Myeloma & Waldenstroms

Indianapolis Hematology Review

2020

Epidemiology

- Blacks > Whites
- Slight male predominance
- Median age: 65 years
- Monoclonal Gammopathy Undetermined Significance is a predisposing factor

Revised IMWG Criteria

- <10% BMPC AND
- <3 gm/dL M protein AND
- No MDE

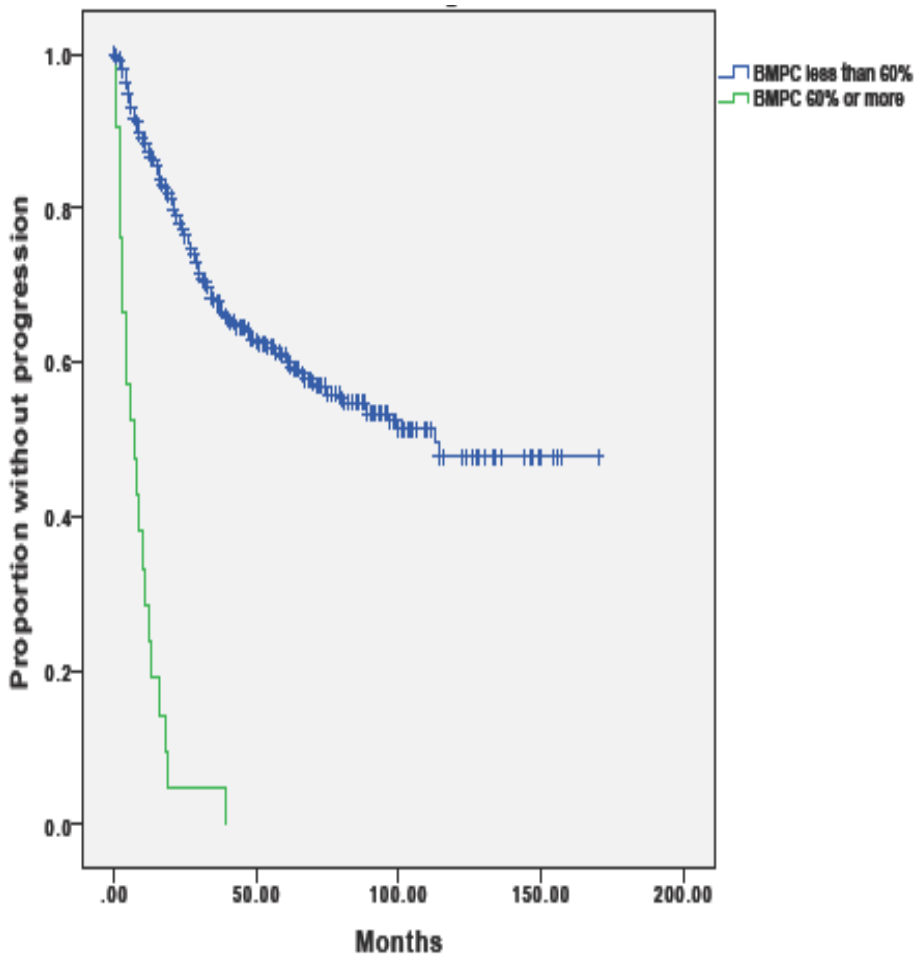
- ≥10%-60% BMPC OR
- ≥3 gm/dL S. M protein OR
- ≥500 mg/24h Ur. M protein AND
- No MDE

- PCPD, AND
- 1 or more MDE
  CRAB
  - ≥60% BMPC
  - ≥100 FLC ratio
  - >1 MRI focal lesion

Rajkumar SV, Dimopoulos M, Palumbo A, et al. Lancet Oncol. 2014;15(12):e538-e548.

MDE, myeloma-defining events

Bone Marrow Plasma Cell ≥60%

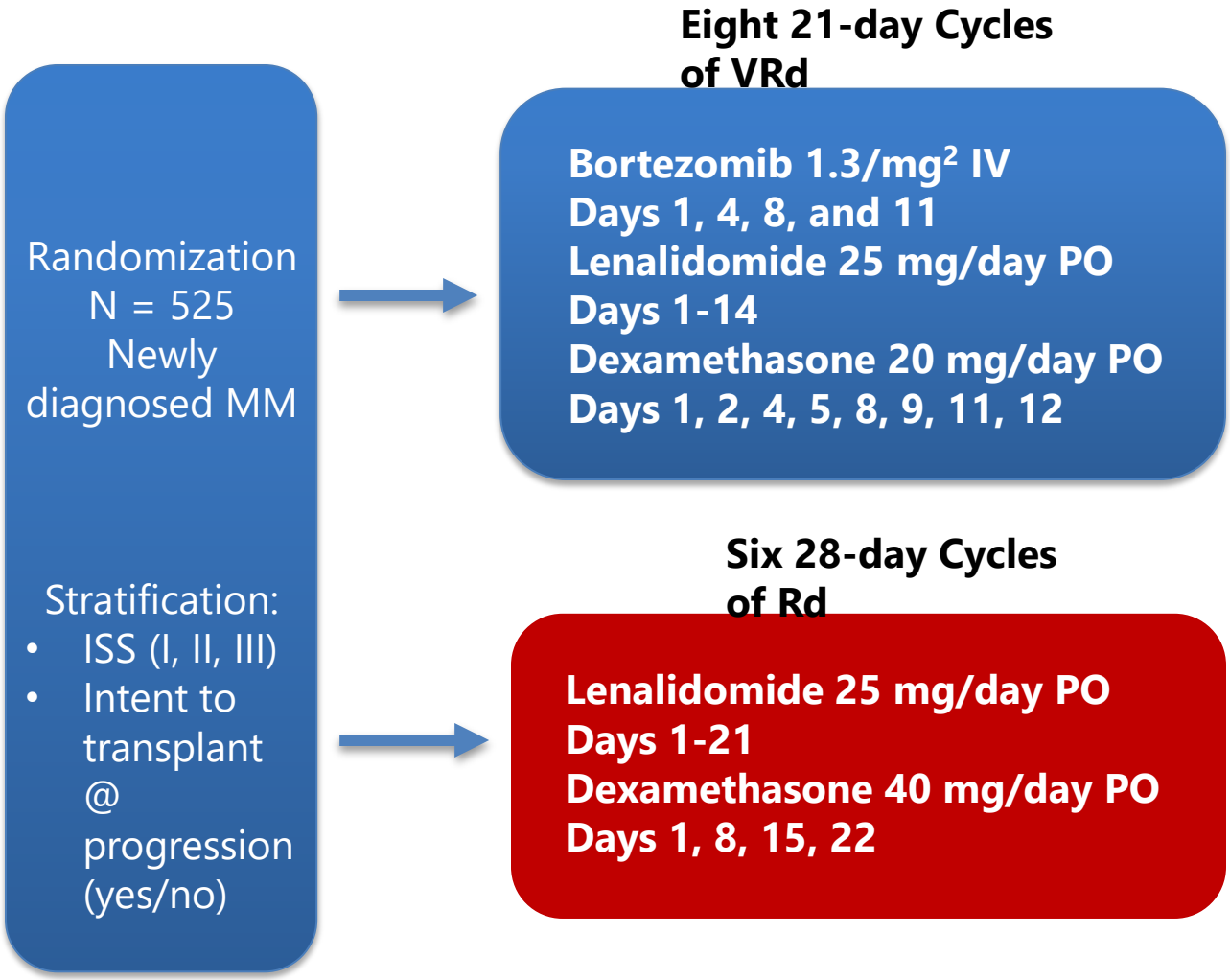


Rajkumar SV et al. N Engl J Med 2011; N Engl J Med 2011; 365:474-475

Common Regimens in Newly Diagnosed MM

- VRd
- DRd
- VCd (CyBorD)
- VTD
- Rd
- KRd

SWOG VRd vs Rd

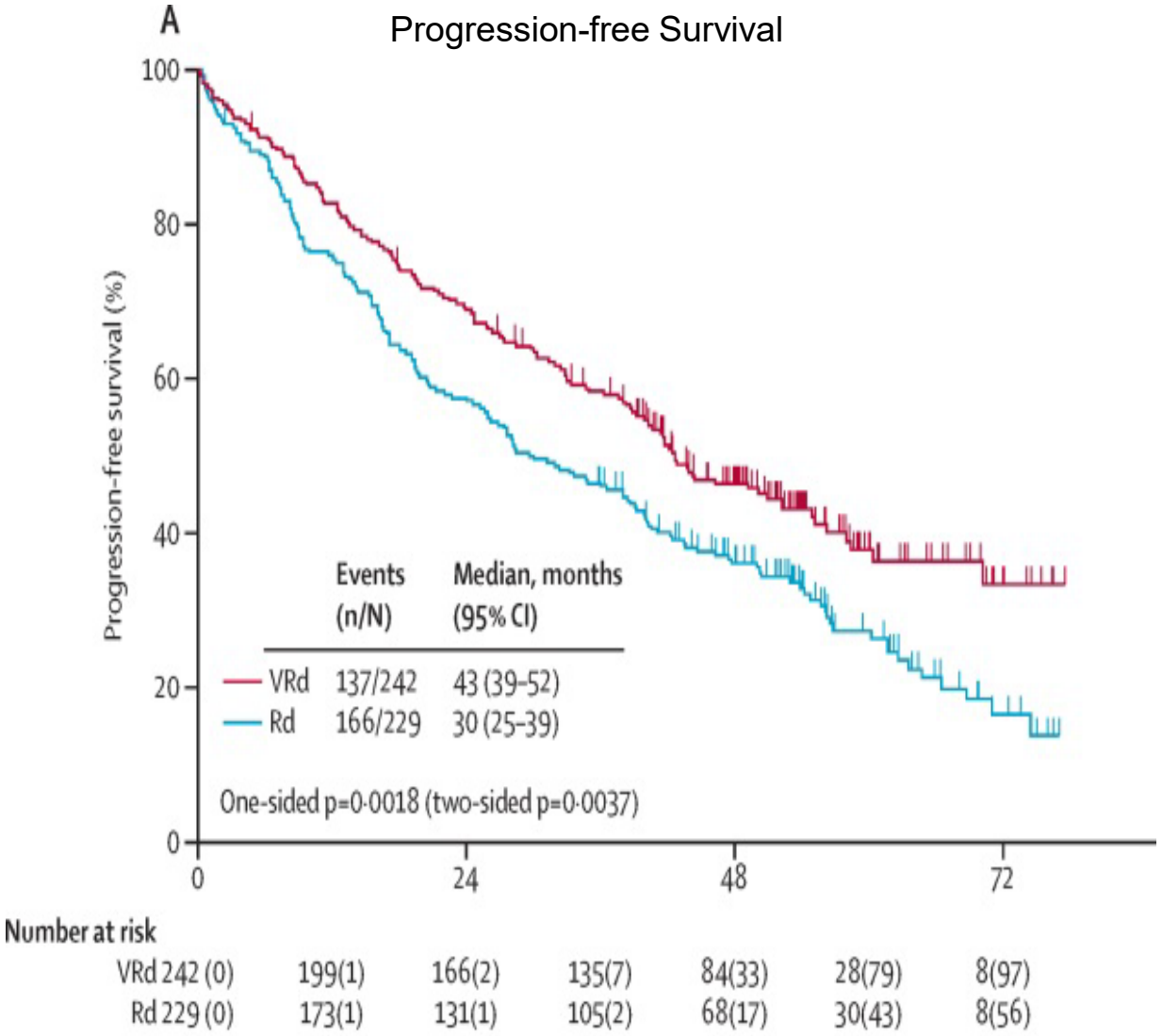


After induction; Both arms recevied Rd Maintenance Until PD, Toxicity or Withdrawal

Durie BGM, et al. ASH 2015

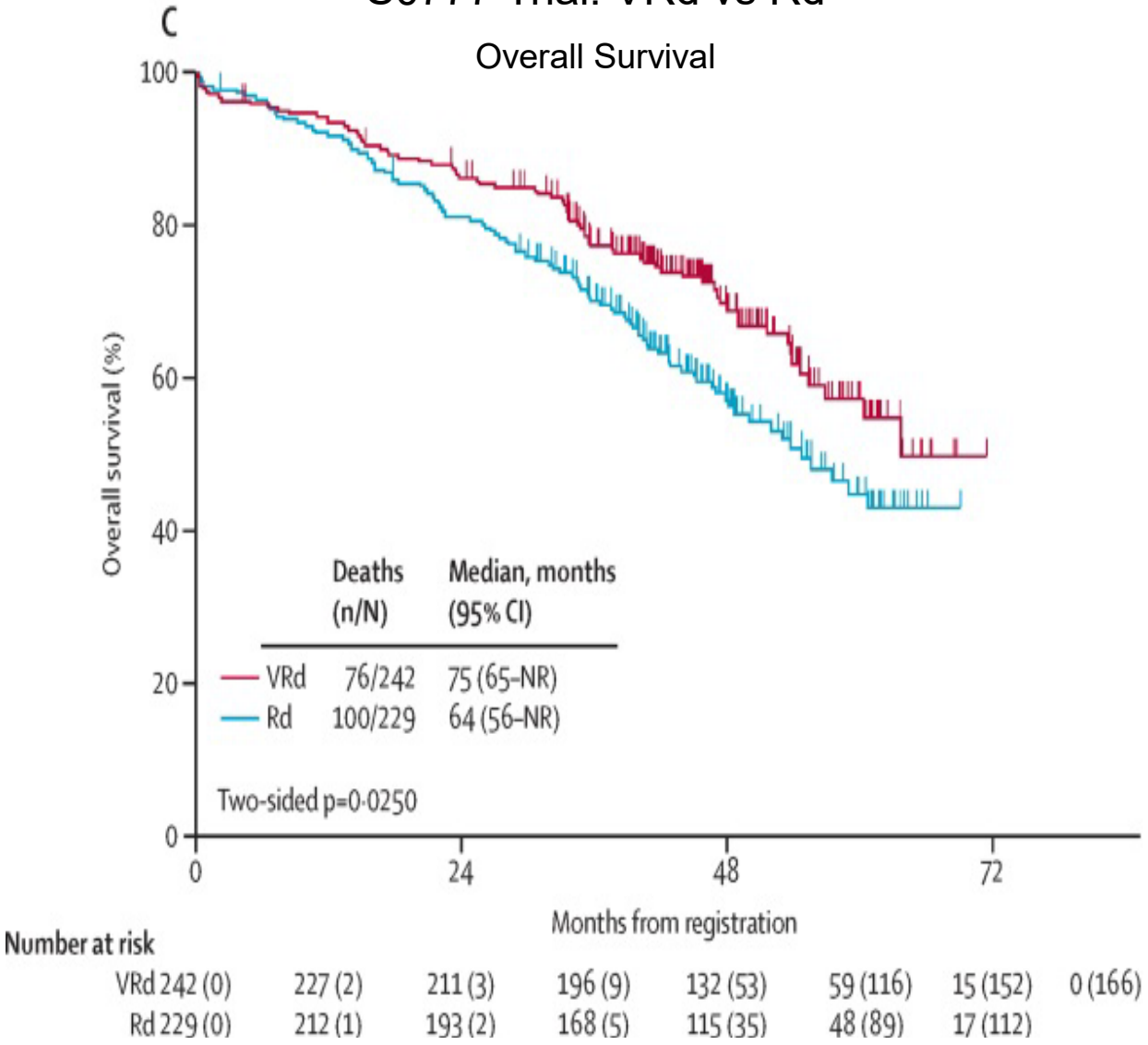
NCI National Clinical Trials Network
a National Cancer Institute program

S0777 Trial: VRd vs Rd



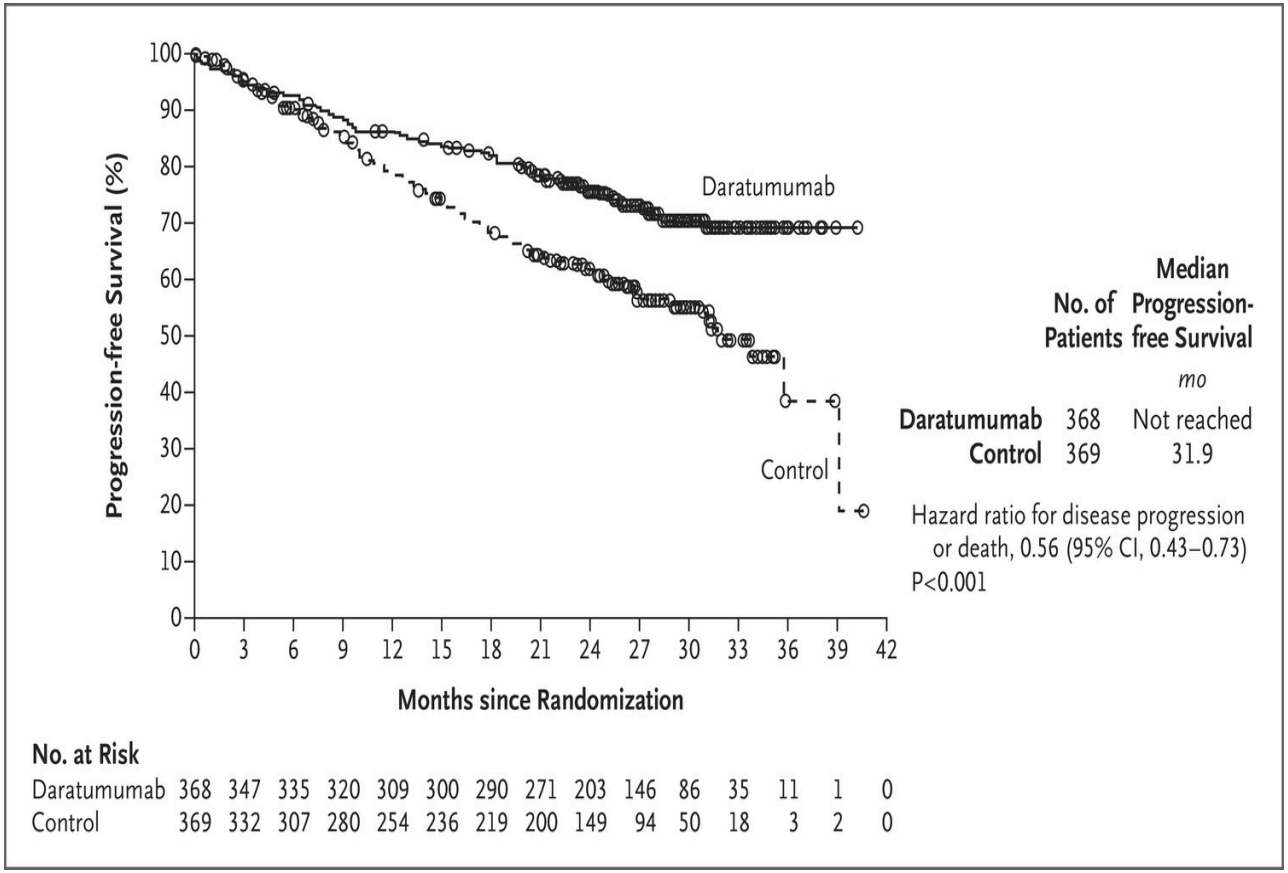
Durie et al. The Lancet 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)

S0777 Trial: VRd vs Rd



Durie et al. The Lancet 2017 389, 519-527DOI: (10.1016/S0140-6736(16)31594-X)

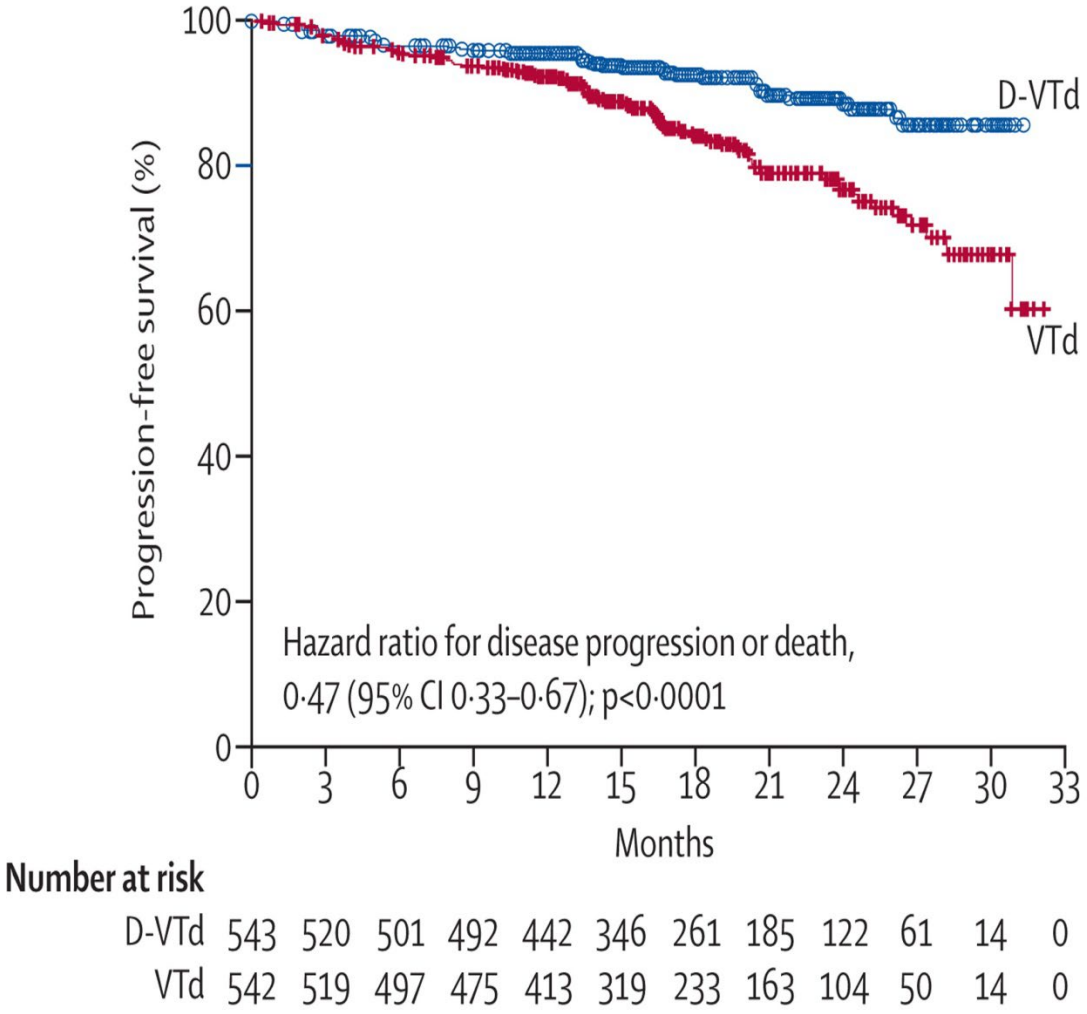
Dara-Rd vs Rd (MAIA trial): PFS



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

The NEW ENGLAND JOURNAL of MEDICINE

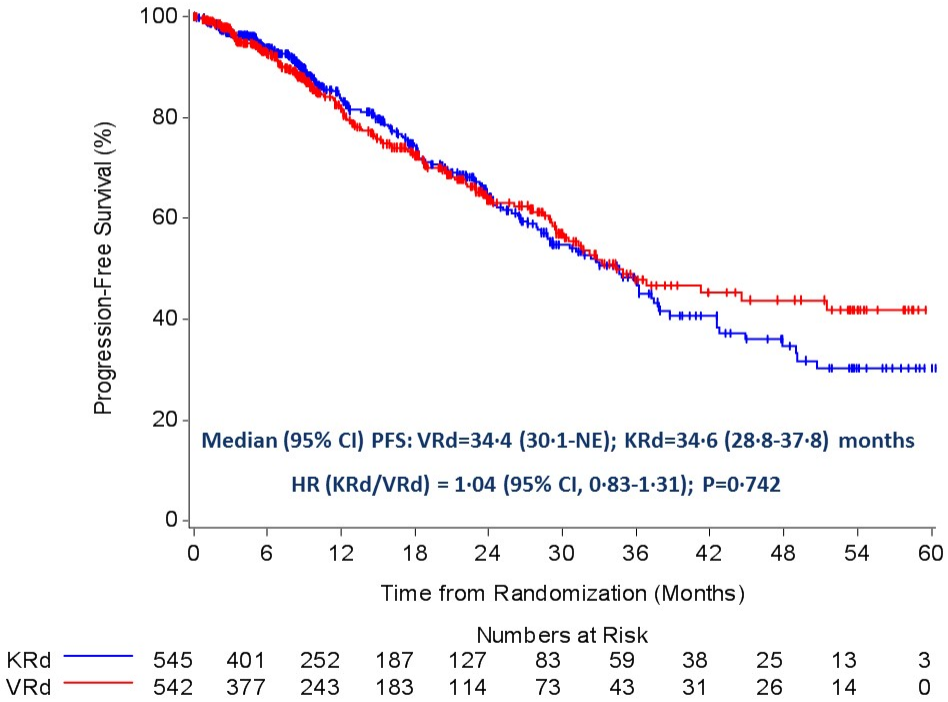
Dara-VTd vs VTd (CASSIOPEIA trial): PFS



Moreau et al.

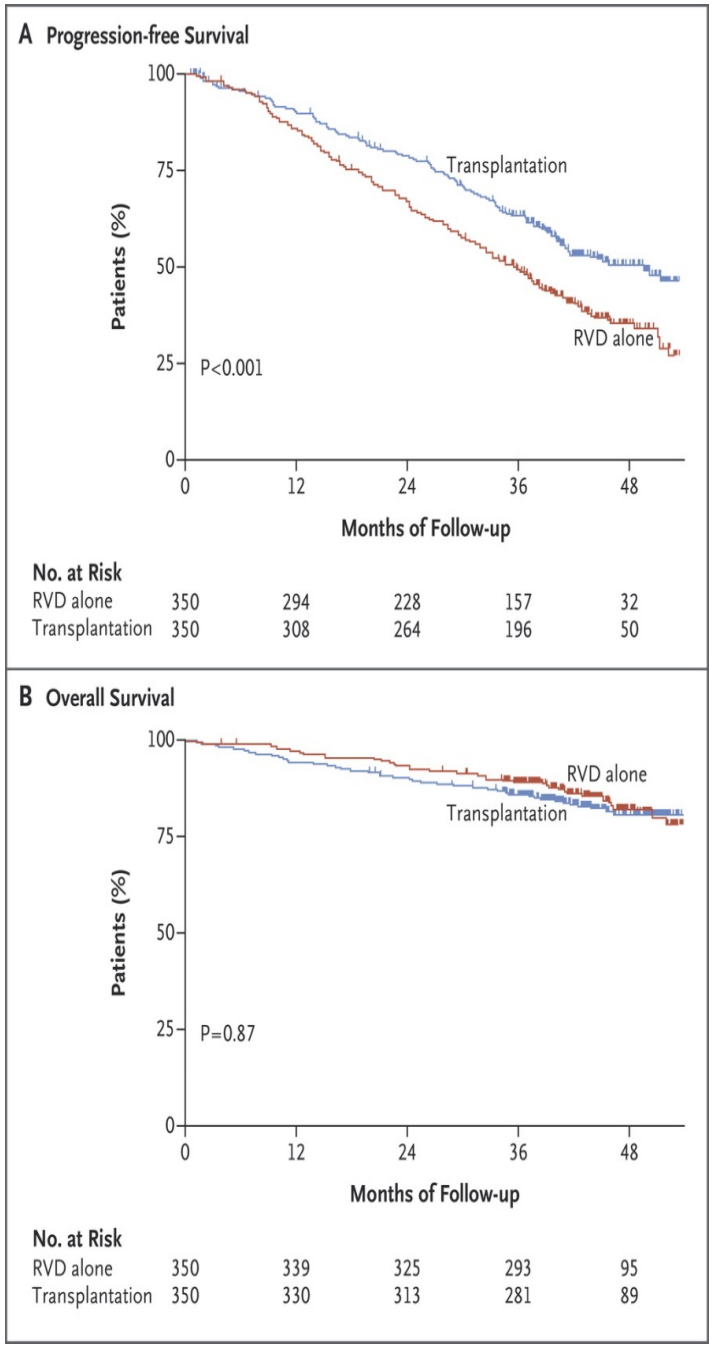
The Lancet DOI: (10.1016/S0140-6736(19)31240-1)

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

ROLE OF TRANSPLANT



Progression-free Survival and Overall Survival with ASCT in Myeloma

Attal M et al. N Engl J Med 2017;376:1311-1320.

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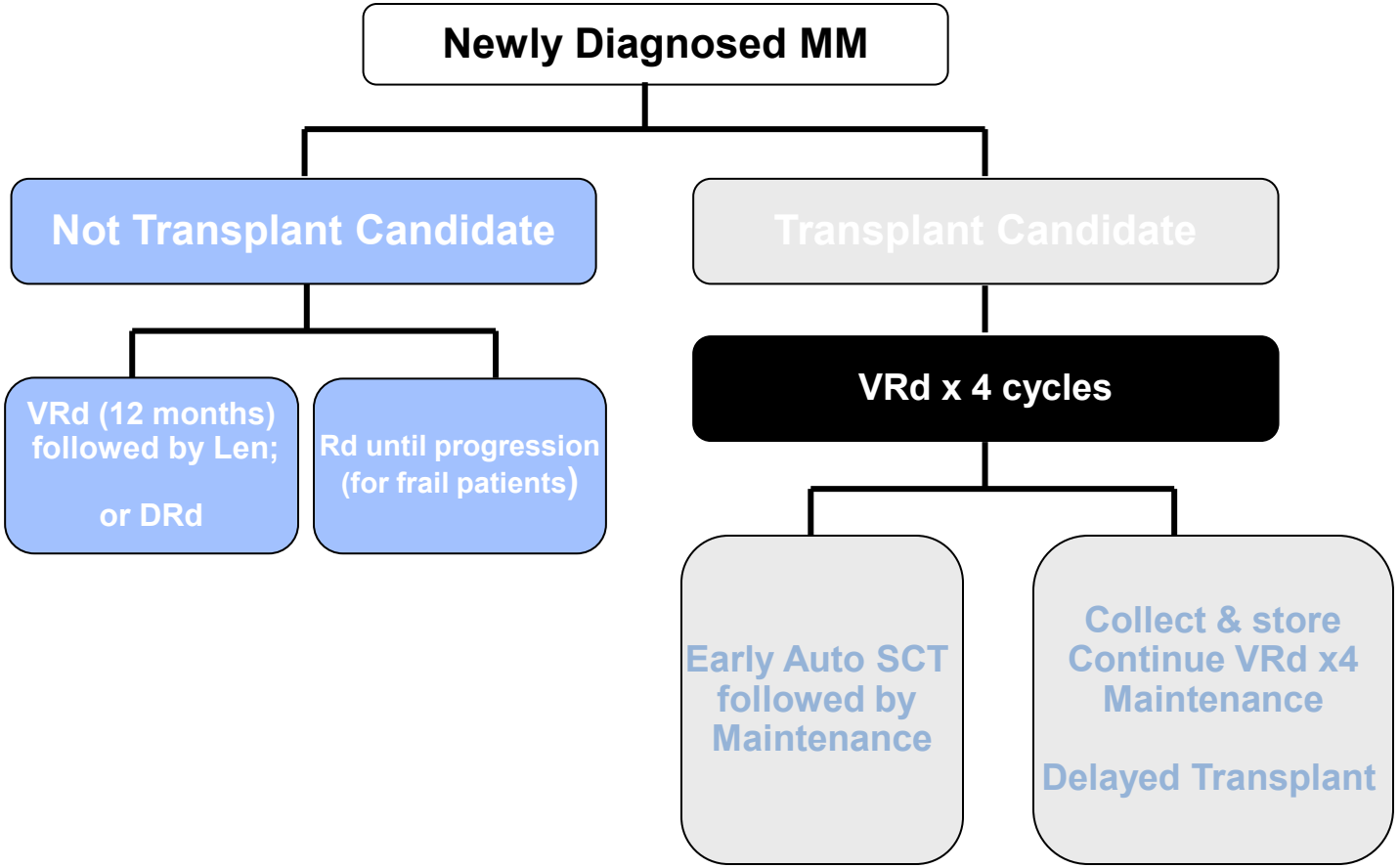
Initial Treatment of Myeloma

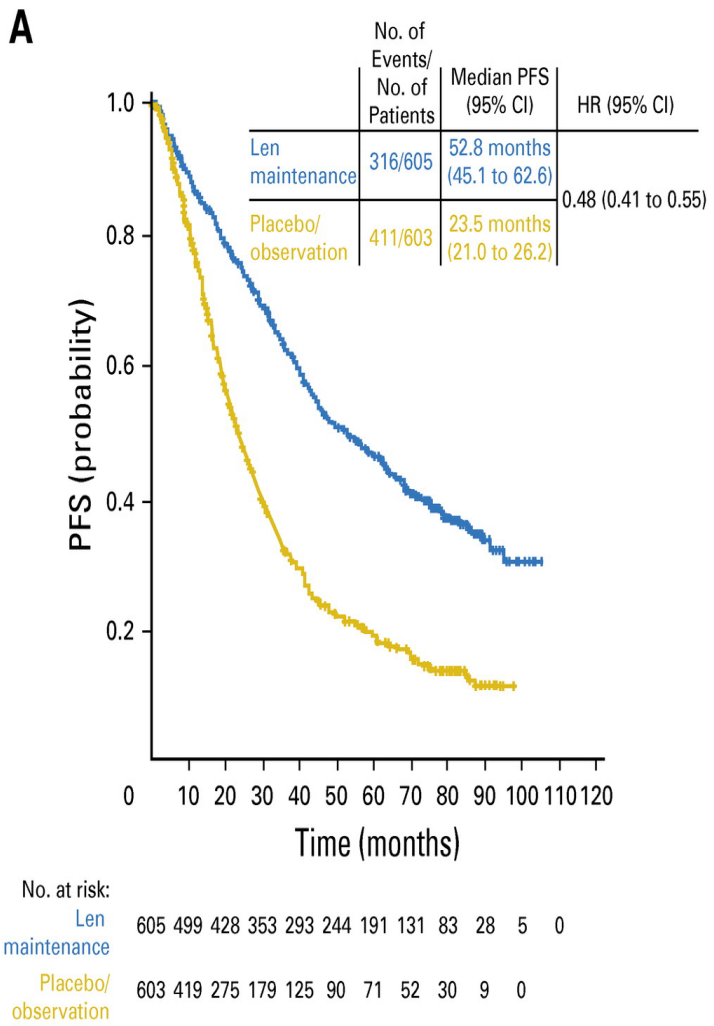


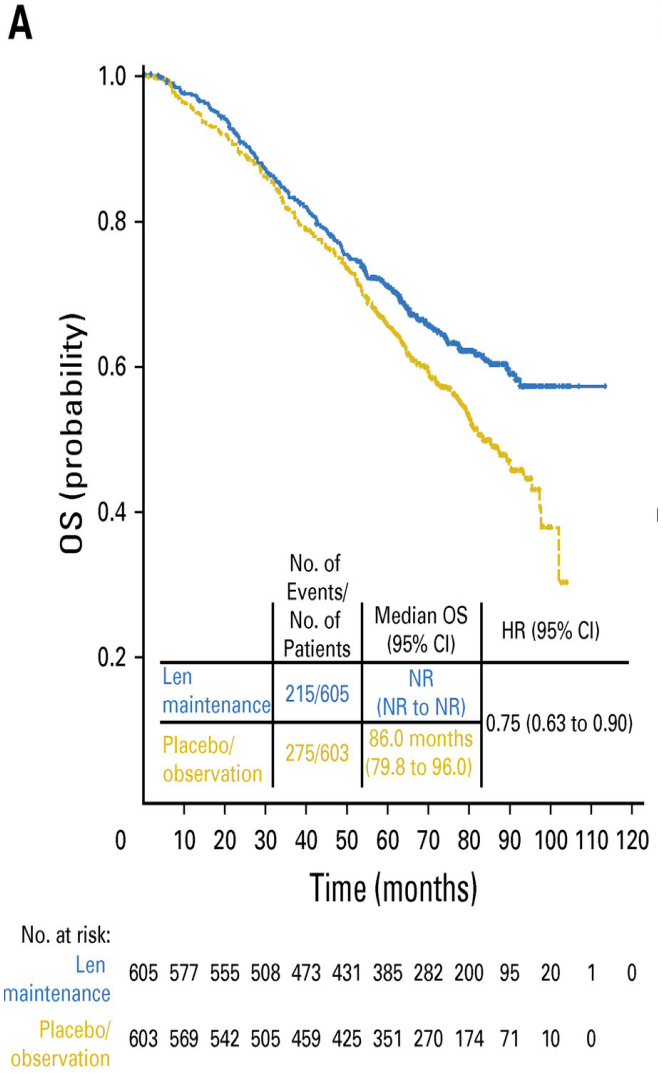
Rajkumar SV. 2019

MAINTENANCE THERAPY

Lenalidomide Maintenance Meta-analysis

PFS and OS





Published in: Philip L. McCarthy; et al. JCO 2017, 35, 3279-3289.
DOI: 10.1200/JCO.2017.72.6679

RELAPSED MYELOMA

Active Drugs in Multiple Myeloma

Old Drugs	Drugs approved 2003-2007	Drugs Approved 2013-2015
▪ Alkylators ▪ Steroids ▪ Interferon ▪ Anthracyclines	▪ **Bortezomib** ▪ **Thalidomide** ▪ **Lenalidomide**	▪ Carfilzomib ▪ Ixazomib ▪ Pomalidomide ▪ Daratumumab ▪ Panobinostat ▪ Elotuzumab ▪ Selinixor

Rajkumar SV. 2018

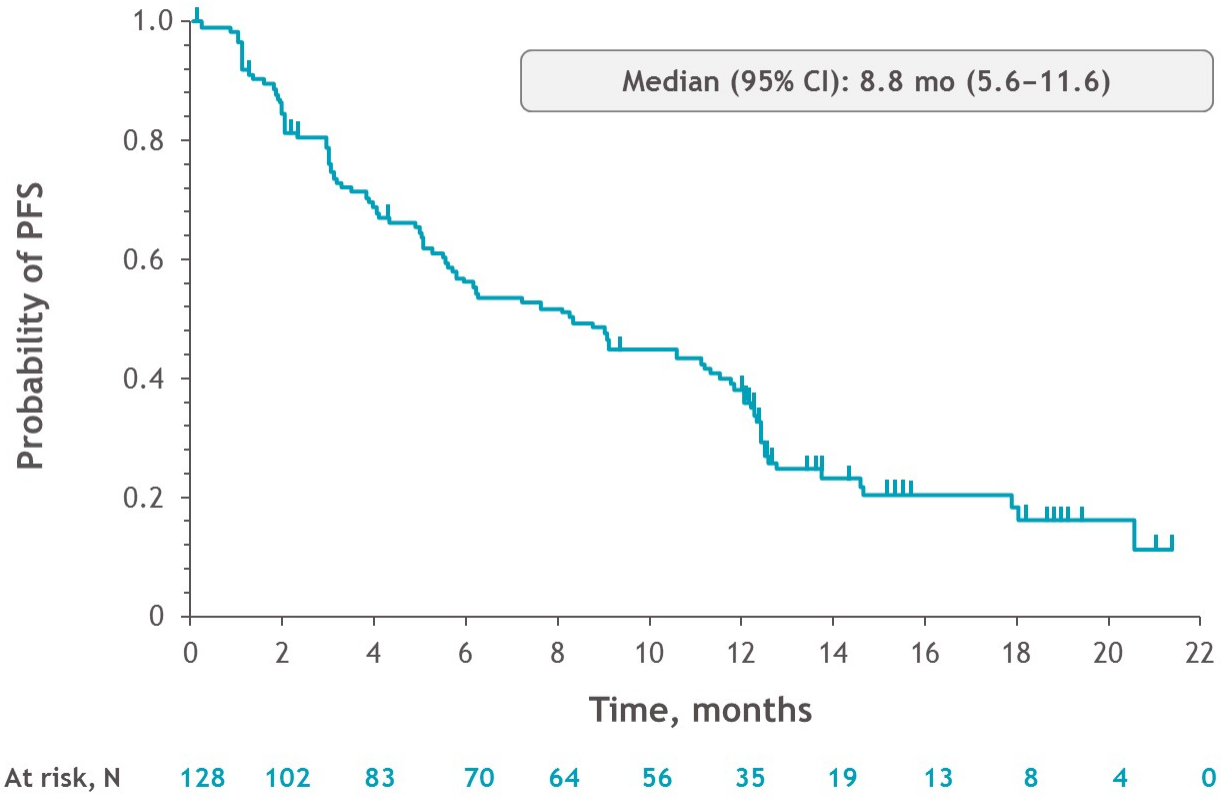
Table 1. Results of New Regimens for the Treatment of Relapsed Multiple Myeloma.*

Trial and Regimen†	Complete Response	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	P Value
	% of patients	*mo*		
Lenalidomide-based regimen				
TOURMALINE-MM1[6]			0.74 (0.59–0.94)	0.01
Lenalidomide–dexamethasone	7	14.7		
Ixazomib–lenalidomide–dexamethasone	12	20.6		
ELOQUENT-2[7]			0.70 (0.57–0.85)	<0.001
Lenalidomide–dexamethasone	7	14.9		
Elotuzumab–lenalidomide–dexamethasone	4	19.4		
ASPIRE[4]			0.69 (0.57–0.83)	<0.001
Lenalidomide–dexamethasone	14	17.6		
Carfilzomib–lenalidomide–dexamethasone	32	26.3		
POLLUX[10]			0.37 (0.27–0.52)	<0.001
Lenalidomide–dexamethasone	19	18.4		
Daratumumab–lenalidomide–dexamethasone	43	NR		
Bortezomib-based regimen				
PANORAMA1[5]			0.63 (0.52–0.76)	<0.001
Bortezomib–dexamethasone	6	8.1		
Panobinostat–bortezomib–dexamethasone	11	12.0		
CASTOR[9]			0.39 (0.28–0.53)	<0.001
Bortezomib–dexamethasone	9	7.2		
Daratumumab–bortezomib–dexamethasone	19	NR		

Rajkumar SV, Kyle RA. N Engl J Med 2016;375:1390-1392.

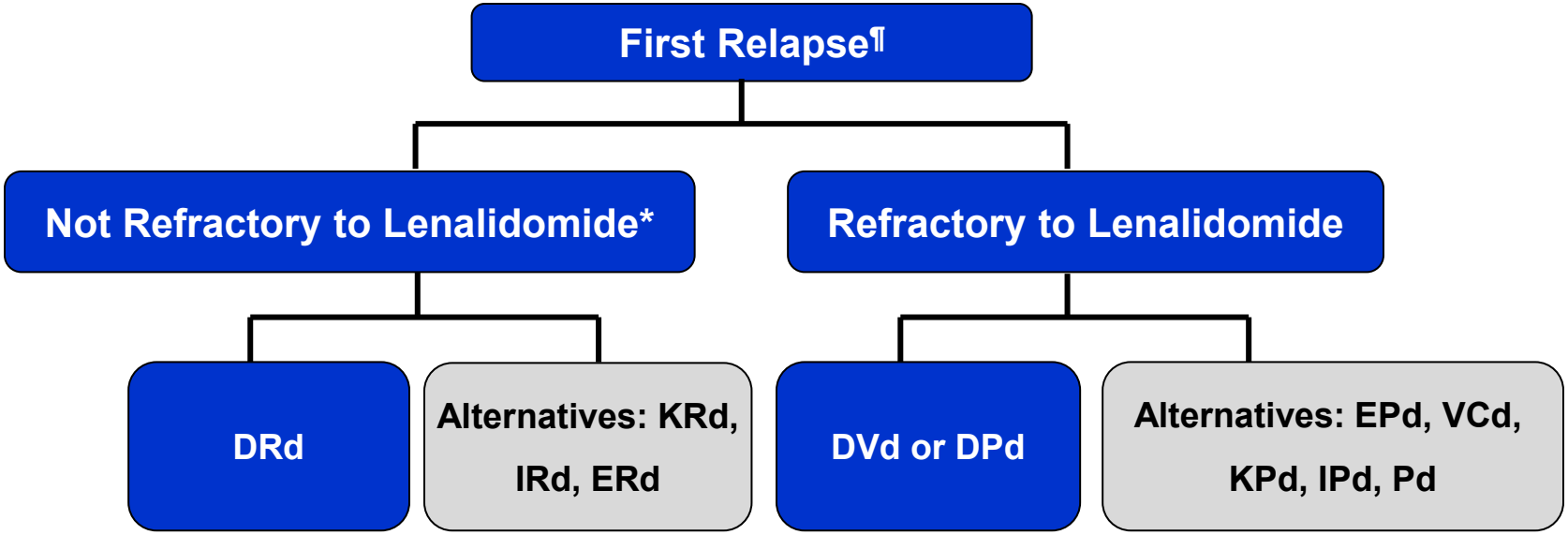
The NEW ENGLAND JOURNAL of MEDICINE

Progression-Free Survival



Data cutoff: 14 Jan 2020. PFS, progression-free survival.

Myeloma: First Relapse

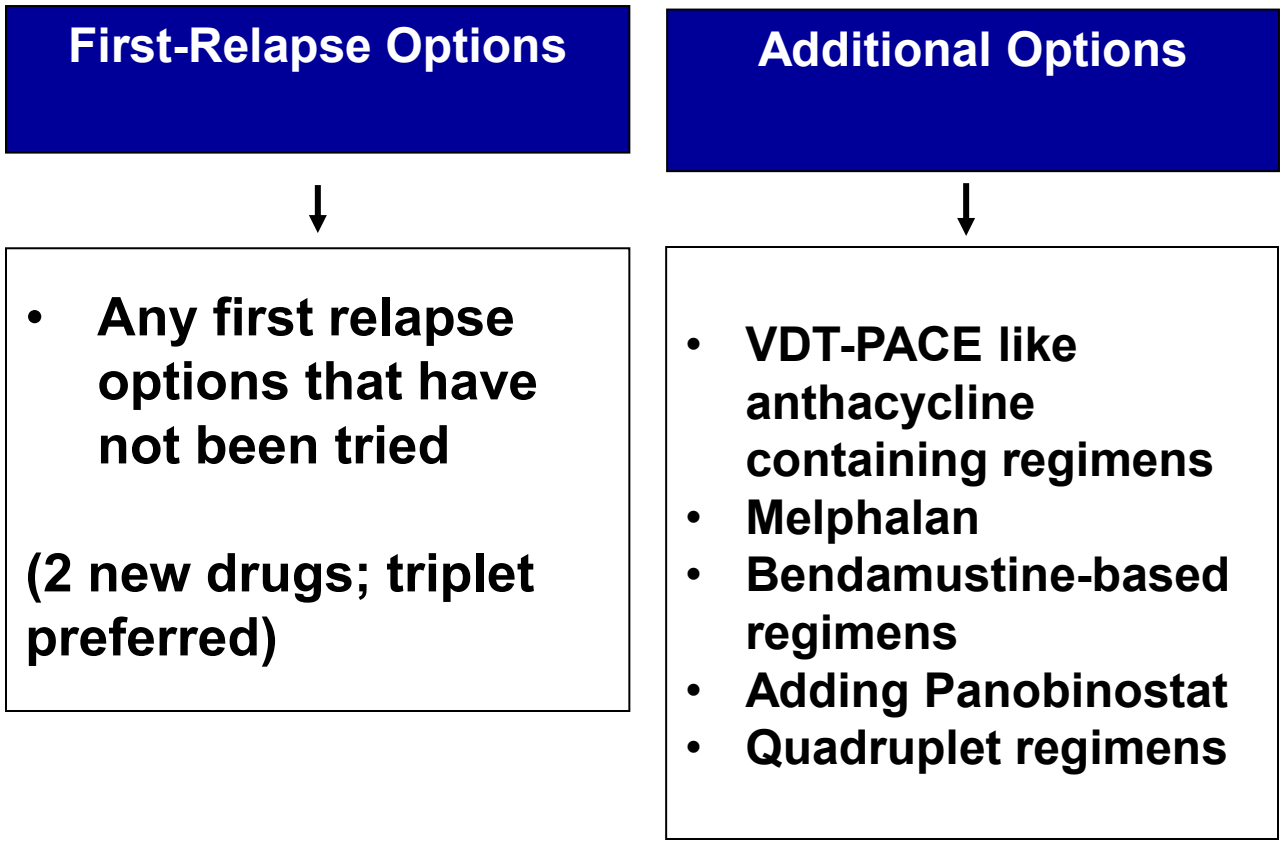


*Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

¶ Consider salvage auto transplant in eligible patients

Rajkumar SV, Kyle RA. Progress in Myeloma: A Monoclonal Breakthrough. N Engl J Med 2016;375:1390-1392

Myeloma: Second or higher relapse



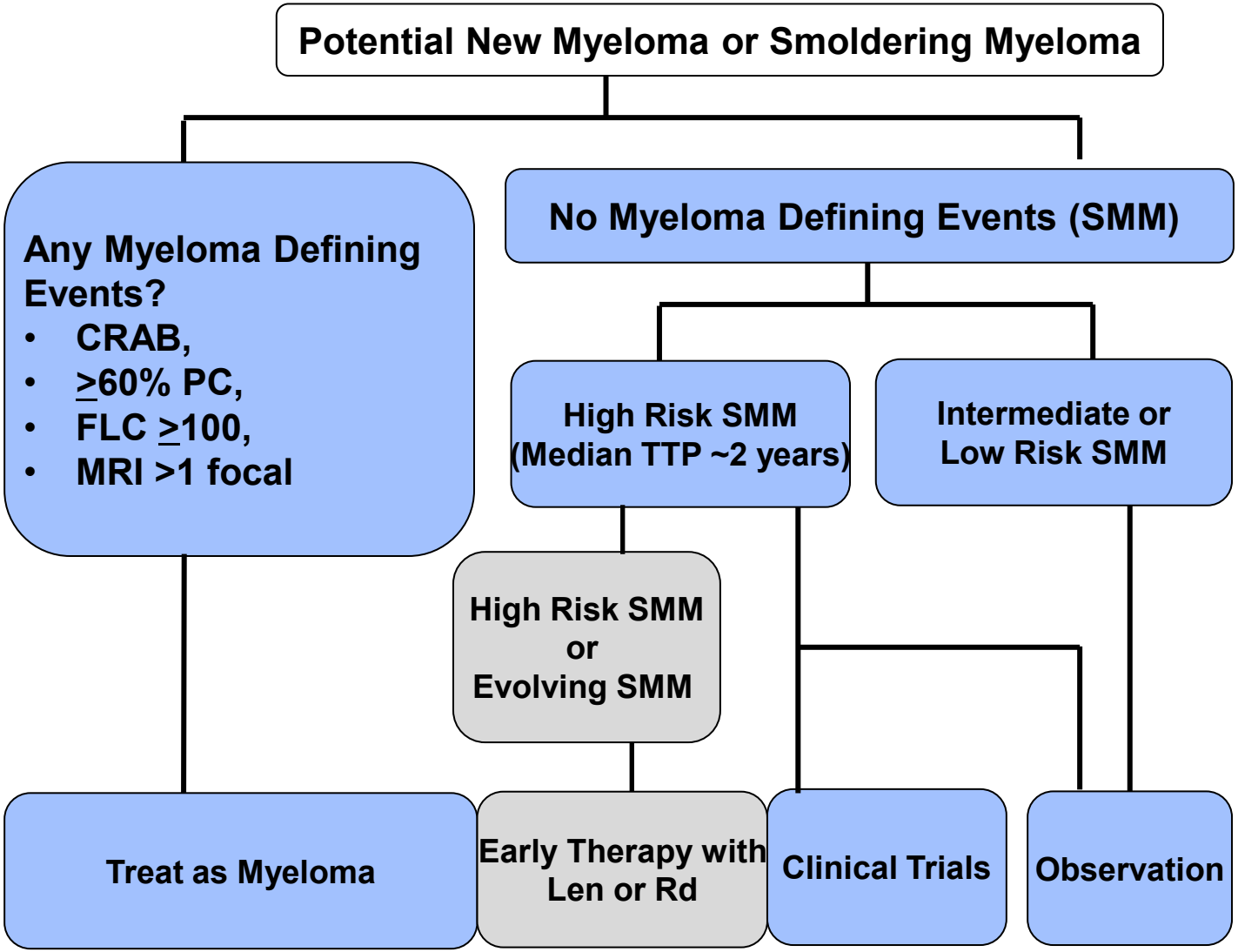
Management of MGUS

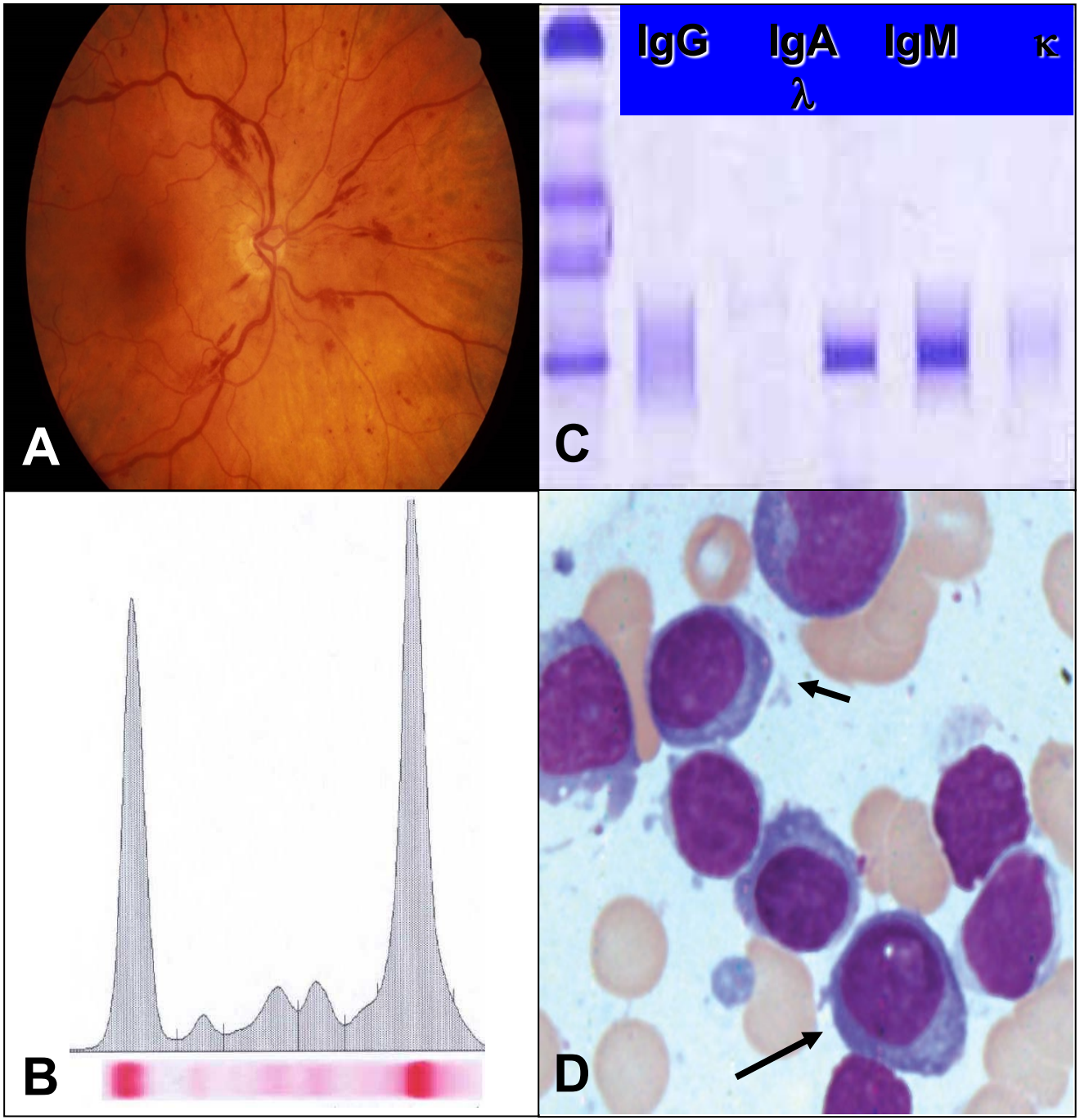
IgM MGUS	Low risk Non-IgM MGUS	All other MGUS
• Can omit BM Biopsy if <1.5 gm/dl & uncomplicated • Can omit bone imaging • Follow up in 6 months • Then, at time of symptoms	• Can omit BM Biopsy • Can omit bone imaging • Follow up in 6 months • Then, at time of symptoms	• Bone marrow biopsy • Bone imaging • Follow up in 6 months • Once yearly thereafter

*IgG, <1.5gm/dL, Normal FLC ratio; or free light chain only MGUS with FLC ratio <8

Rajkumar SV. Up To Date; Rajan AM, Rajkumar SV. Eur J Haematol 2014; Eur J Haematol. 2013 Dec;91(6):561-2

When Should Treatment Be Initiated?




A
IgG
IgA
IgM
κ
λ
C
B
D

MACROGLOBULINEMIA Definitions

	Monoclonal Serum IgM	Marrow Infiltration	Sx. Due to IgM Protein	Sx due to Tumor Mass
WM Symptomatic	+	+	+	+
WM Smoldering	+	+	-	-
IgM related disorder	+	-	+	-
MGUS	+	-	-	-

Bendamustine

- 41 patients with WM, of whom 22 received bendamustine and rituximab and 19 received R-CHOP
- In both groups, the response rate was 95%
- The median PFS for R-CHOP was 36 mo Vs not reached with bendamustine and rituximab ($P<.0001$). At analysis, 4 relapses (18%) in the bendamustine and R group & 11 relapses (58%) in the R-CHOP group

Lancet. 2013 Feb 19

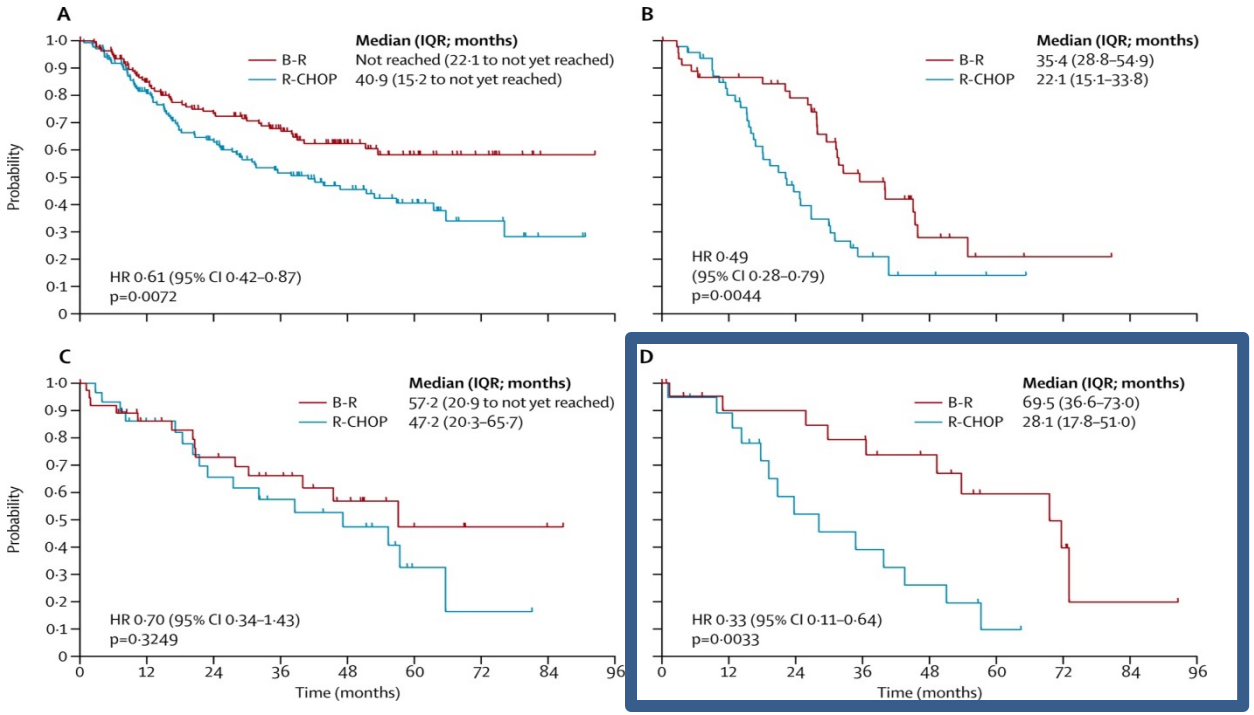


Figure 3 Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D) B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Mathias J Rummel , Norbert Niederle , Georg Maschmeyer , G Andre Banat , Ulrich von Gr?nhagen , Christoph Losem , ...

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

The Lancet null 2013 null

http://dx.doi.org/10.1016/S0140-6736(12)61763-2

BortDR Response Assessment

N = 23

Overall Responses

- CR: 3 (13%)
- nCR 2 (9%)
- VGPR: 3 (10%)
- PR: 11 (48%)
- MR: 3 (13%)

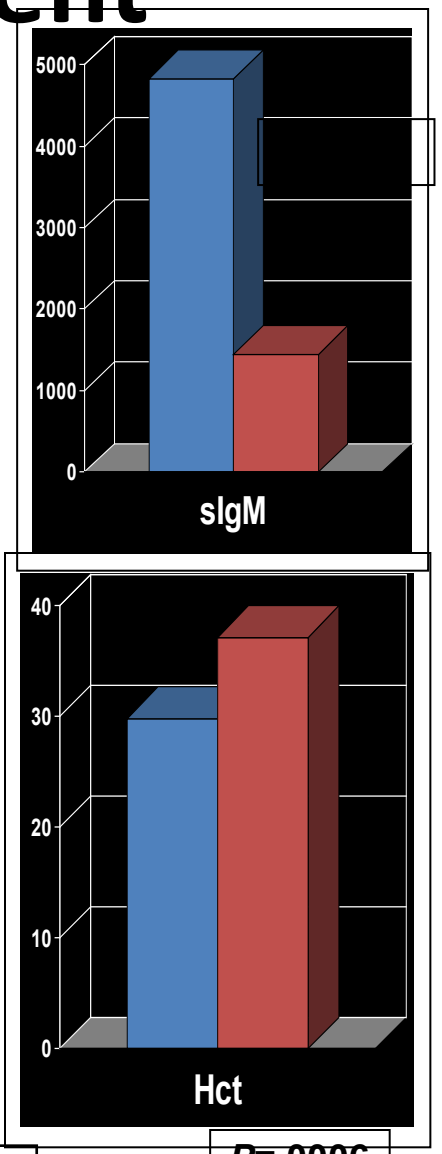
83%

91%

Median time to response 1.4 months

With a median follow-up of 22.8 months (range, 3.3 to 33.2 months), all patients are alive

18/23 patients remain free of disease progression

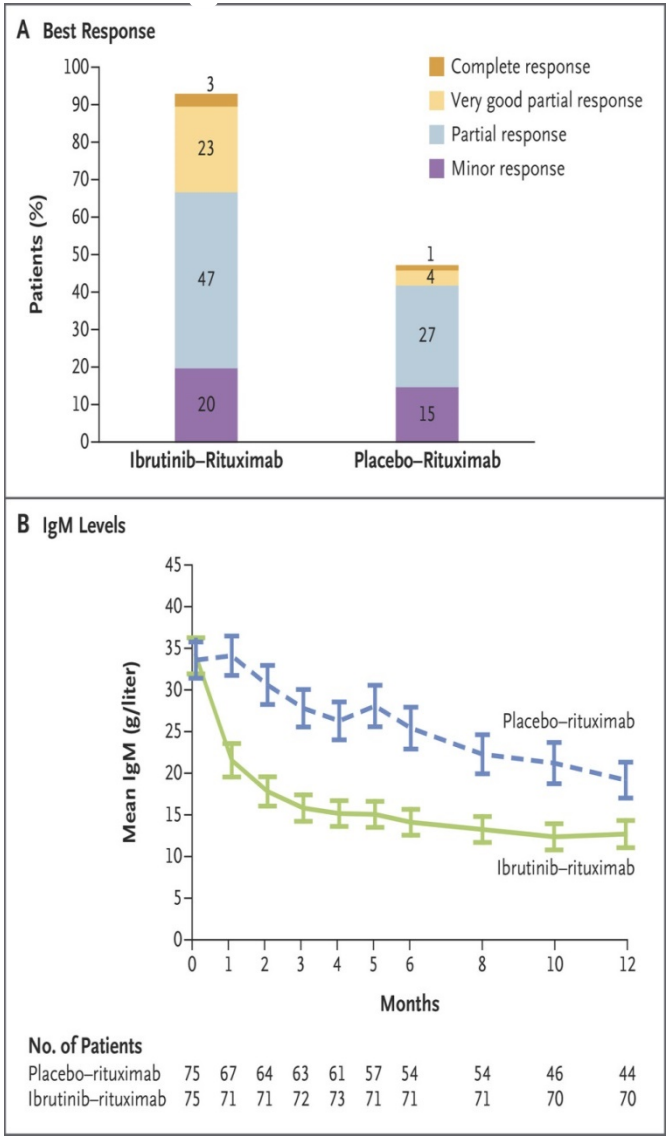


Treon SP et al. J Clin Oncol. 2009; 27(1):120-126

Ibrutinib for newly diagnosed WM

- 30 patients who were newly diagnosed and received ibrutinib was recently reported. The major response rate was **80** percent with no difference between patients with wild type or mutated CXCR4.

Ibrutinib Is Highly Active As First Line Therapy in Symptomatic Waldenstrom's Macroglobulinemia
Steven P Treon, Joshua Gustine, Kirsten Meid, Toni Dubeau, Patricia Severns, Christopher Patterson, Lian Xu, Guang Yang, Xia Liu, Maria Demos, Amanda Kofides, Jiaji Chen, Manit Munshi, Nickolas Tsakmaklis, Gloria Chan, Andrew J Yee, Noopur Raje, Elizabeth O'Donnell, Zachary Hunter and Jorge J. Castillo
Blood 2017 130:2767;

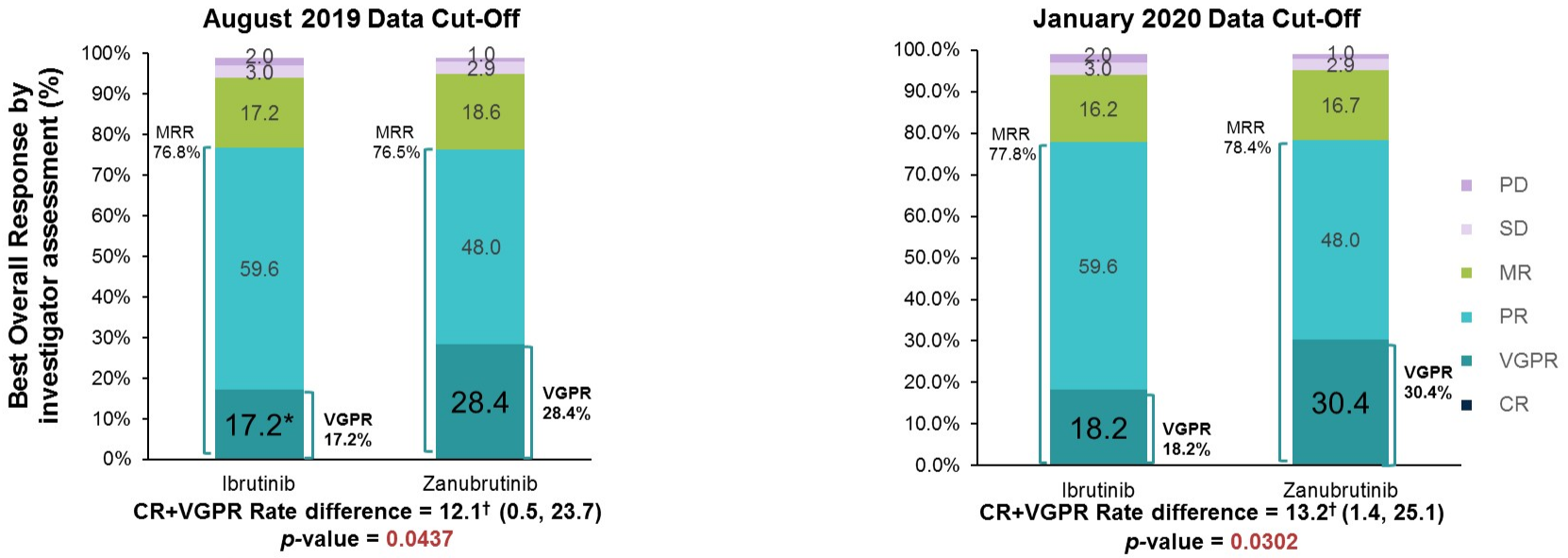


Dimopoulos et al. N Engl J Med 2018. DOI: 10MA .1056/NEJMoa1802917

ASPEN: Secondary Efficacy Endpoints

Assessment of Response According to Investigator and IgM Analysis

Investigator-Assessed Response



IgM Reduction

- Area-under-the-curve (AUC) for IgM reduction over time was significantly greater for zanubrutinib vs ibrutinib (p=0.037)

CR, complete response; EMD, extramedullary disease; IgM, Immunoglobulin M; IRC, independent review committee; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SPEP, serum protein electrophoresis; VGPR, very good PR.
*Excluded two patients with VGPR by IRC: MR (EMD present) and PR (IgM assessment by local SPEP M-protein)
†Adjusted for stratification factors and age group. *P* value is for descriptive purpose only.

ASPEN: AE Categories of Interest (BTKi Class AEs) with additional 5 months follow-up (Data cutoff: 31 January 2020)

- **An additional 5 patients had discontinued ibrutinib treatment due to AEs versus 0 in the zanubrutinib arm (14.3% vs 4%)**

AE *Categories*, n (%) *(pooled terms)*	All Grades		Grade ≥ 3	
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)
Atrial fibrillation/ flutter†	**18 (18.4)**	3 (3.0)	**7 (7.1)**	0 (0.0)
Diarrhea (PT)	**32 (32.7)**	22 (21.8)	2 (2.0)	3 (3.0)
Hemorrhage	**59 (60.2)**	51 (50.5)	9 (9.2)	6 (5.9)
Major hemorrhage[a]	10 (10.2)	6 (5.9)	9 (9.2)	6 (5.9)
Hypertension	20 (20.4)	13 (12.9)	**15 (15.3)**	8 (7.9)
Neutropenia[b]†	15 (15.3)	**32 (31.7)**	8 (8.2)	**23 (22.8)**
Infection	70 (71.4)	70 (69.3)	23 (23.5)	19 (18.8)
Second Malignancy	12 (12.2)	13 (12.9)	1 (1.0)	3 (3.0)

Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.

[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.

[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.

† Descriptive two-sided *P*-value < 0.05.

- Incidental finding of elevated IgM
- No fatigue
- Hb >10
- Lymph nodes modesty enlarged
- No symptoms consistent with amyloidosis
- No nasal gingival bleeding

Begin

- Monitoring
- Schedule for changes in Hb and IgM/M-spike

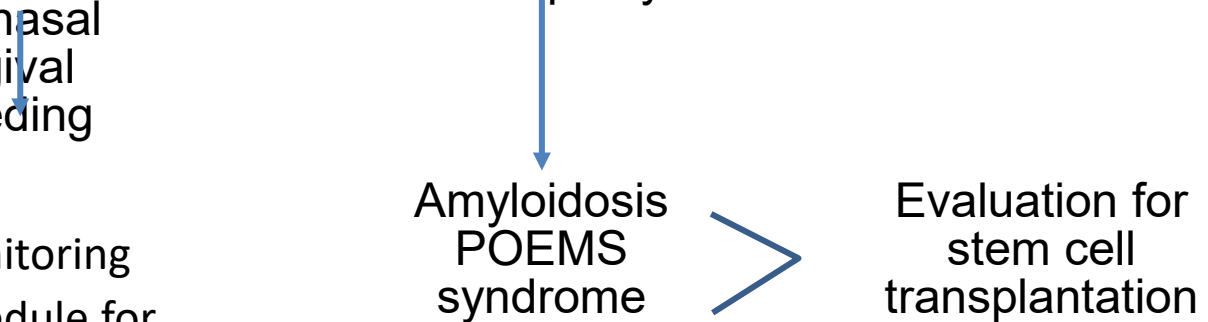
Symptomatic due to the IgM protein not related to rumor mass

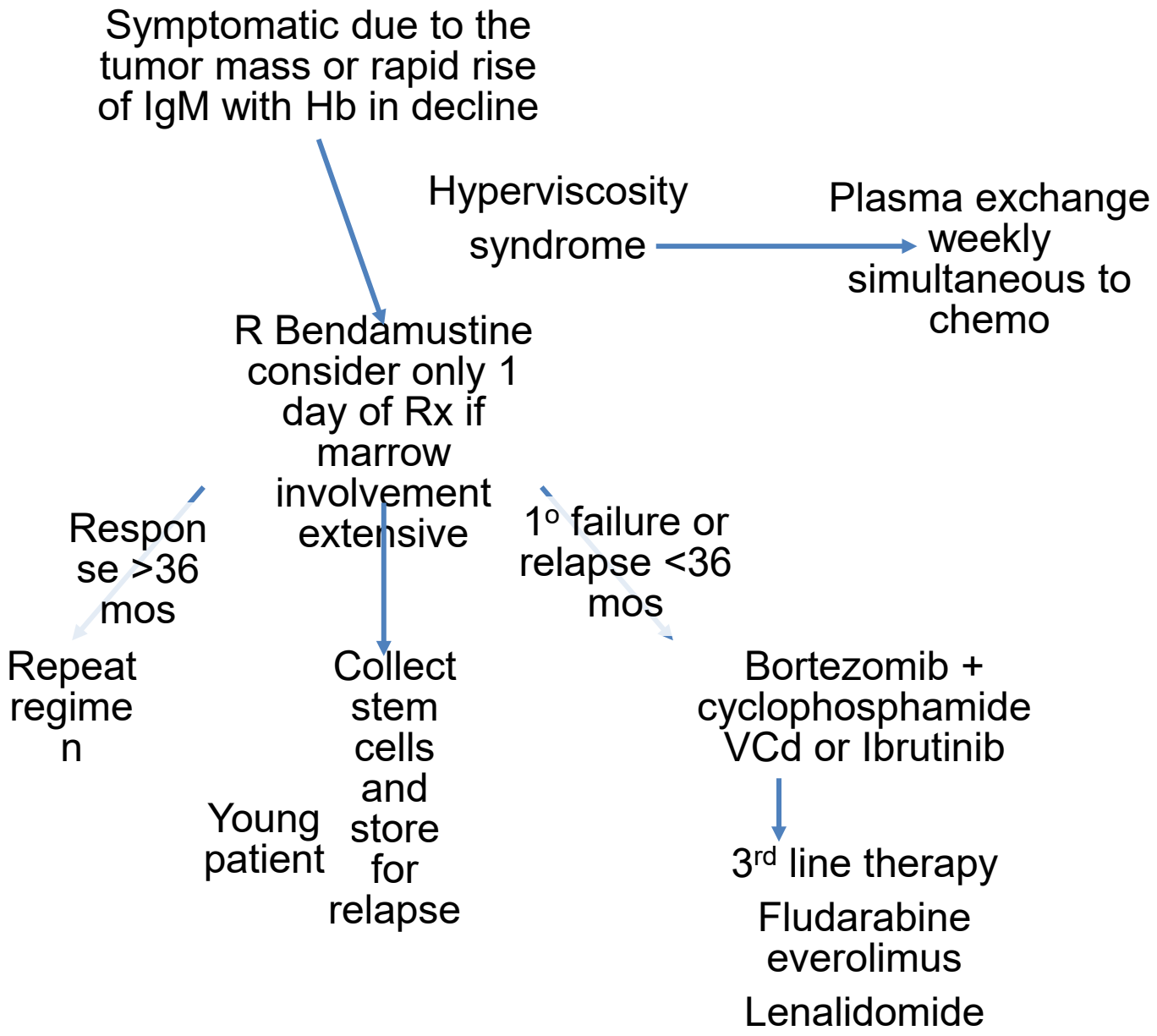
Type II cryoglobulin cold agglutinin hemolysis IgM associated neuropathy

Trial of rituximab

Amyloidosis POEMS syndrome

Evaluation for stem cell transplantation




Symptomatic due to the tumor mass or rapid rise of IgM with Hb in decline
Hyperviscosity syndrome
Plasma exchange weekly simultaneous to chemo
R Bendamustine consider only 1 day of Rx if marrow involvement extensive
Respon se >36 mos
1o failure or relapse <36 mos
Repeat regime n
Collect stem cells and store for relapse
Young patient
Bortezomib + cyclophosphamide VCd or Ibrutinib
3rd line therapy
Fludarabine everolimus
Lenalidomide