Myeloma & Waldenström

Indianapolis Hematology Review

2021

Financial Disclosures

- DSMB AbbVie
- DSMB Celgene
- Akcea Honoraria and consulting
- i3Health educational materials
- Prothena consulting
- Research to Practice Honoraria
- Alnylym consulting
- Ambry Genetics honorarium
- Amgen honorarium
- Janssen Honorarium
- Celgene Honorarium
- Stock Options Aurora Bio
- Ionis Advisory Board
- Karyopharm Honorarium
- Pfizer honorarium to institution
- Sanofi honorarium

Objectives

- Master sequencing of therapies
- Understand when intervention can be delayed
- Review of new therapies

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.

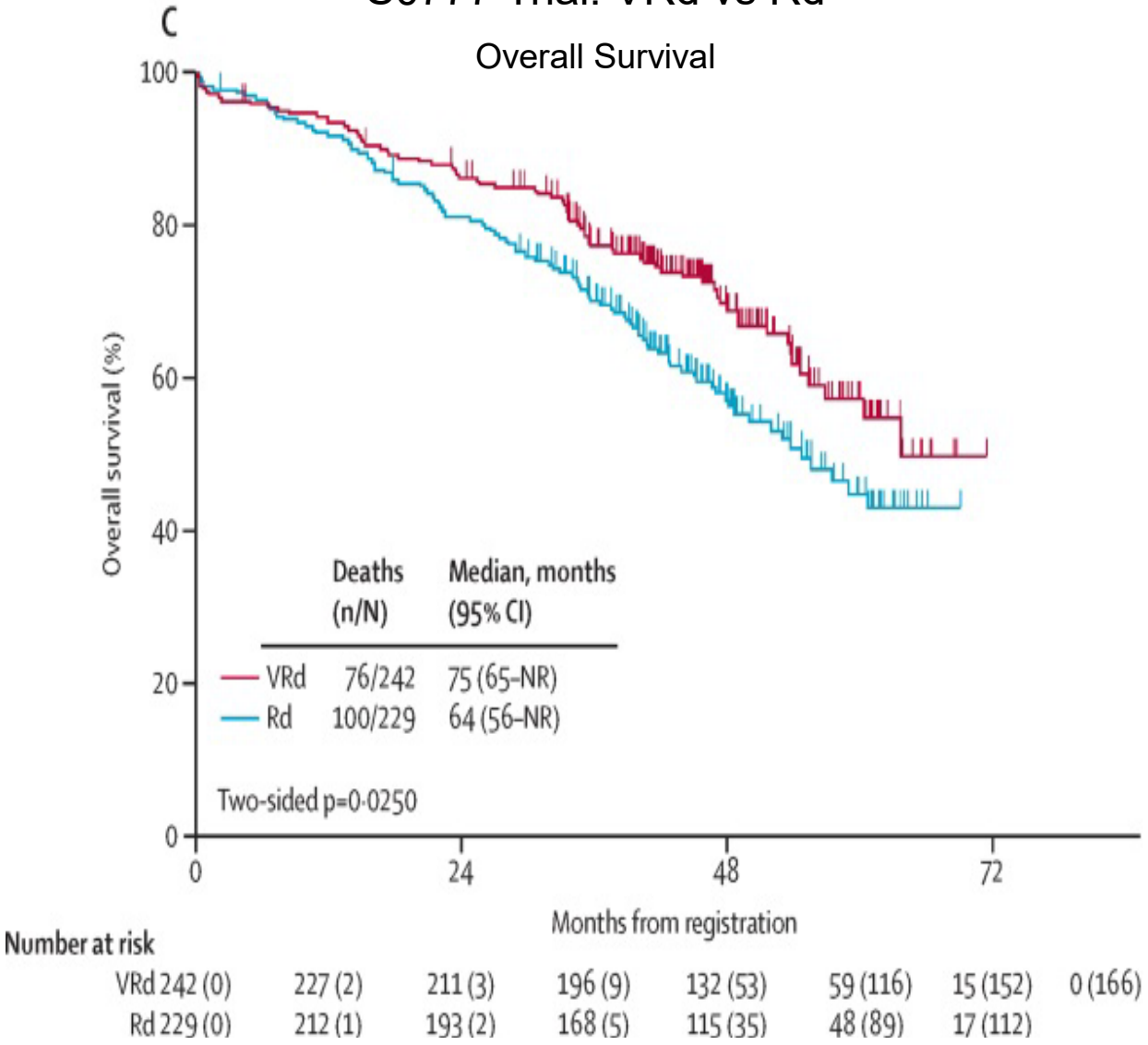
MDE, myeloma-defining events

Common Regimens in Newly Diagnosed MM

- DaraVRd
- DRd
- VCd (CyBorD)
- VTD
- DaraRd
- KRd

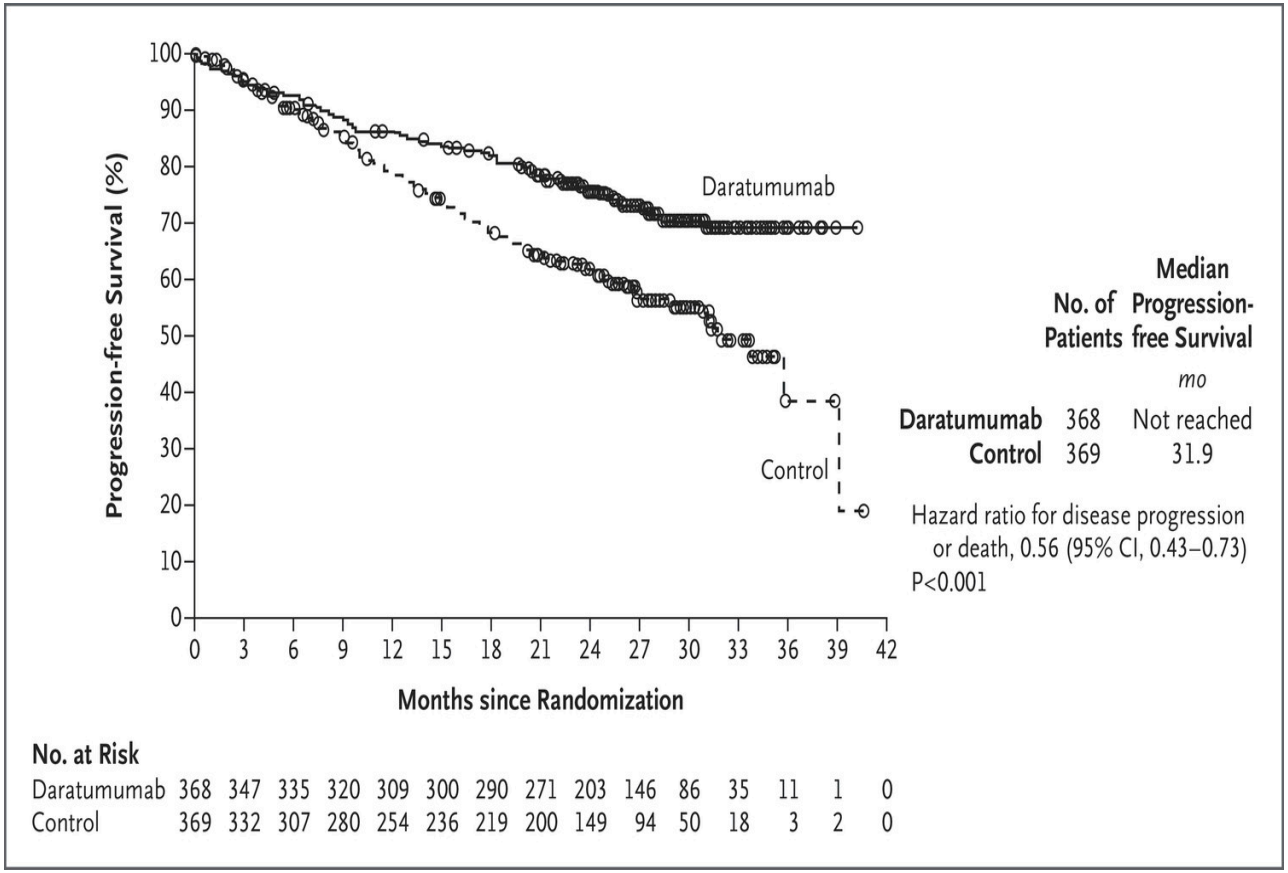
Yang, Y., Li, Y., Gu, H. *et al.* Emerging agents and regimens for multiple myeloma. *J Hematol Oncol* **13,** 150 (2020). https://doi.org/10.1186/s13045-020-00980-5

S0777 Trial: VRd vs Rd



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

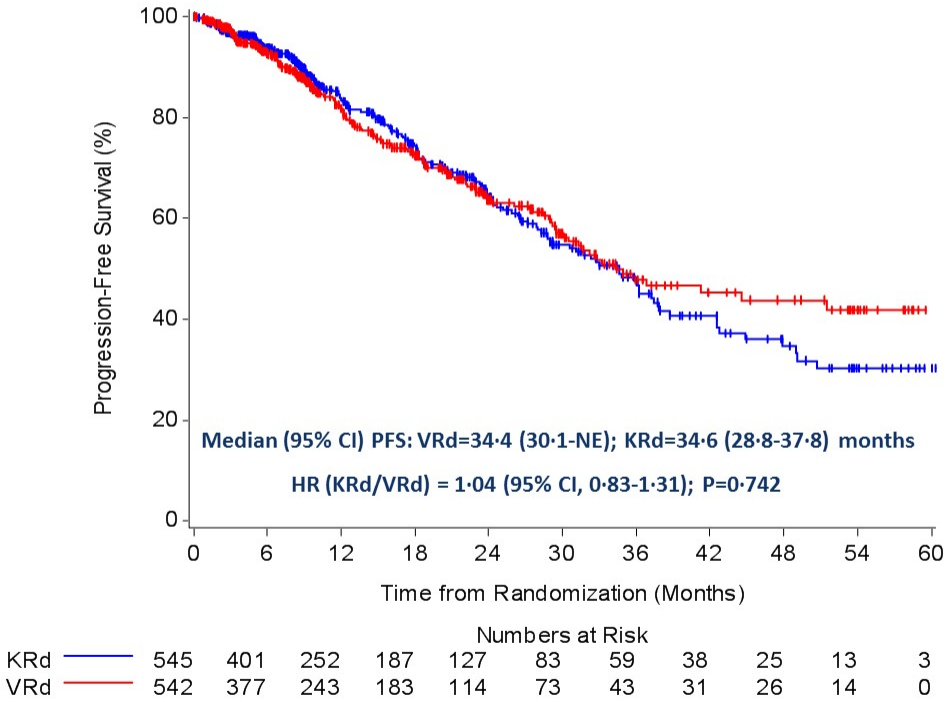
Dara-Rd vs Rd (MAIA trial): PFS



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

The NEW ENGLAND JOURNAL of MEDICINE

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

Selected Approaches: Primary Therapy + SCT for Transplant-Eligible NDMM

Study	IFM 2009[1,2] RVd-SCT vs RVd		FORTE[3,4] KRd-SCT vs KRd		GRIFFIN[6,7] SCT DaraVRd vs VRd	
N	350	350	158	157	104	103
Median F/u, mos	89.9[2]		45		27.4	
No days (28-d cycles) chemo induction to post induction	105 (**3.75**)	168 (**6**)	224 (**8**)	336 (**12**)	126 (**4.5**)	
SCH mobilization	Cy 3 gm/m^2		Cy 2 gm/m^2		Plerixafor	
Postconsolidation ORR	N/A	N/A	N/A	N/A	99%	91.8%
Postconsolidation ≥ VGPR	78%	69%	89%	87%	90.9%	73.2%
Postconsolidation sCR	N/A	N/A	50%	48%	42.4%	32%
Median PFS, mos	47.3[2]	35[2]	NR	57	NR	NR
PFS, HR (95% CI)	0.70 (0.59-0.83)[2]		0.64, *P* = .023		NR	
MRD Negativity, %	**79**	**65**	**65**	**66**	**62.5**	**27.2**

Ongoing studies:

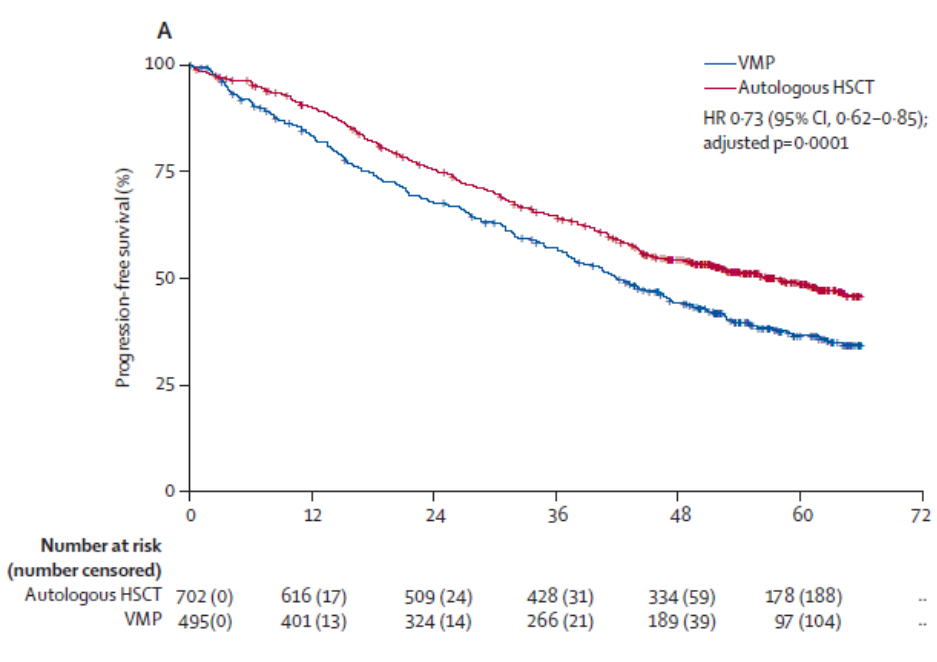
- Perseus: Daratumumab(SQ)-RVd vs RVd
- GMMG HD7: Isatuximab-RVd vs RVd

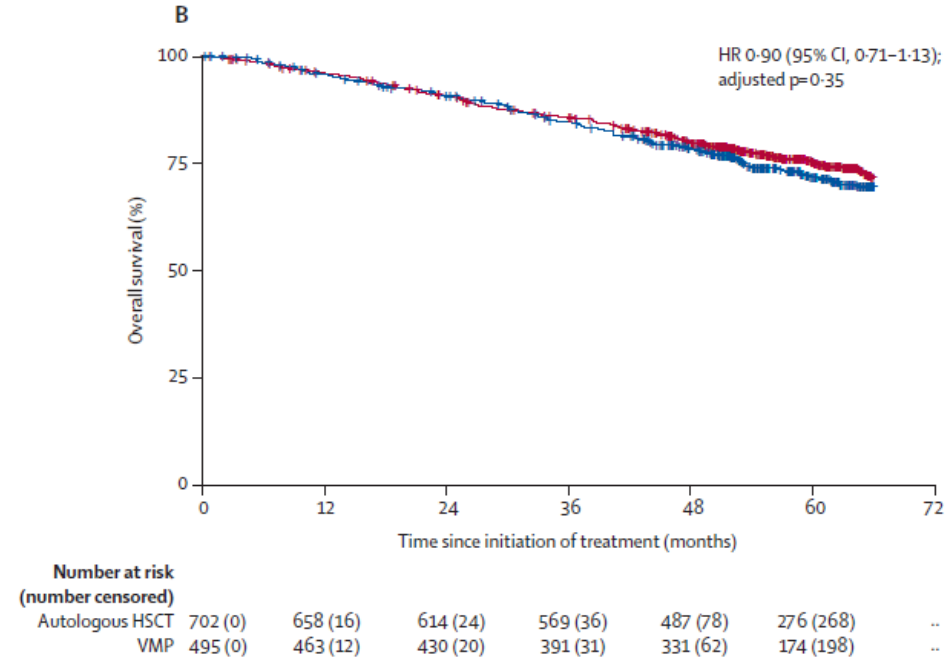
Slide courtesy A Chari.

Al Hamed, R., Bazarbachi, A.H., Malard, F. *et al.* Current status of autologous stem cell transplantation for multiple myeloma. *Blood Cancer J.* **9,** 44 (2019). https://doi.org/10.1038/s41408-019-0205-9

ROLE OF TRANSPLANT

EMN02/H095

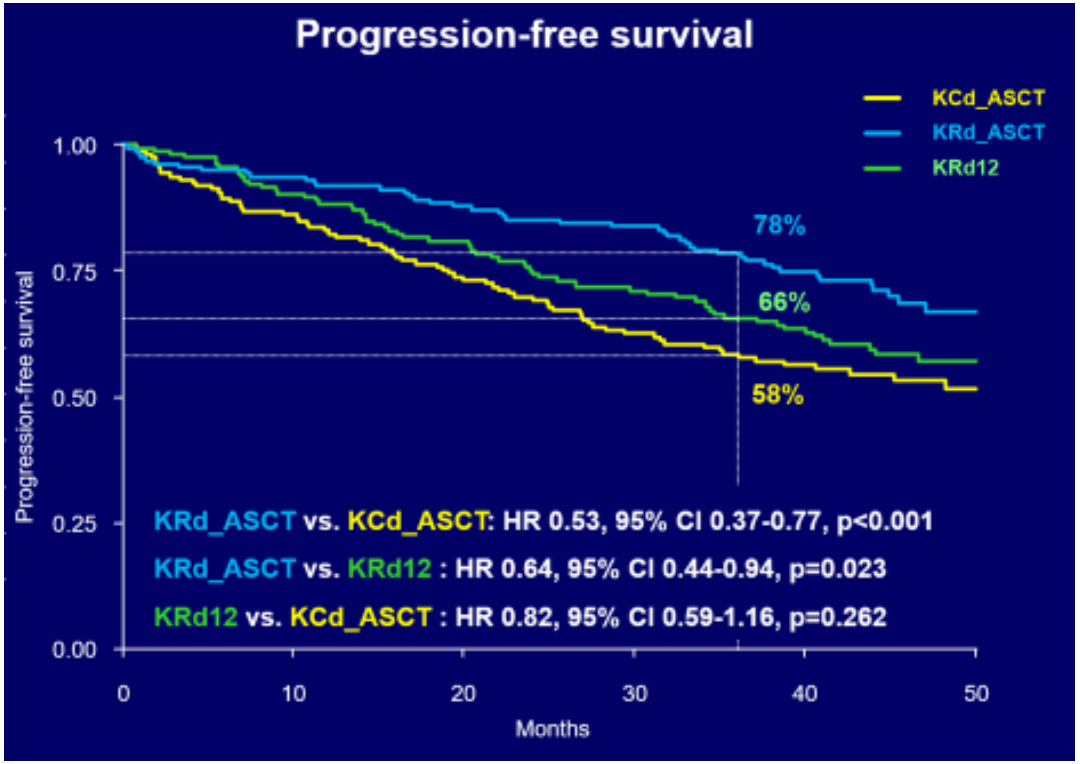


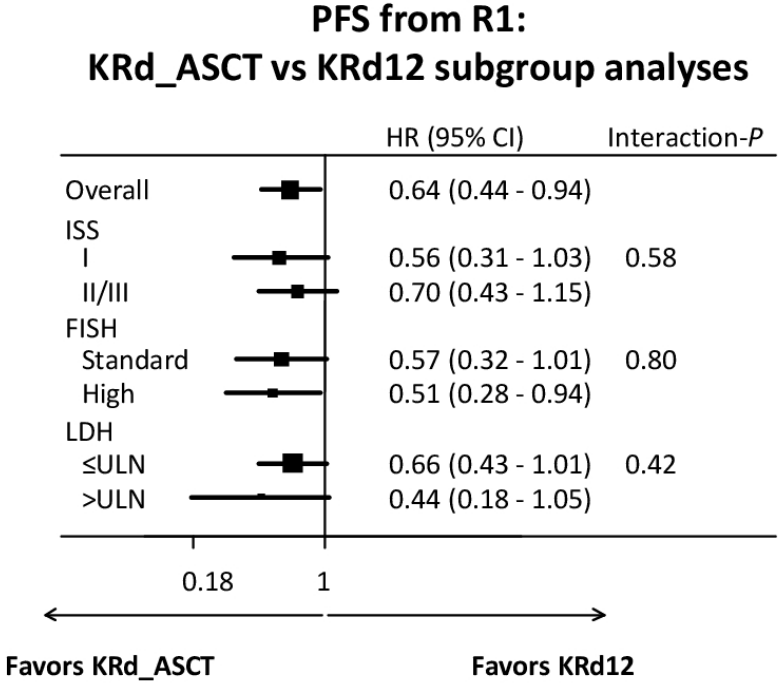


Cavo et al, 2020

Lancet Haematology, The, 2020-06-01, Volume 7, Issue 6, Pages e456-e468

FORTE: Results from first randomization





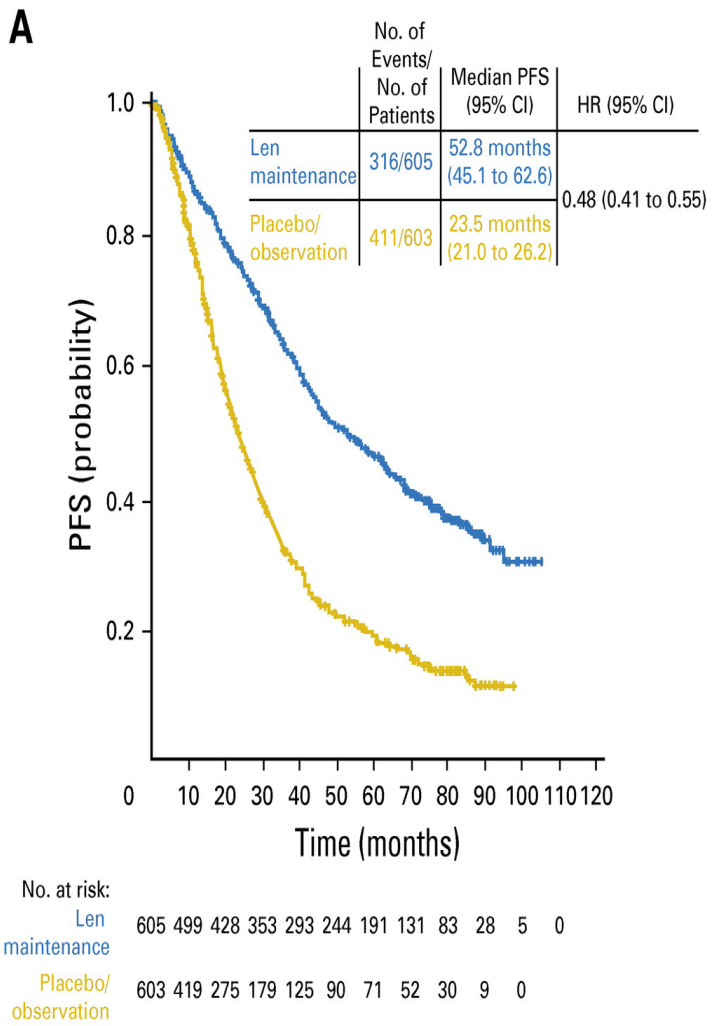
Gay F, et al. ASH 2020. Abstract 141 Saturday, December 5, 2020: 9:30 AM.

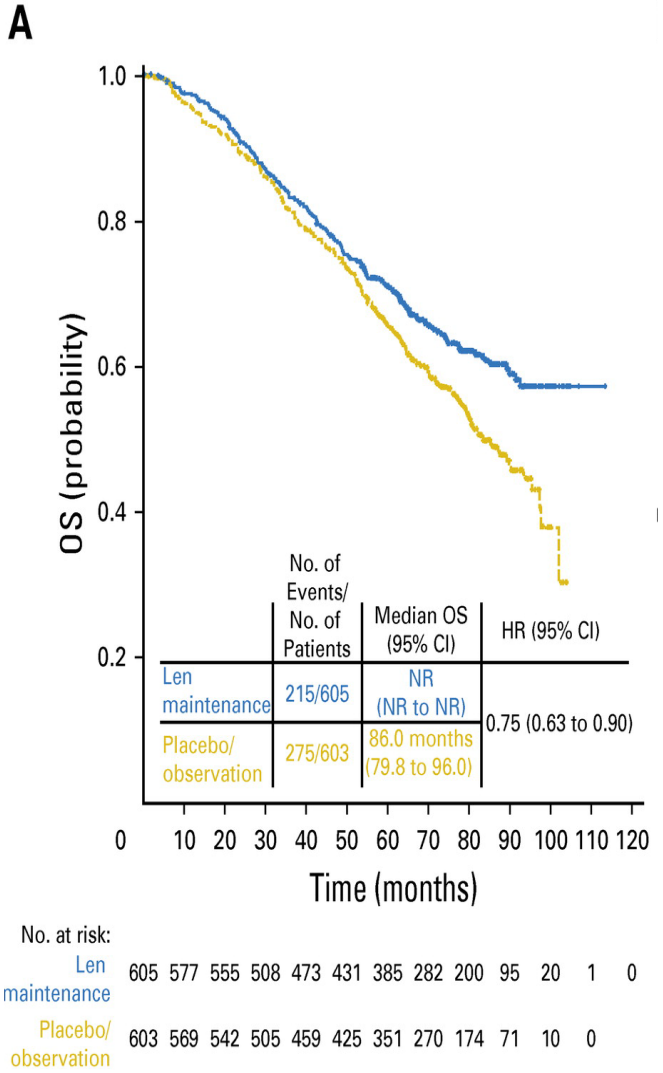
141 Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

MAINTENANCE THERAPY

Lenalidomide Maintenance Meta-analysis

PFS and OS

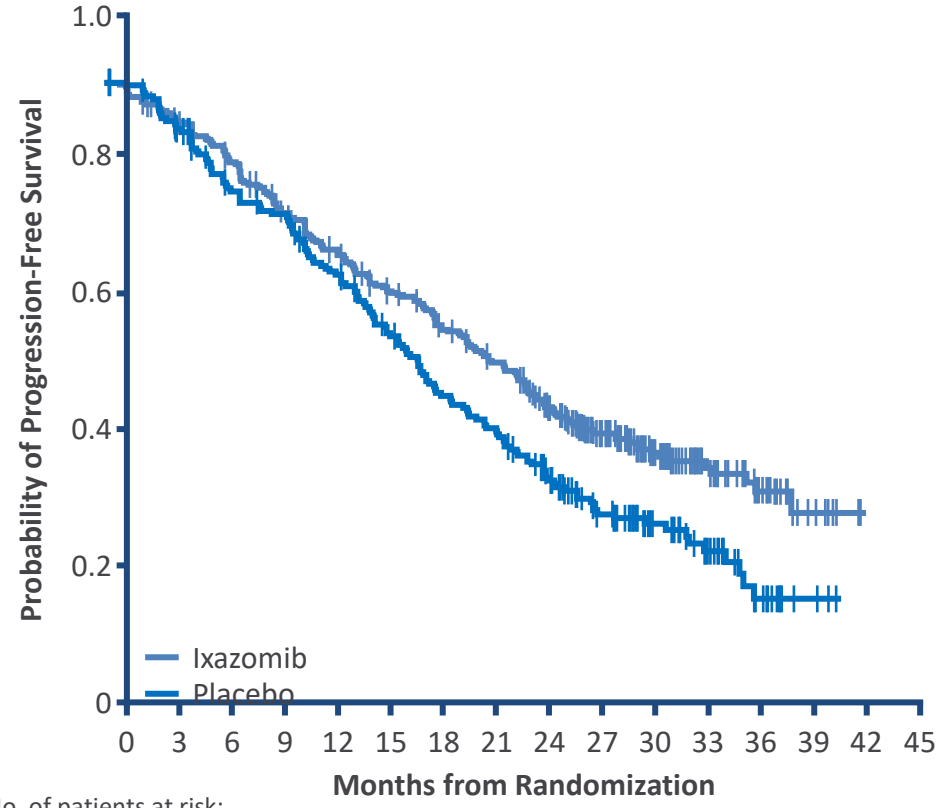




Published in: Philip L. McCarthy; et al. JCO 2017, 35, 3279-3289.
DOI: 10.1200/JCO.2017.72.6679

Improvement in overall PFS with ixazomib vs. placebo

- There was a significant 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs. placebo maintenance:
  - Median 26.5 months vs. 21.3 months
- With only 14% of deaths reported, at a median follow-up of 31 months, median OS has not been reached in either treatment arm and follow up continues
- Improved Depth of response resulted in better PFS



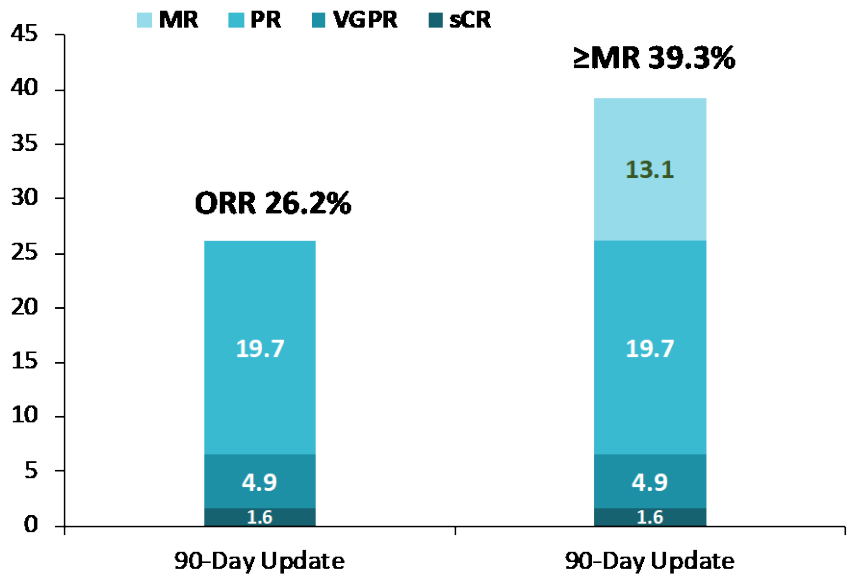
No. of patients at risk:

Ixazomib	395	363	340	311	279	255	238	213	187	135	93
56	35	9	3	0							
Placebo	261	238	210	195	174	153	130	117	100	69	46
32	15	3	0	0							

Meletios A Dimopoulos et al, Blood 2018 132:301
Dimopoulos MA et al. Lancet 2019 Jan 19;393(10168):253-264.
Goldschmidt et al. leukemia 2020; 34(11): 3019–3027

RELAPSED MYELOMA

STORM: Selinexor Dex

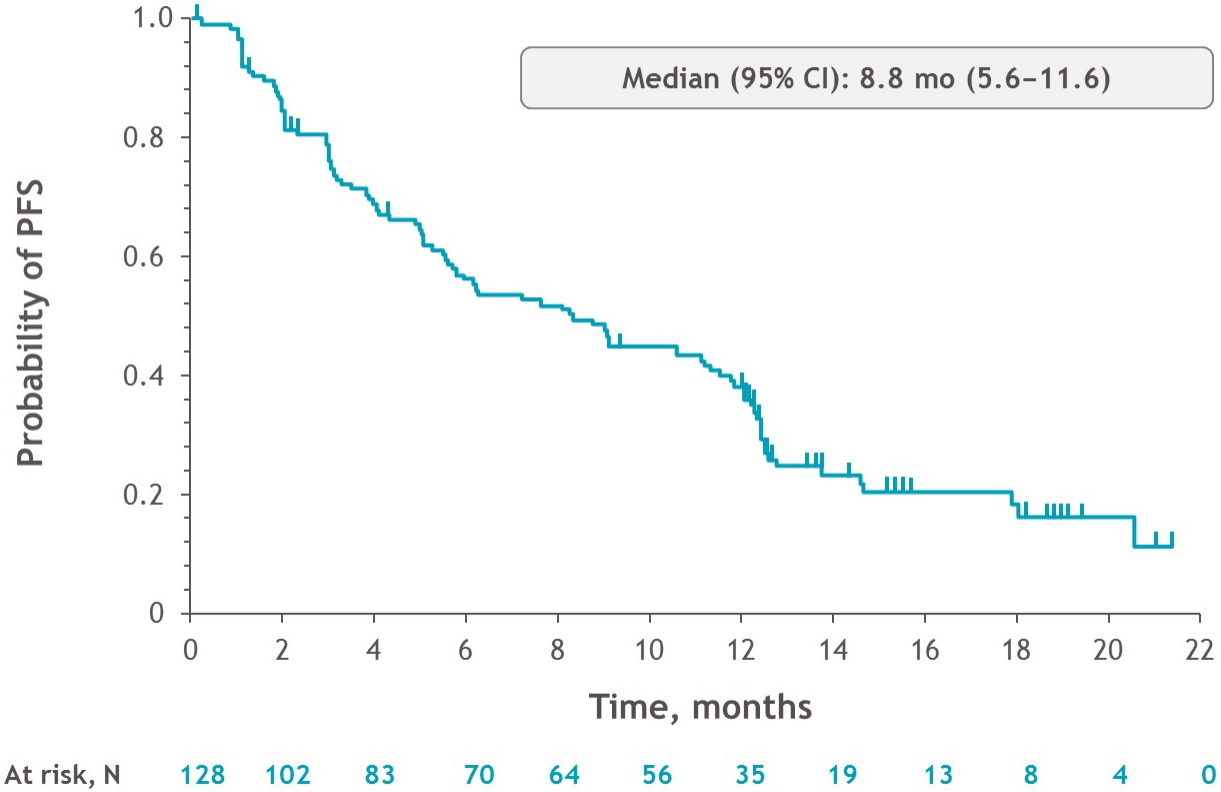


- Median of 7 prior treatment regimens, **ORR of 26.2%,** including **2 stringent CRs**
  - **sCRs MRD negative** at 10^{-6} and 10^{-4}
- Two patients with prior progression after CAR-T achieved a PR
- Median time to response was 1 month (range 1-14 weeks)
- Median duration of response was 4.4 months

Chari et al, ASH 2018N Engl J Med 2019; 381:727-738
DOI: 10.1056/NEJMoa1903455

BCMA CAR-T

Progression-Free Survival



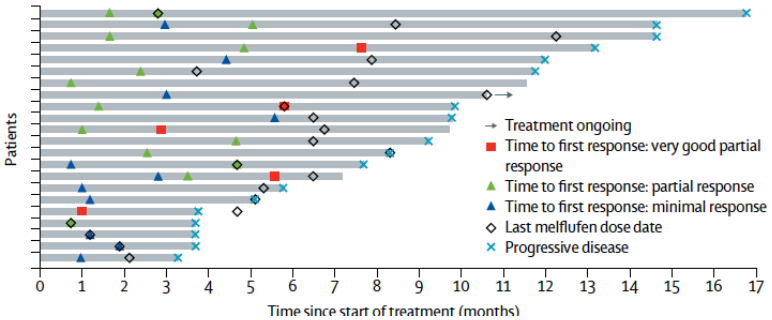
Data cutoff: 14 Jan 2020. PFS, progression-free survival.

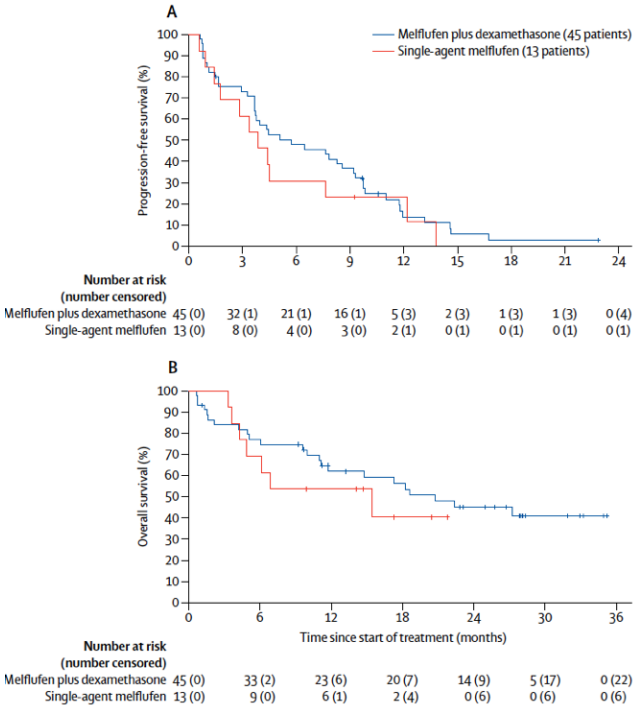
February 25, 2021
N Engl J Med 2021; 384:705-716
DOI: 10.1056/NEJMoa2024850

Presented By Nikhil Munshi at TBD

Melflufen – with or without Dex

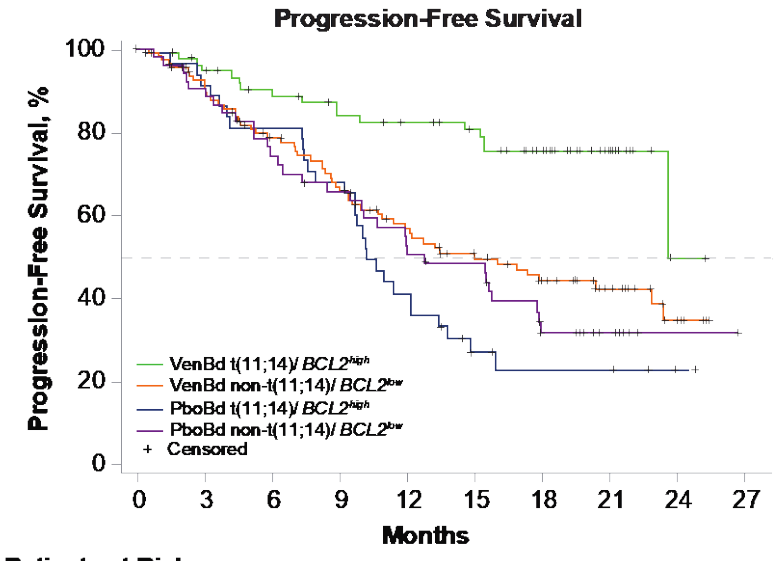
	Melflufen plus dexamethasone group (n=45)	Melflufen group (n=13)
Overall response rate	14 (31%; 18·2–46·6)	1 (8%; 0·2–36·0)
Clinical benefit rate	22 (49%; 33·7–64·2)	3 (23%; 5·0–53·8)
Complete response	0 (0·0–7·9)	0 (0·0–24·7)
Very good partial response	5 (11%; 3·7–24·1)	0 (0%; 0·0–24·7)
Partial response	9 (20%; 9·6–34·6)	1 (8%; 0·2–36·0)
Minimal response	8 (18%; 8·0–32·1)	2 (15%; 1·9–45·4)
Stable disease	12 (27%; 14·6–41·9)	9 (69%; 38·6–90·9)
Progressive disease	7 (16%; 6·5–29·5)	1 (8%; 0·2–36·0)





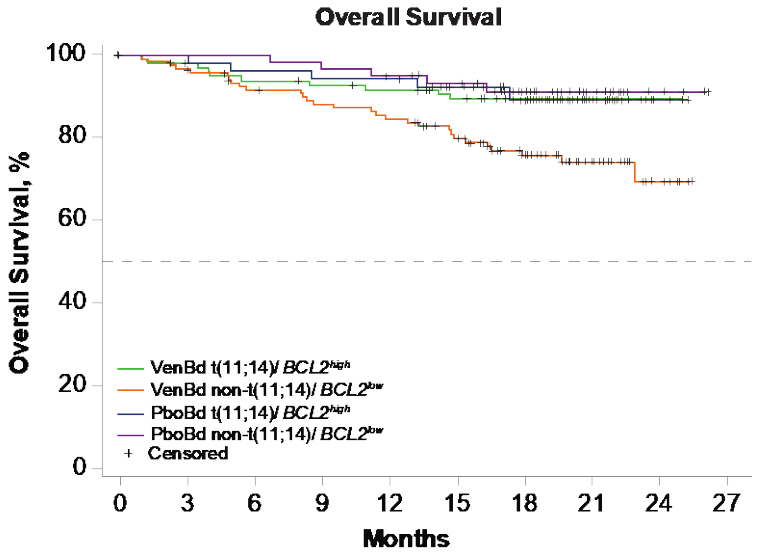
Richardson P et al Melflufen plus dexamethasone in relapsed and refractory multiple myeloma (O-12-M1): a multicentre, international, open-label, phase 1-2 study. Lancet Haematol. 2020 May;7(5):e395-e407. doi: 10.1016/S2352-3026(20)30044-2. Epub 2020 Mar 23. PMID: 32213344.

BELLINI: t(11:14) and bcl2



Patients at Risk

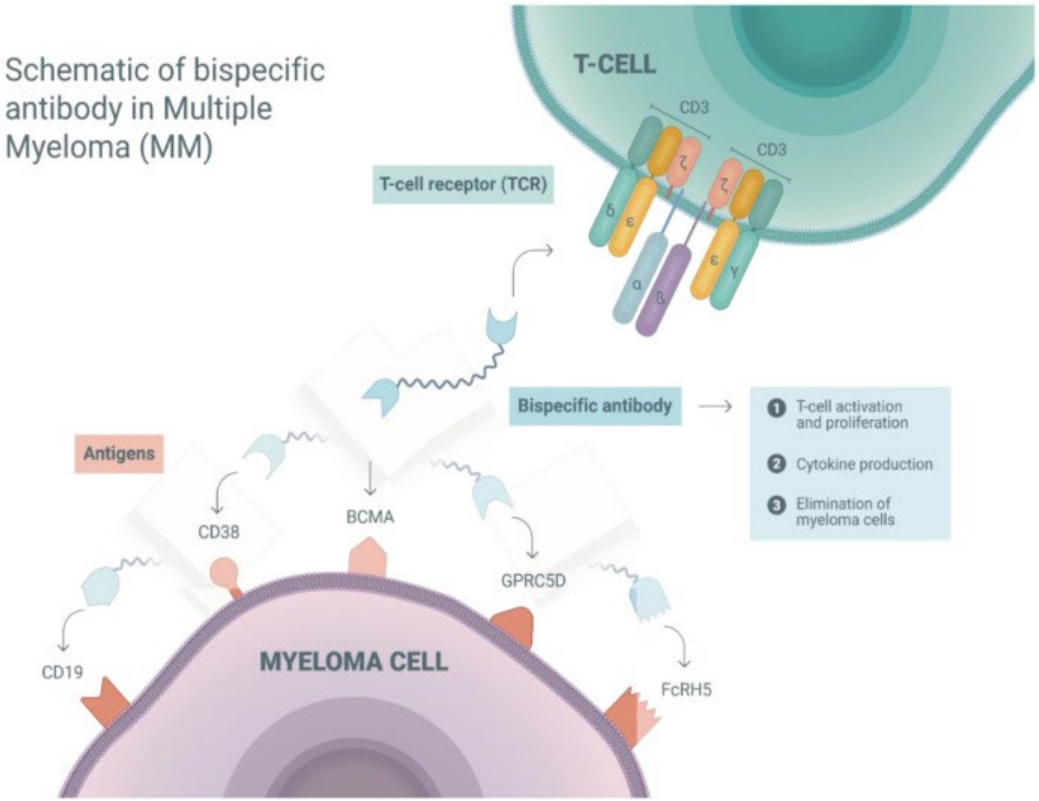
VenBd	74	65	59	54	51	44	29	4	1	0
PboBd	40	35	32	25	14	7	4	1	0	
Ven Bd	110	92	76	61	47	38	29	14	5	0
PboBd	54	46	36	31	24	18	12	2	1	0



Patients at Risk

VenBd	74	70	65	63	61	56	39	12	1	0
PboBd	40	39	37	36	36	27	15	6	1	0
Ven Bd	110	106	96	90	86	75	50	22	7	0
PboBd	54	53	53	51	49	45	27	13	3	0

Kumar SK, etal. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2020 Dec;21(12):1630-1642. doi: 10.1016/S1470-2045(20)30525-8. Epub 2020 Oct 29. PMID: 33129376.

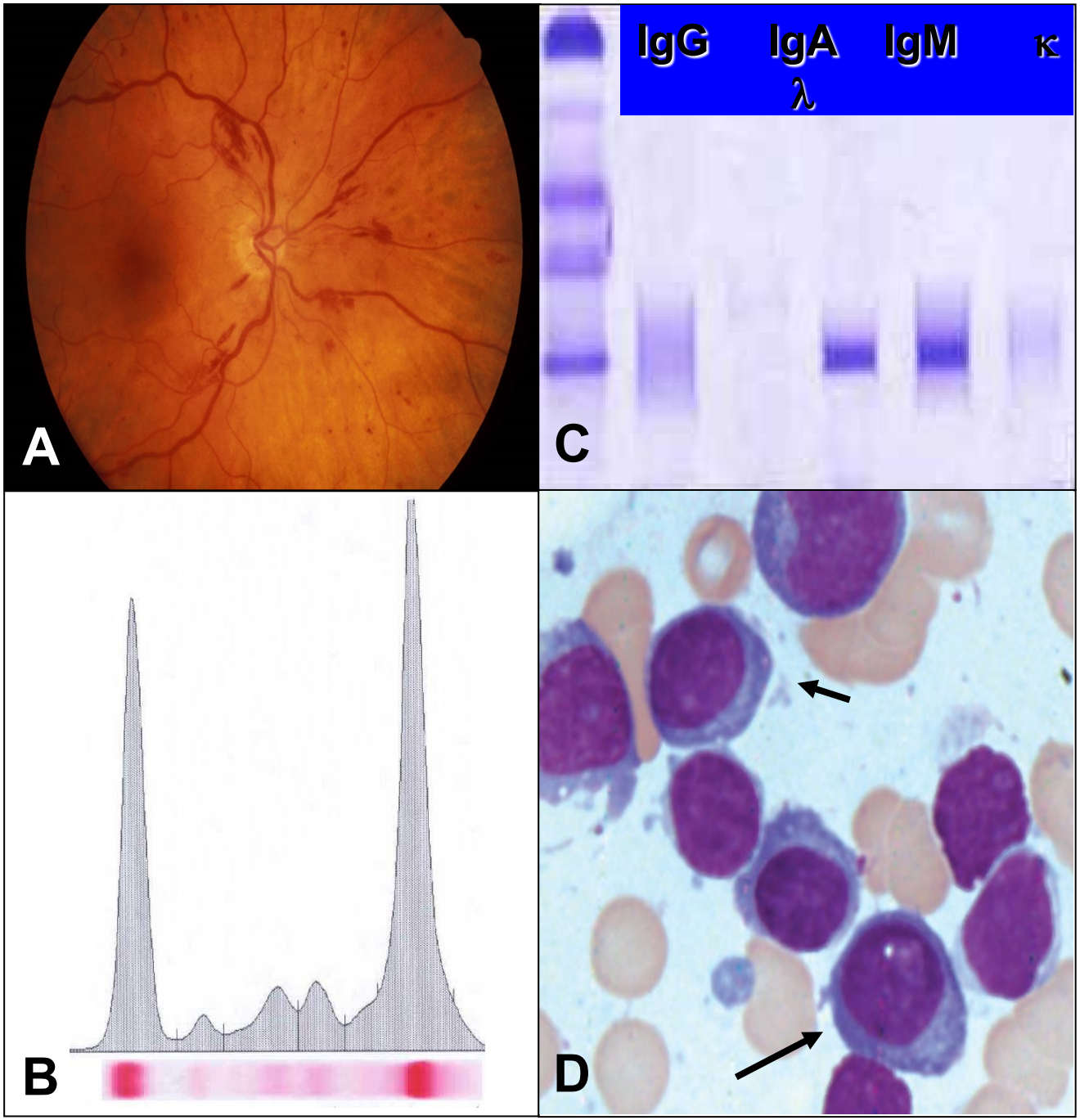


Zhou et al, J Clin Med. 2020 Jul; 9(7): 2166

Summary of results: BCMA

Agent	Target	Trial phase	Admin.	ORR	Toxicities
Teclistamab	BCMA	I, 84 (IV)+44 (SC), 80% 3ple, **38% penta refractory**	IV→SC weekly	69% at higher dosel (SC)	39% ≥Gr. 3 AEs (cytopenias, **infections**, **no CRS**)
AMG701	BCMA	I, N=82, 62% triple refractory	Weekly IV	26% (36% for 3-18mg dose)	SAEs 39% -**ID** (17%) -CRS (9%)-not G3
TNB-383B	BCMA	I, N=58, 64% 3ple refractory, **34% penta.**	**IV q 3 weeks**	47% (80% with higher doses)	57% % ≥Gr. 3 AEs (Cytopenias, **infections**)
REGN-5458	BCMA	I, N=49 (**57% penta-refractory**)	Weekly→q 2 wks	36% (60% highest dose)	29% ≥Gr. 3 AEs (cytopenias, **infections**, **no CRS**)
PF-06863135	BCMA	I, N=17 (IV)+18 (SC)	IV→SQ weekly	61% (SC)	66% ≥Gr. 3 AEs (cytopenias, **infections no CRS**)
CC-93269	BCMA	I, 19 (89% dara-refractory)	IV →**monthly**	53% (83% >6mg dose)	79% ≥Gr. 3 AEs (cytopenias, **infections**, 1 pt CRS)

Nishida H. Rapid Progress in Immunotherapies for Multiple Myeloma: An Updated Comprehensive Review. Cancers (Basel). 2021 May 31;13(11):2712. doi: 10.3390/cancers13112712. PMID: 34072645; PMCID: PMC8198014.


A
IgG
IgA
IgM
κ
λ
C
B
D

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

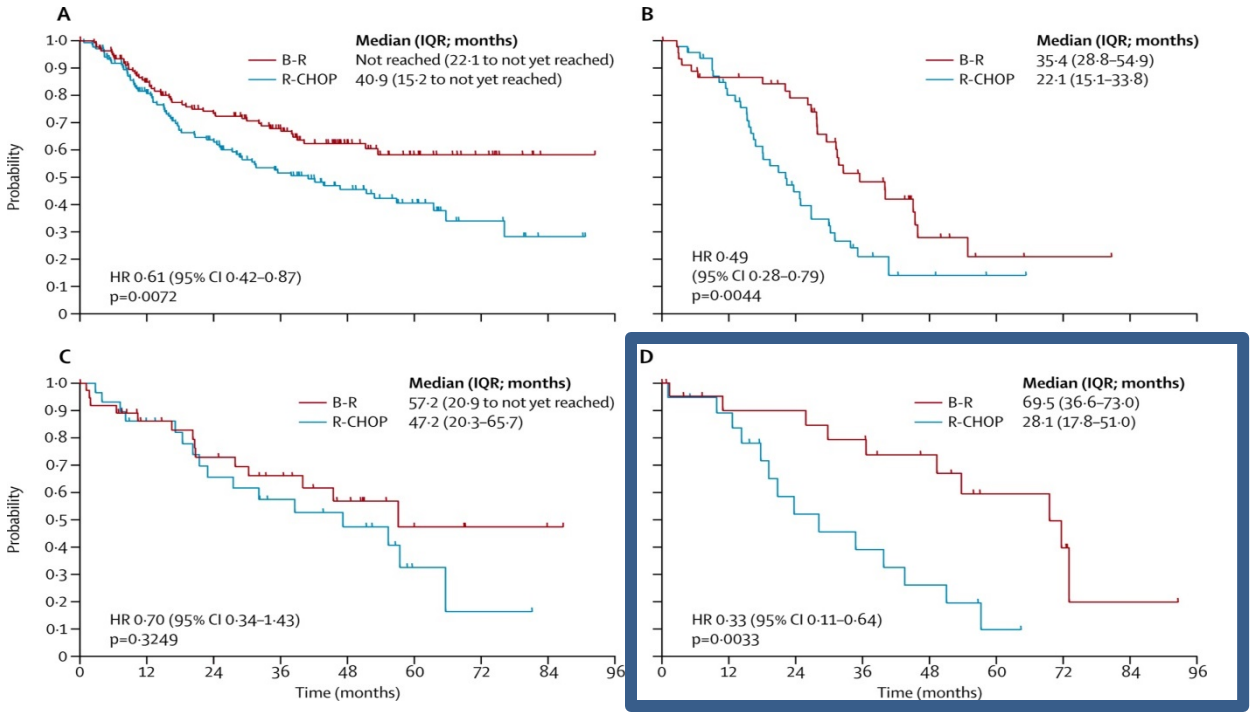


Figure 3 Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D) B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

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%)

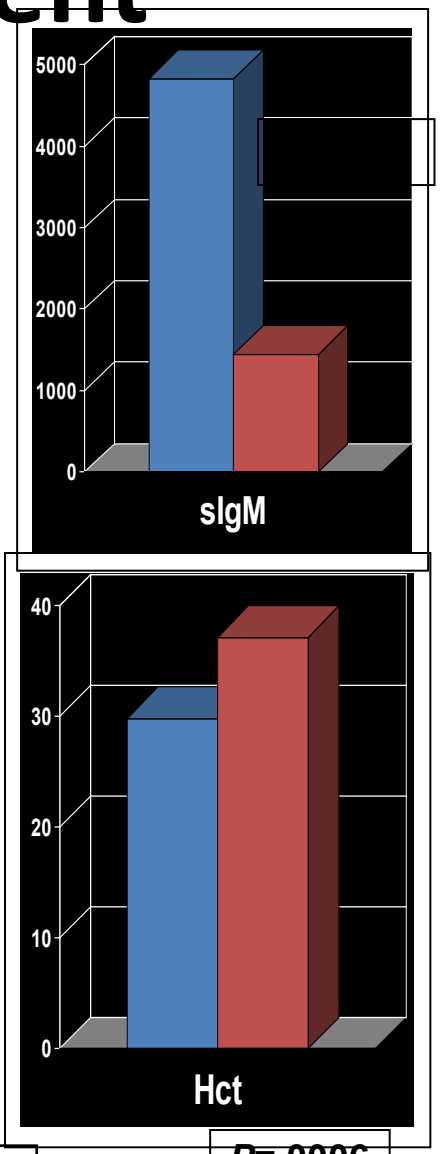
83%

91%

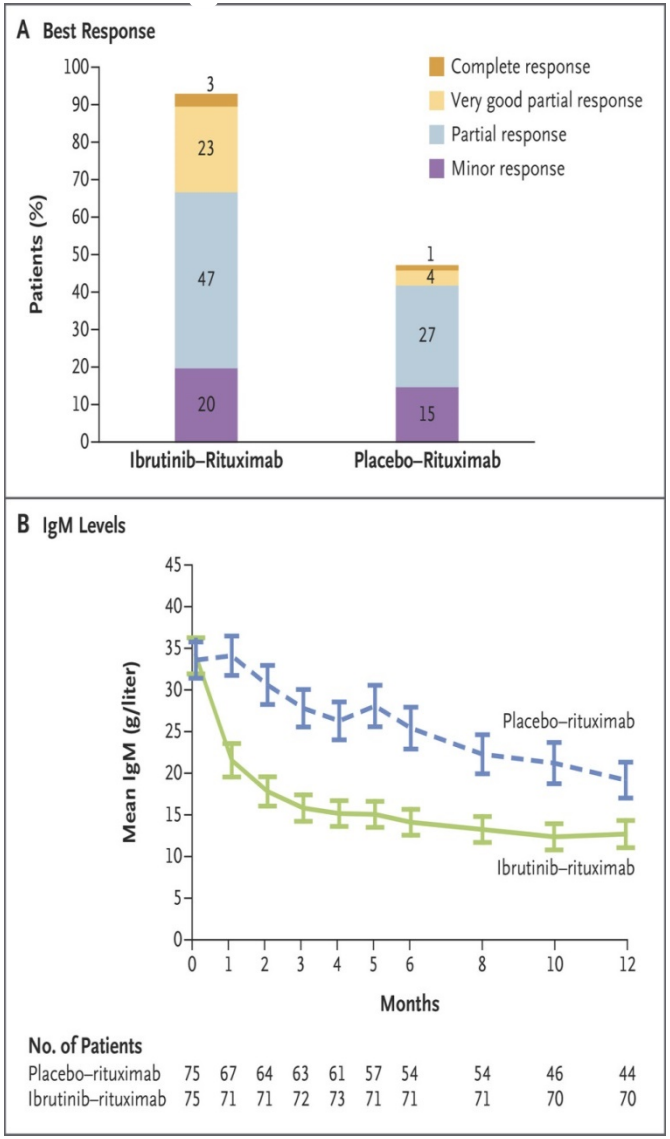
Median time to response 1.4 months

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



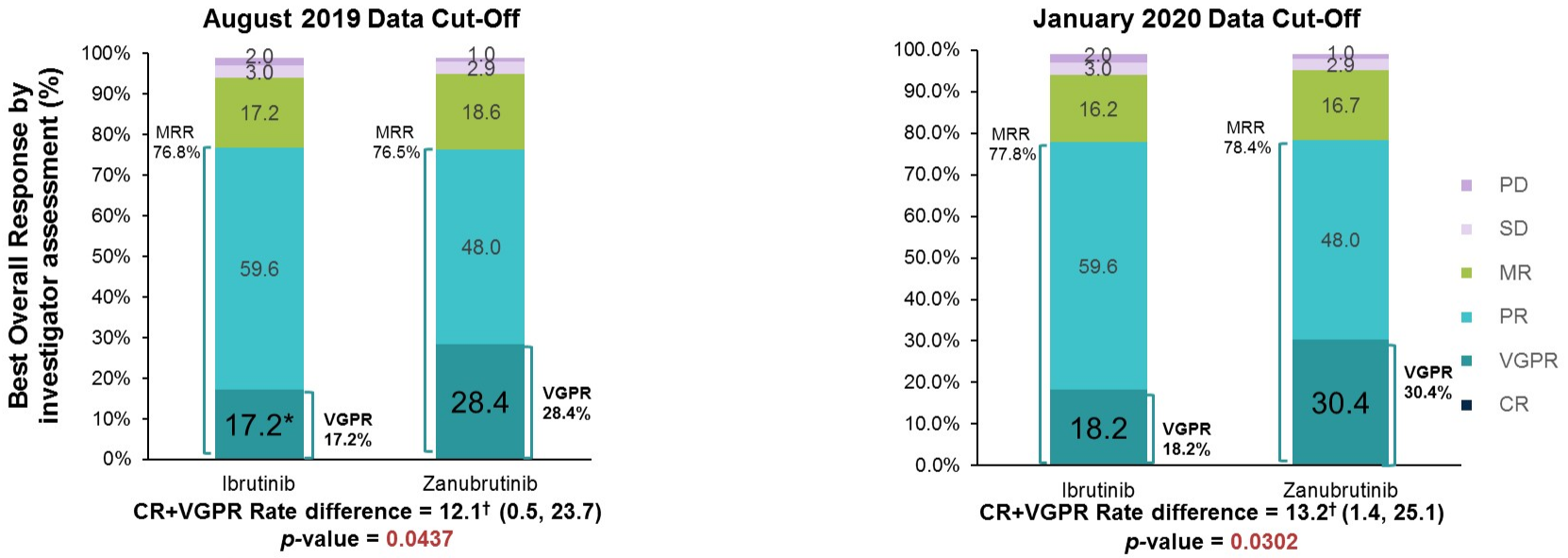
Dimopoulos et al. N Engl J Med 2018. DOI: 10MA .1056/NEJMoa1802917

Phase III Ibrutinib vs Zanubrutinib

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.

Dimopoulos M, etal. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv. 2020 Dec 8;4(23):6009-6018. doi: 10.1182/bloodadvances.2020003010. PMID: 33284944; PMCID: PMC7724905.

Presented By Constantine Tam at TBD

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

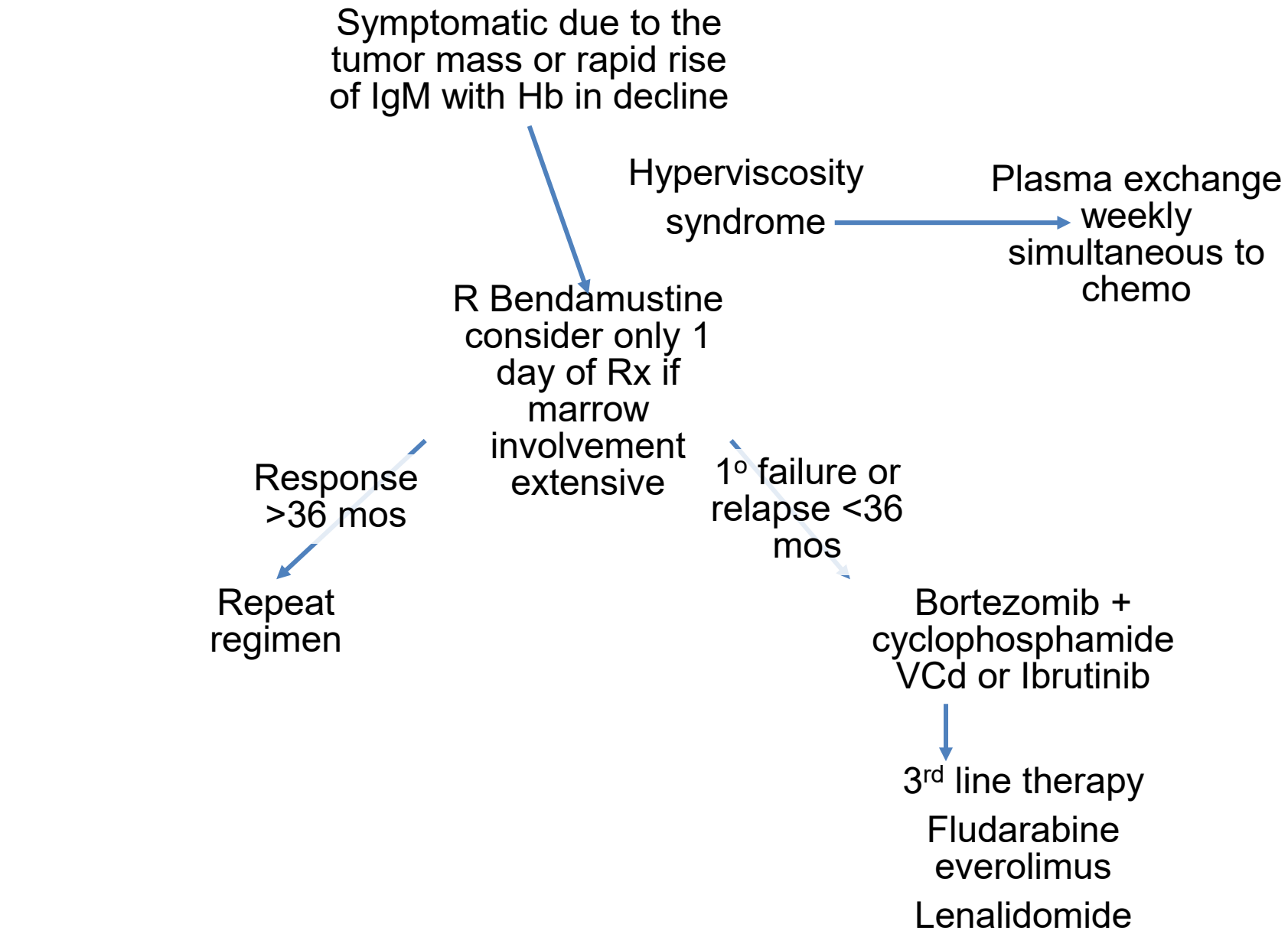
- **An additional 5 patients had discontinued ibrutinib treatment due to AEs versus 0 in the zanubrutinib arm (14.3% vs 4%)**

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.

Dimopoulos M, etal. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv. 2020 Dec 8;4(23):6009-6018. doi: 10.1182/bloodadvances.2020003010. PMID: 33284944; PMCID: PMC7724905.

Presented By Constantine Tam at TBD


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
Response >36 mos
1o failure or relapse <36 mos
Repeat regimen
Bortezomib + cyclophosphamide VCd or Ibrutinib
3rd line therapy
Fludarabine everolimus
Lenalidomide