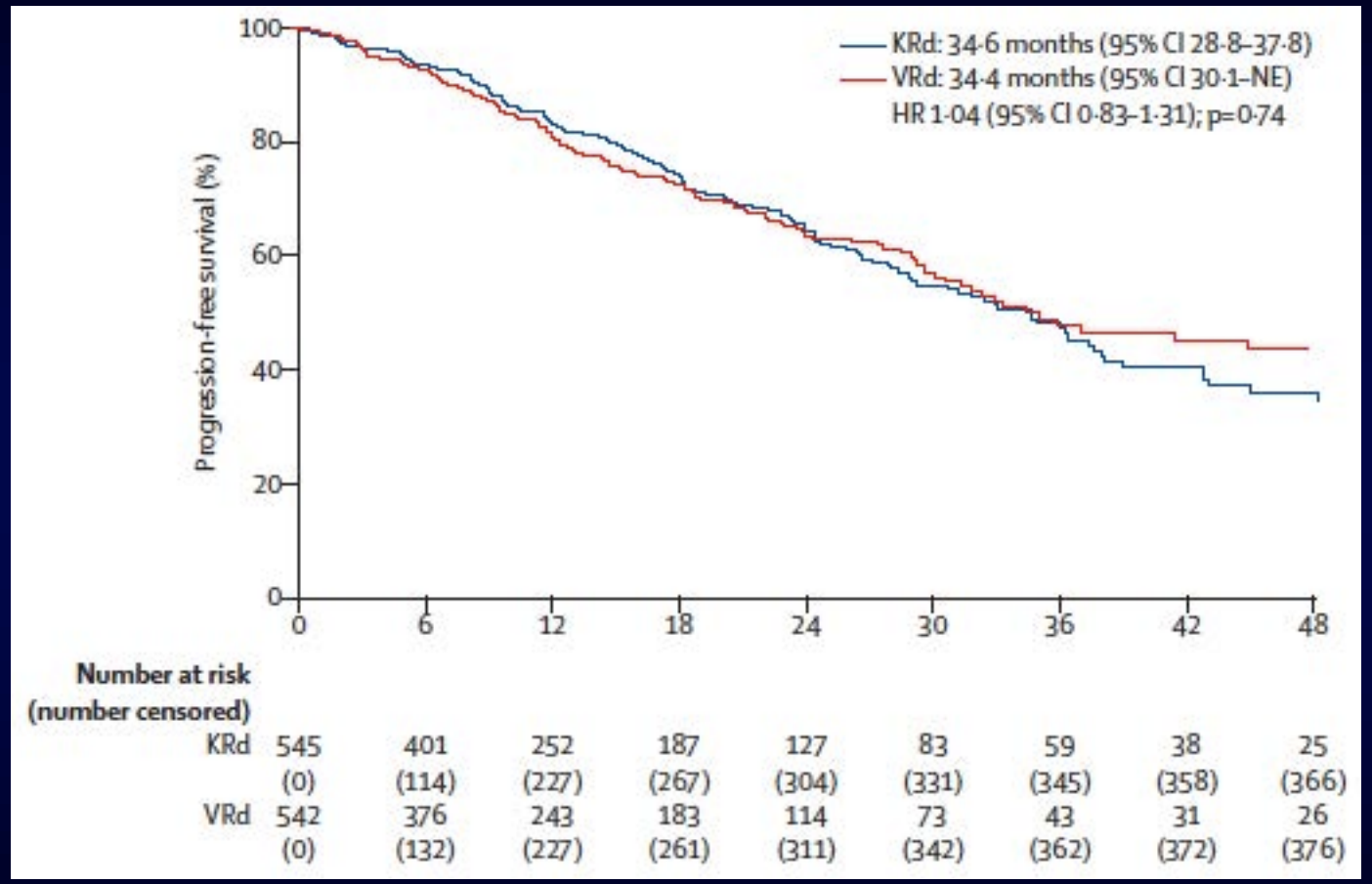
ENDURANCE Trial



Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

ENDURANCE: PFS Data

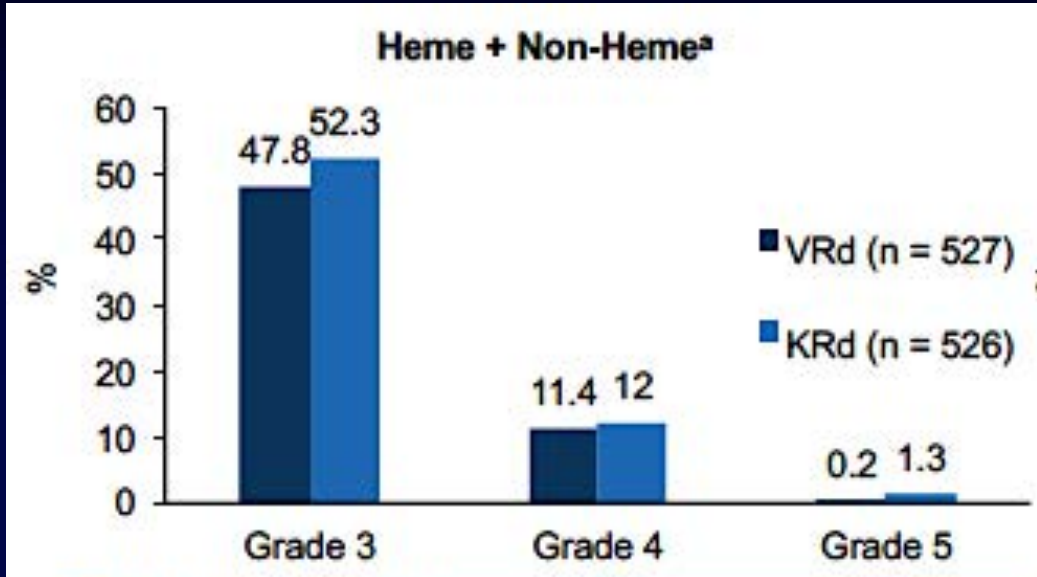


- Median PFS for patients ≥ 70 yrs
  - VRd: 37 mos (95% CI: 29-NE)
  - KRd: 28 mos (95% CI: 24-36)
- Median PFS with censoring at SCT or alternative treatment
  - VRd: 31.7 mos (95% CI: 28.5-44.6)
  - KRd: 32.8 mos (95% CI: 27.2-37.5)
- Median OS not reached in either arm (29-mo median follow-up)
  - HR: 0.98 (95% CI: 0.71-1.36; *P* = .923)
- 3-yr OS rate
  - VRd: 84% (95% CI: 80%-88%)
  - KRd: 86% (95% CI: 82%- 89%)

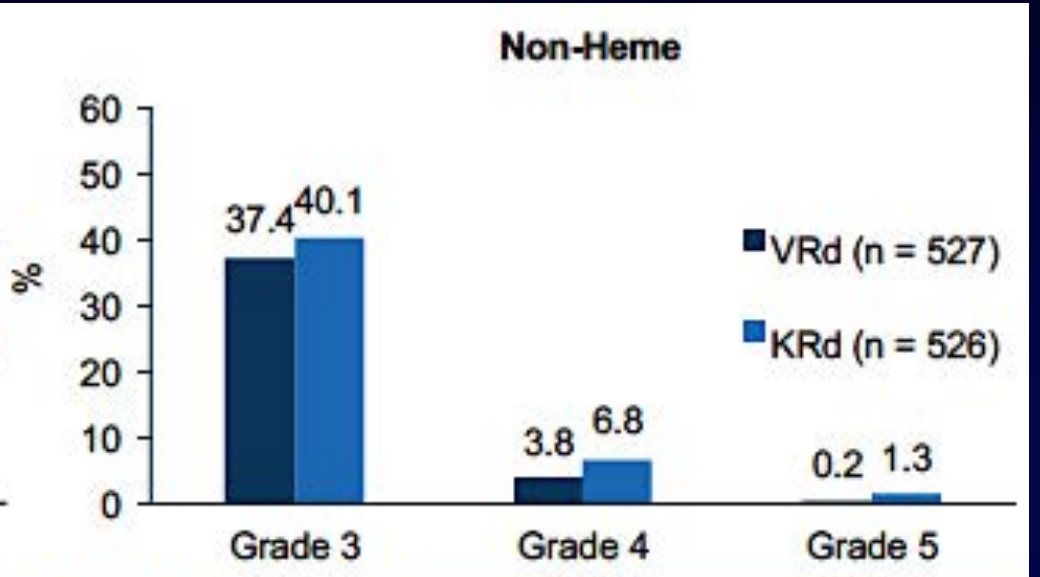
Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

ENDURANCE: Adverse Events



Step 1 Treated Patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-RVd	Chi Square *P*
Grades 3-5	313 (59.4)	345 (65.6)	6.2	.038
(95% CI)	(55.1-63.6)	(61.3-69.6)		
Grades 4-5	61 (11.6)	70 (13.3)	1.7	.394
(95% CI)	(9.0-14.6)	(10.5-16.5)		



Step 1 Treated Patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-RVd	Chi Square *P*
Grades 3-5	218 (41.4)	254 (48.3)	6.9	.024
(95% CI)	(37.1-45.7)	(44.0-52.6)		
Grades 4-5	21 (4.0)	43 (8.2)	4.2	.004
(95% CI)	(2.5-6.1)	(6.0-10.9)		

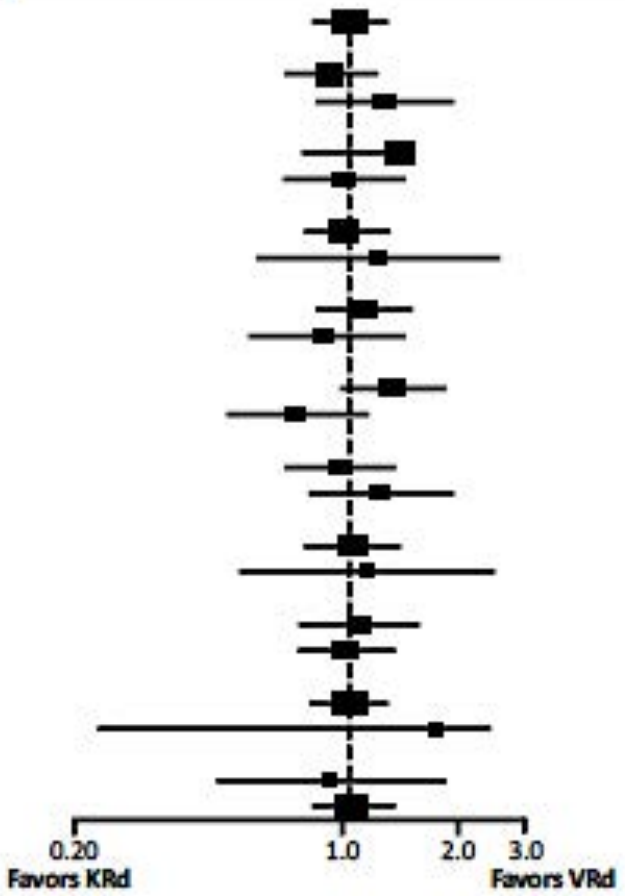
Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

ENDURANCE: Subgroups

Subgroup	Patients/Events, n	Treatment HR (KRd/VRD)
Overall	1087/298	1.04 (0.83-1.31)
Age		
< 70 yrs	743/199	0.93 (0.71-1.23)
≥ 70 yrs	344/99	1.29 (0.86-1.94)
Sex		
Male	642/182	1.04 (0.77-1.39)
Female	445/116	1.01 (0.70-1.45)
Race		
White	891/254	1.02 (0.80-1.31)
Non-white	152/31	1.24 (0.60-2.56)
ISS stage		
I/II	711/186	1.14 (0.85-1.52)
III	243/71	0.90 (0.57-1.44)
Cytogenetics		
Normal	657/166	1.35 (0.99-1.64)
Abnormal	255/93	0.75 (0.50-1.15)
13q status		
Absent	534/146	0.98 (0.71-1.36)
Present	316/85	1.25 (0.81-1.94)
t(4;14) status		
Absent	770/203	1.07 (0.81-1.42)
Present	80/28	1.16 (0.54-2.47)
ECOG PS		
0	453/118	1.10 (0.77-1.59)
> 0	634/180	1.02 (0.76-1.36)
Creatinine		
< 2 mg/dL	1026/283	1.04 (0.82-1.31)
≥ 2 mg/dL	61/15	0.75 (0.23-2.42)
Measurable disease type		
Light chain MM	109/35	0.93 (0.47-1.84)
Non-light chain MM	978/263	1.05 (0.83-1.34)

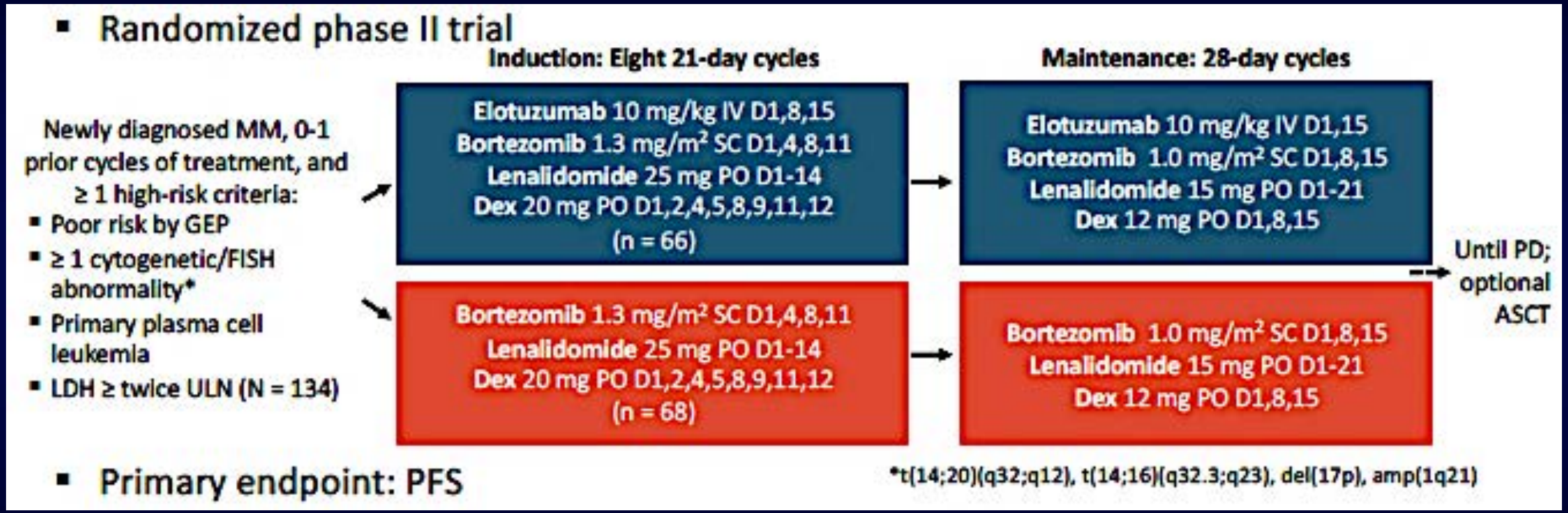
*Box size adjusted for number of events



Kumar, S et al. Lancet Oncol. 21: 1317, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

High Risk: SWOG-S1211 Trial



Usmani, S et al. ASCO Abstract 8507, 2020. Adapted from clinicaloptions.com.

Courtesy of Robert Z Orlowski, MD, PhD

SWOG-S1211: Response Rates & PFS

Response, n (%)	Elotuzumab + RVd (n = 47)	RVd (n = 50)
ORR	39 (83)	44 (88)
▪ ≥ CR	1 (2.1)	3 (6)
▪ VGPR	10 (21.3)	10 (20)
▪ PR	28 (59.6)	31 (62)
▪ uPR	2 (4.3)	3 (6)
▪ SD	6 (12.8)	3 (6)

Parameter	Elotuzumab + RVd (n = 48)	RVd (n = 52)	*P* Value
Median PFS, mos	31 (19-54)	34 (20-NR)	.449
▪ Events, n	31	31	—
Median OS, mos	68 (61-68)	NR	.239
▪ Deaths, n	16	19	—

- Median follow-up: 53 mos

Usmani, S et al. ASCO Abstract 8507, 2020. Adapted from clinicaloptions.com.

Courtesy of Robert Z Orlowski, MD, PhD

Dara for High Risk?

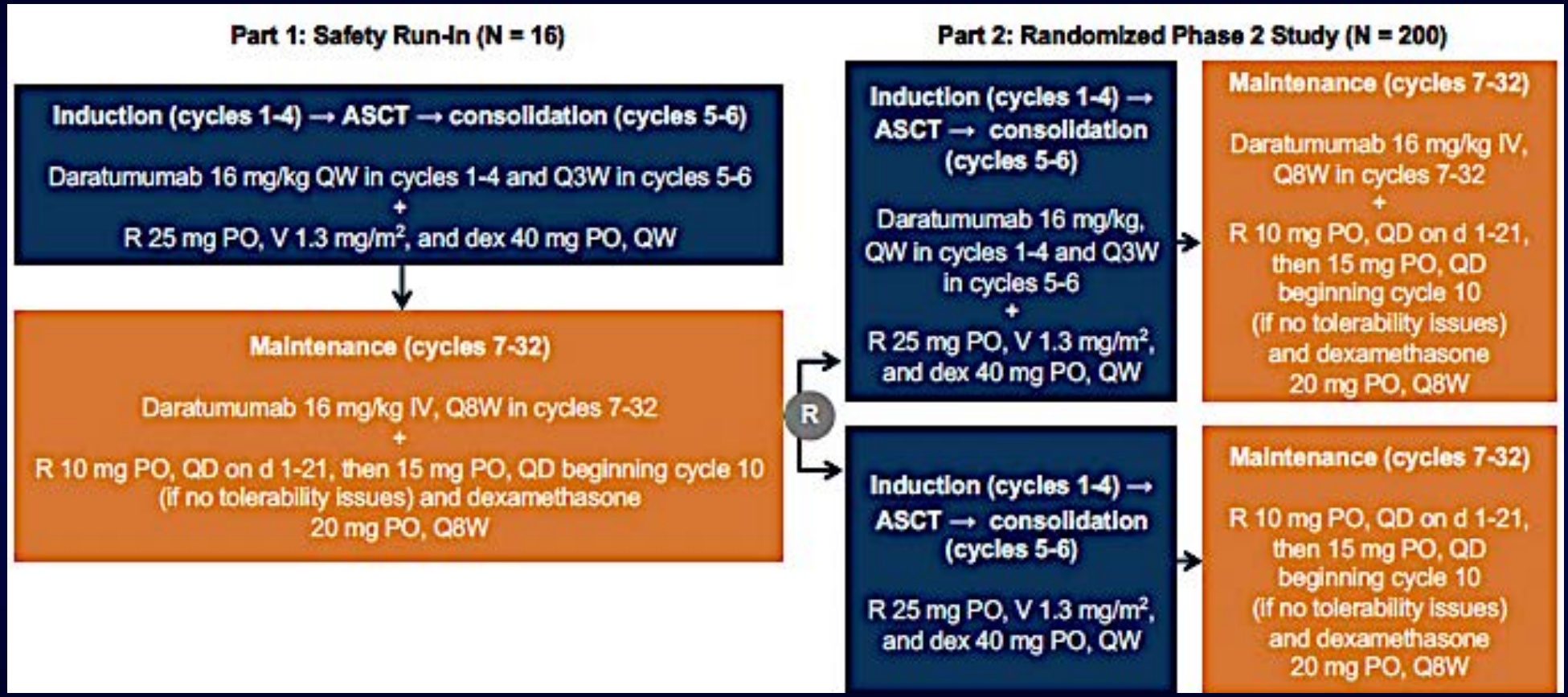
Study Name	Intervention	Control	Hazard Ratio	95% CI	p-Value
Alcyone	DaraVMP	VMP	0.78	0.43-1.42	0.42
Maia	DaraRD	RD	0.57	0.32-1.03	0.06
Cassiopeia	DaraVTD	VTD	0.67	0.35-1.29	0.23
Pooled Effect Size ($I^2$0%, Cochran's Q p = 0.77)			**0.67**	**0.47-0.95**	**0.025**
Castor	DaraVD	VD	0.41	0.21-0.83	0.01
Pollux	DaraRD	RD	0.37	0.18-0.76	0.01
Candor	DaraKD	KD	0.58	0.30-1.12	0.11
Pooled Effect Size (($I^2$0%, Cochrans Q p = 0.63)			**0.45**	**0.30-0.67**	**< 0.001**

358 NDMM patients

Giri, S et al. ASCO Abstract 8540, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

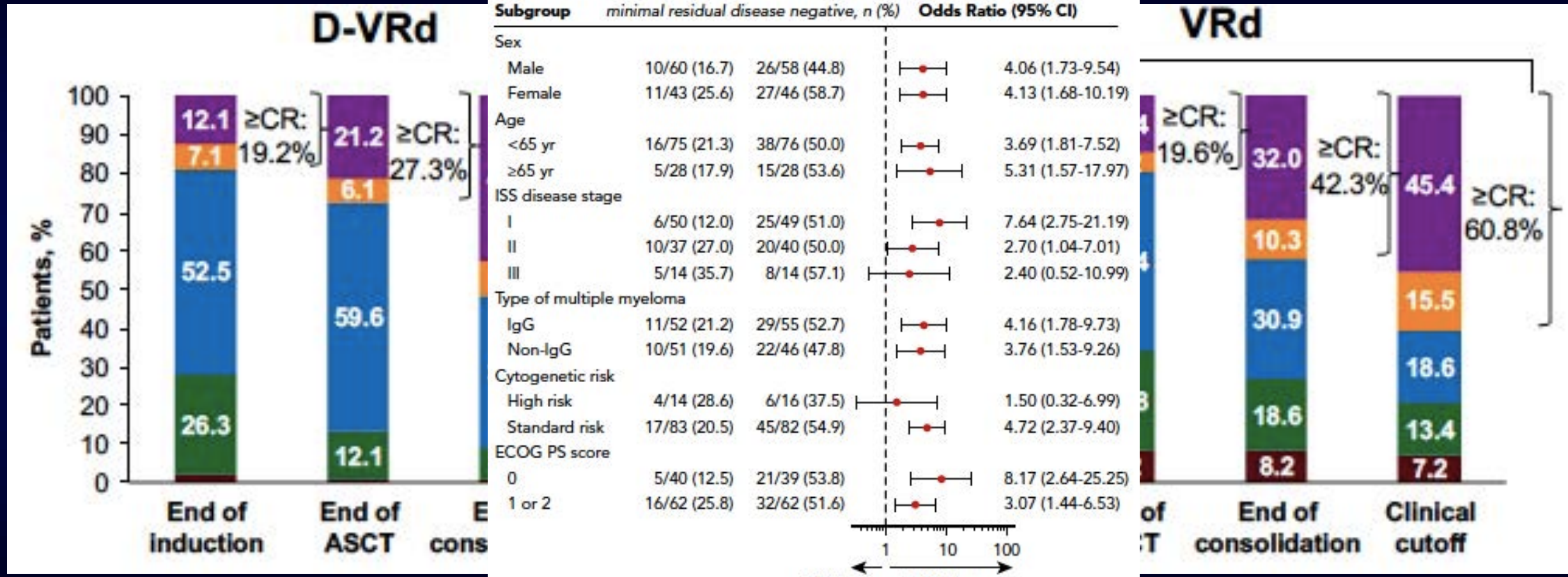
Griffin Trial



Voorhees, P et al. Blood 136: 936, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

Responses Over Time



Voorhees, P et al. Blood 136: 936, 2020.

Courtesy of Robert Z Orlowski, MD, PhD

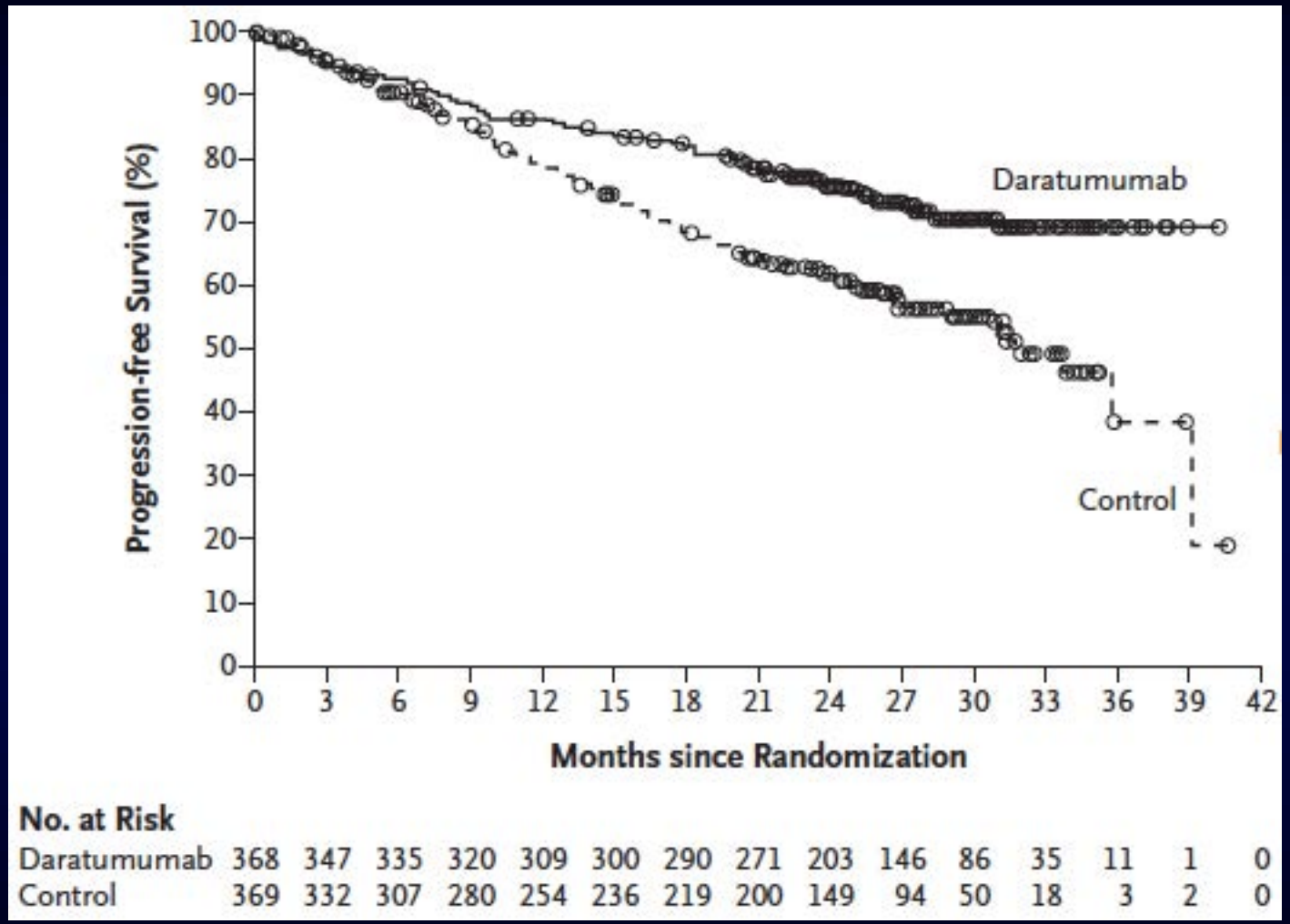
Transplant Eligible Patients

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1)[j] • Daratumumab[r]/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[k] • Bortezomib/cyclophosphamide/dexamethasone[θ]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Daratumumab[r]/bortezomib/melphalan/prednisone (category 1) • Daratumumab[r]/cyclophosphamide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[θ]

http://www.nccn.org/ Version 4.2020.

Courtesy of Robert Z Orlowski, MD, PhD

Dara/Len/dex: MAIA Data



Facon, T et al. N Engl J Med. 380: 2104, 2019.

Courtesy of Robert Z Orlowski, MD, PhD

But, Not All Triplets Are Superior

TOURMALINE-MM2[2]

TOURMALINE-MM2 (NCT01850524) is a randomized, double-blind, placebo-controlled phase III clinical trial evaluating IRd *vs* placebo plus Rd, in transplant-ineligible patients with NDMM (N = 705). The primary endpoint is PFS and secondary endpoints include complete response rate and OS.

The analysis demonstrated non-significant 13.5 months improvement in PFS in the IRd group *vs* Rd group (35.3 *vs* 21.8 months; HR 0.83; p = 0.073). The safety profile was generally consistent with previous reports.[5]

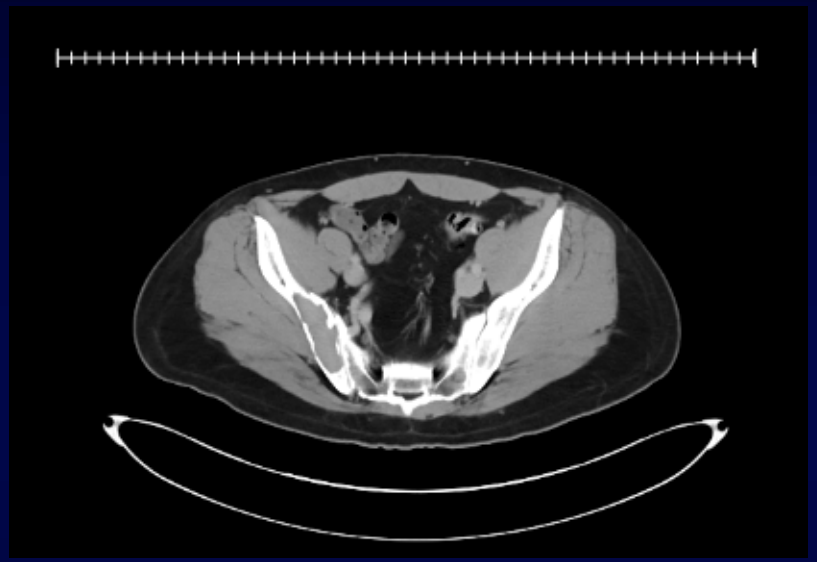
presented at a future medical meeting.

https://multiplemyelomahub.com/medical-information/eloquent-1-and-tourmaline-mm2-studies-report-no-improvement-in-pfs-in-patients-with-newly-diagnosed-mm

Courtesy of Robert Z Orlowski, MD, PhD

Case #1

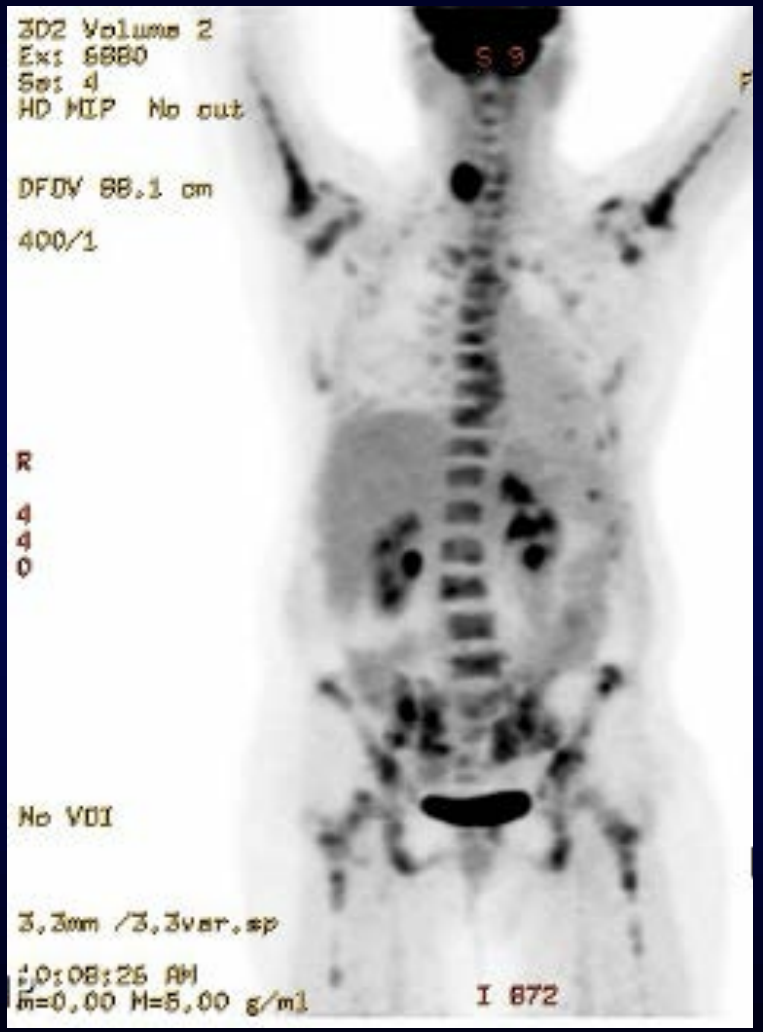
- 65 yo M p/w pelvic pain & fatigue
- Initial labs show anemia (Hgb 8.8)
- Imaging shows a pelvic lytic lesion
- Bone marrow 56% PCs, FISH del 17p
- Induction with VRd
- Followed by ASCT with BuMel preparative regimen
- Post-ASCT maintenance with ixazomib/lenalidomide



Courtesy of Robert Z Orlowski, MD, PhD

Case #2

- 83 yo F p/w foamy urine & bony aches
- Initial labs with 3.5 g protein in 24 hr urine
- Imaging shows multiple lytic lesions
- Bone marrow 44% PCs, FISH t(11;14)
- Induction with DRd
- Entered VGPR and therapy ongoing



Courtesy of Robert Z Orlowski, MD, PhD