Choosing the Best Therapy for Relapsed/Refractory Multiple Myeloma Patients:
Understanding the Vast Data to take Evidence-Based Decisions

Sikander Ailawadhi, M.D.
Professor of Medicine
Division of Hematology/Oncology
Departments of Medicine and Cancer Biology
Mayo Clinic, Florida

Learning Objectives

- Outline factors to consider when selecting therapy for patients with RRMM, including patient age and frailty, history of prior treatments, early versus late relapse, and others.

- Summarize current evidence regarding available therapeutic options in RRMM and strategies to select the most optimal option for a given patient.

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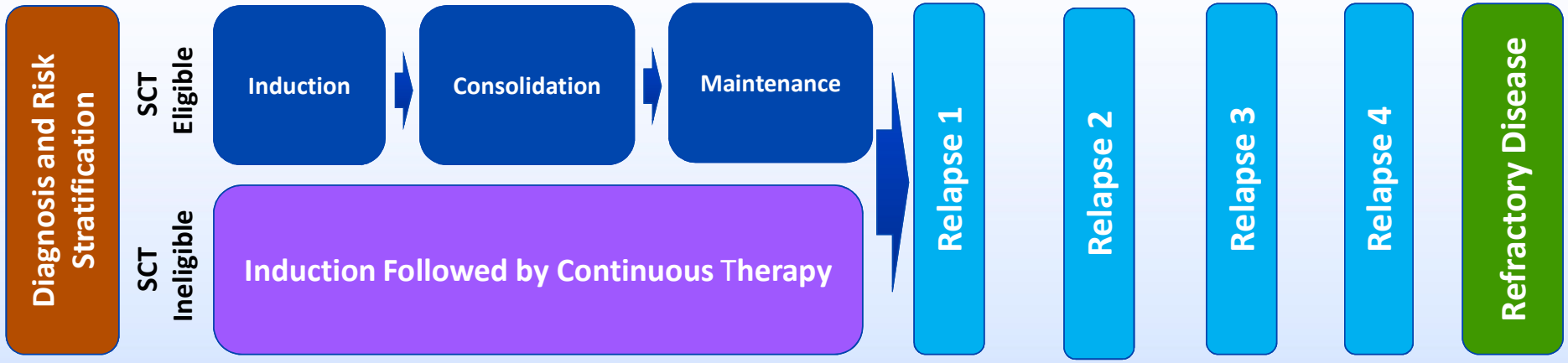
Myeloma Disease Burden



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Abundance of Randomized Data

- KRd vs. Rd
- IRd vs. Rd
- DRd vs. Rd
- DVd vs. Vd
- ERd vs. Rd
- PVd vs. Vd
- Kd vs. Vd
- Kd (weekly) vs. Kd (Biweekly)
- EPd vs. Pd
- IPd vs. Pd
- KDd vs. Kd

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And Abundance of Non-Randomized Data, Leading to…

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Multiple Myeloma

NCCN Guidelines Index
Table of Contents
Discussion

MYELOMA THERAPY[a-d]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[l,m]

Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)[n]
- Daratumumab[f]/bortezomib/dexamethasone (category 1)
- Daratumumab[f]/carfilzomib/dexamethasone (category 1)
- Daratumumab[f]/lenalidomide/dexamethasone (category 1)
- Isatuximab-irfc/pomalidomide/dexamethasone (category 1)[o]
- Ixazomib/lenalidomide/dexamethasone (category 1)[n]
- Ixazomib/pomalidomide[p]/dexamethasone
- Pomalidomide[p]/bortezomib/dexamethasone (category 1)

Other Recommended Regimens

- Belantamab mafodotin-blmf[q]
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Carfilzomib (twice weekly)/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
- Daratumumab[f]/pomalidomide[r]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Elotuzumab[s]/lenalidomide/dexamethasone (category 1)[n]
- Elotuzumab/pomalidomide/dexamethasone[r]
- Ixazomib/cyclophosphamide/dexamethasone
- Panobinostat[u]/bortezomib/dexamethasone (category 1)
- Pomalidomide[p]/cyclophosphamide/dexamethasone
- Pomalidomide[p]/carfilzomib/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Bortezomib/dexamethasone (category 1)
- Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
- Carfilzomib (weekly)/dexamethasone
- Daratumumab[f,v]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[h]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[h] ± bortezomib (VTD-PACE)[h]
- High-dose cyclophosphamide
- Ixazomib/dexamethasone
- Lenalidomide/dexamethasone[t] (category 1)
- Panobinostat[u]/carfilzomib
- Panobinostat[u]/lenalidomide/dexamethasone
- Pomalidomide[p]/dexamethasone[t] (category 1)
- Selinexor/dexamethasone[w]
- Venetoclax/dexamethasone only for t(11;14) patients

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of Myeloma Therapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I).
[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[h] Generally reserved for the treatment of aggressive multiple myeloma.
[l] Consideration for appropriate regimen is based on the context of clinical relapse.
[m] If a regimen listed on this page was used as a primary induction therapy and relapse is >6 mo, the same regimen may be repeated.
[n] Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[o] Indicated for patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.
[p] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[q] Indicated for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.
[r] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor.
[s] Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[t] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.
[u] Indicated for the treatment of patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent.
[v] Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[w] Indicated for patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

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.

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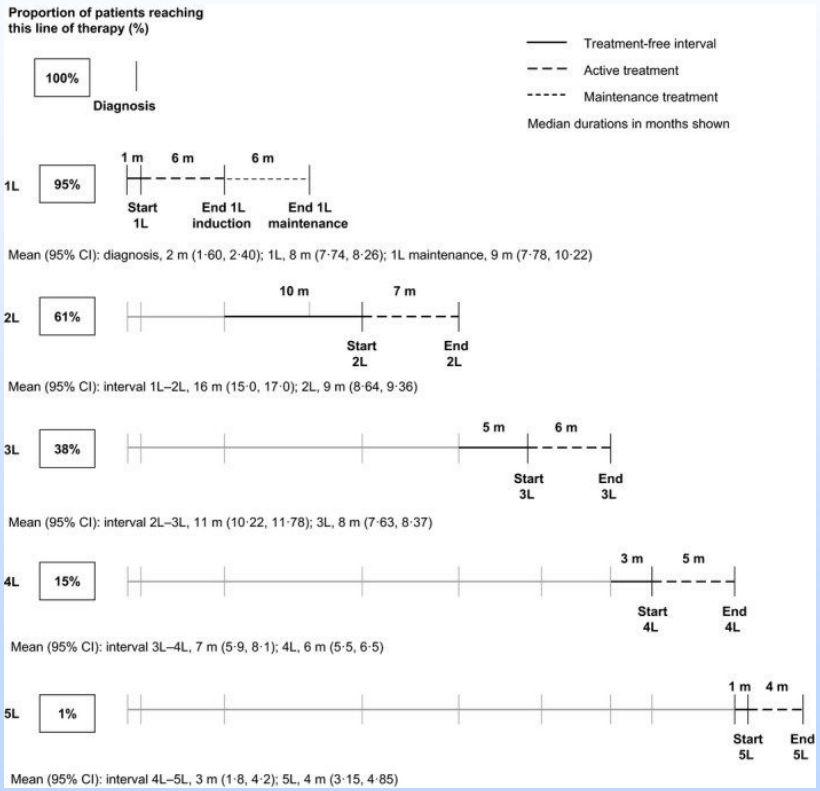
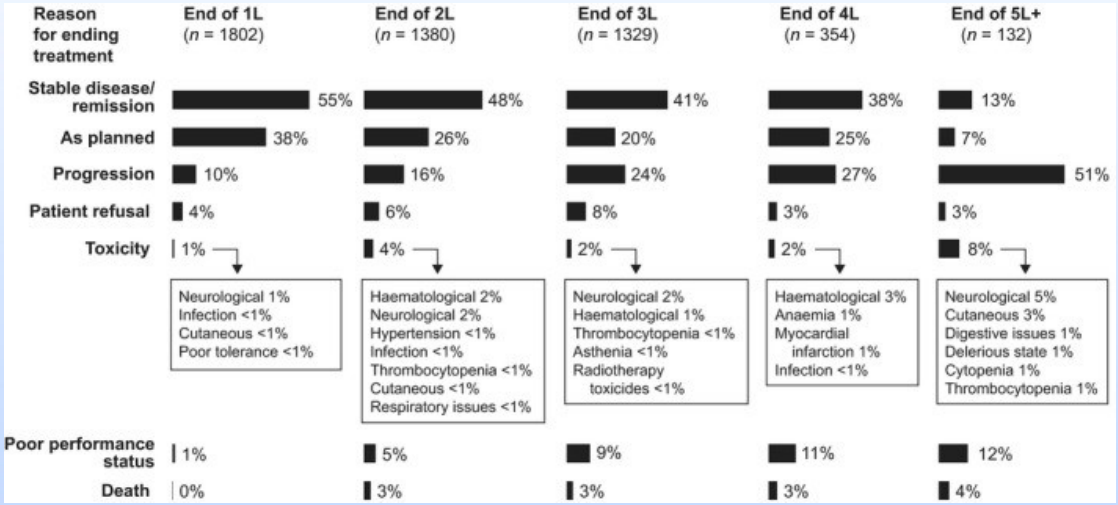
High Rate of Attrition with Subsequent Lines of Treatment in RRMM





Br J Haematol. 2016 Oct;175(2):252-264

Factors to Consider…

Risk Stratification

Early vs. Late Relapse

Age

Transplant Intended or Not

Prior Therapy

Biochemical vs. Clinical Relapse

Relapsed and/or Refractory

Frailty Index

Comorbidities

Residual Adverse Events

Patient Preferences

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Informed Decision Making

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Factors to Consider…

- What are your main treatment goals of therapy? Stable disease vs CR?
- What factors influence you to either re-challenge with previous therapy or switch to a new regimen?
- What are the pros and cons of various therapies currently available?
  - Carfilzomib, Daratumumab, Elotuzumab, Ixazomib, IMiDs
- How do you optimally sequence available therapies?
- Some attempts at assimilating the data, since all regimens cannot be compared in prospective randomized trials.

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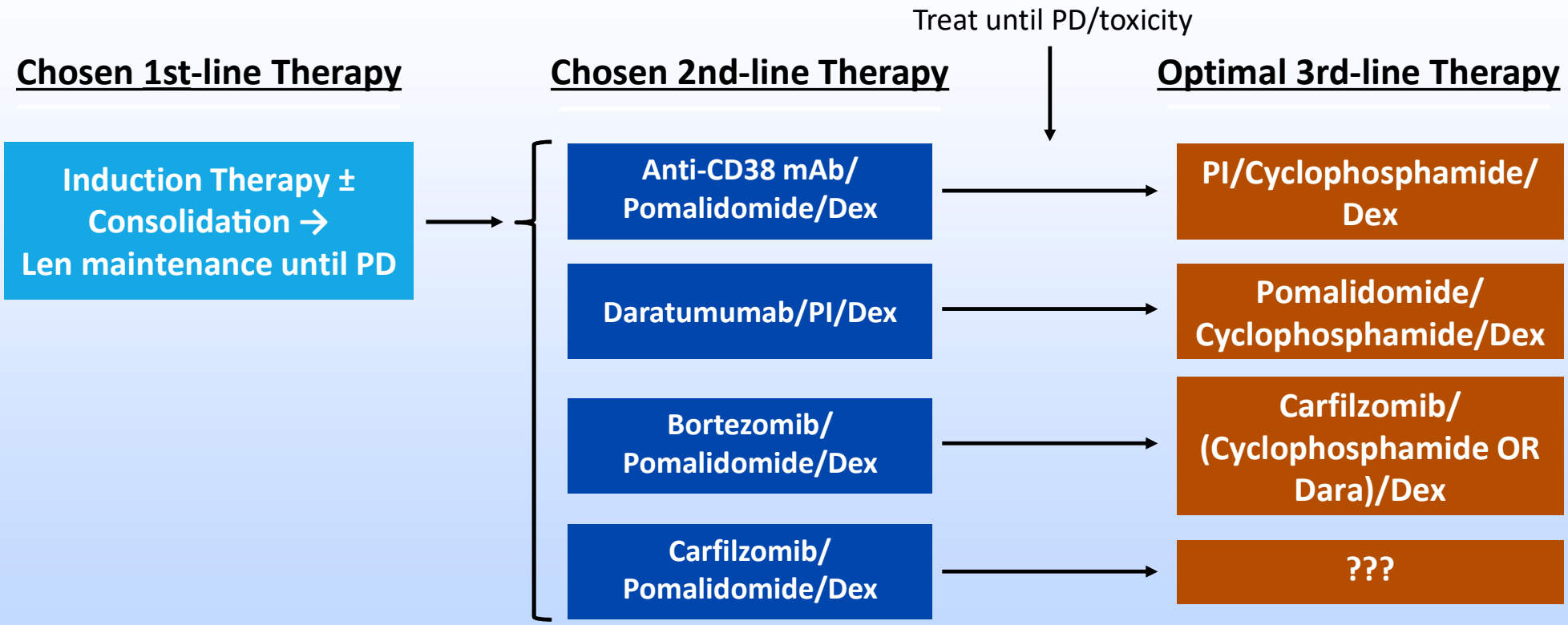
Therapeutic Strategies for Patients With MM After Relapse



3rd-line treatment choice can largely be chosen based on prior therapy and previous resistance patterns

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General Principles

- Duration of initial response defines disease biology
- Triplets (2 active classes + dex) preferred over doublets
  - Include at least 1 drug from a non-refractory class
- Treat to maximum response and maintain on one drug until progression or intolerability
- Prior drug exposure (refractory), residual toxicities } Drugs/Combinations
- Age, frailty, patient preferences, goals of care, logistics } Dose/Schedule
- Risk stratification, transplant eligibility } Overall goal/approach

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Early Relapse

Not Refractory to Bortezomib

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Agents in Relapsed MM: PI-based Studies

Outcomes	CASTOR DVd vs Vd[1]	ENDEAVOR Kd vs Vd[2]	PANORAMA PVd vs Vd[3,4]	ELOQUENT EVd vs Vd[5]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
ORR, %	83	77	61	66
Median PFS, mos	NR	18.7	12.0	9.7
≥ VGPR, %	59	54	28	36
≥ CR, %	19	13	11	4
DoR, mos	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47-1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Palumbo. NEJM. 2016;375:754. 2. Dimopoulos. Lancet Oncol. 2016;17:27. 3. San-Miguel JF. Lancet Oncol. 2014;15:1195. 4. San-Miguel. Blood. 2015;126. Abstr 3026. 4. Jakubowiak A. Blood. 2016;127:2844.

Early Relapse

Not Refractory to Lenalidomide

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Rd-based Triplet Therapy for Early Relapse

- TOURMALINE-MM1: Rd ± ixazomib for relapsed and R/R MM patients with 1-3 prior lines of therapy[1]
- ELOQUENT-2: Rd ± elotuzumab for R/R MM patients with 1-3 prior lines of therapy[2]
- ASPIRE: Rd ± carfilzomib for relapsed MM patients with 1-3 prior lines of therapy[3,4]
- POLLUX: Rd ± daratumumab for R/R MM patients with ≥ 1 prior line of therapy[5]

Outcome	TOURMALINE-MM1[1]		ELOQUENT-2[2]		ASPIRE[3,4]		POLLUX[5]	
	Rd	IRd	Rd	ERd	Rd	KRd	Rd	Dara-Rd
ORR, %	72*	78*	66	79*	66.7*	87.1*	76.4*	92.9*
≥ VGPR, %	39*	48*	29	35	40.4*	69.9*	49.3*	80.4*
Median PFS, mos	14.7*	20.6*	14.9*	19.4*	17.6*	26.3*	17.5*	44.5*
HR for PFS	0.74 (95% CI: 0.59-0.94)		0.71 (95% CI: 0.59-0.86)		0.69 (95% CI: 0.57-0.83)		0.40 (95% CI: 0.24-0.67)	
Median OS, mos	NR	NR	NR	NR	40.4*	48.3*	NR (42-mo OS: 57%)	NR (42-mo OS: 65%)

*$P < .05$

1. Moreau. NEJM. 2016;374:1621. 2. Dimopoulos. Cancer. 2018;124:4032. 3. Stewart. NEJM. 2015;372:142. 4. Siegel. J Clin Oncol. 2018;36:728. 5. Bahlis. Leukemia. 2020;[Epub].

Early Relapse

Refractory to Lenalidomide AND Bortezomib

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Pomalidomide-based Salvage Therapy for R/R MM

Trial	Patient Population	Primary Endpoint	ORR, %	≥ VGPR, %	Median PFS, Mos	Median OS, Mos
Pom/Dex (N = 302)[1] Phase III trial vs HD Dex	R/R; ≥ 2 lines of tx including len and btz	PFS	31 vs 10	6 vs < 1	4.0 vs 1.9	12.7 vs 8.1
Bortezomib + Pom/Dex (N = 559)[2] OPTIMISMM Phase III trial vs Vd	1-3 lines of tx with len exposure; prior PI ok	PFS	82 vs 50	53 vs 18	11 vs 7	NR
Carfilzomib + Pom/Dex (N = 57)[3]	R/R to most recent tx; 1-3 lines of tx; len refractory	MTD, PR rate	62	23	10.3	NR (1 yr: 67%)
Daratumumab + Pom/Dex (N = 103)[4]	R/R; ≥ 2 lines of tx, including len and btz	MTD	60	42	8.8	17.5
Ixazomib + Pom/Dex (N = 32)[5]	1-5 lines of tx, including len and PI; len refractory	MTD activity	48; high risk: 58	20	--	--
Elotuzumab + Pom/Dex (N = 60)[6] Phase II trial vs Pom/Dex	≥ 2 lines of tx including IMiD and PI; refractory to last tx	PFS	53 vs 26	20	10.3 vs 4.8	--
Isatuximab + Pom/Dex vs no Isa (N = 307) [6] ICARIA-MM Phase III trial	3 prior lines of therapy; 97% len refractory, 77% PI refractory, 72% double refractory	PFS	60 vs 35	32 vs 8	11.5 vs 6.5	--

1. San Miguel. Lancet Oncol. 2013;14:1055. 2. Richardson. Lancet Oncol. 2019;20:781. 3. Bringhen. Leukemia. 2018;32:1803. 4. Chari. Blood. 2017;130:974. 5. Krishnan. Leukemia. 2018;32:1567. 6. Dimopoulos. NEJM. 2018;379:1811. 7. Attal. Lancet. 2019;394:2096.

Early Relapse

Refractory to Lenalidomide, Bortezomib AND Daratumumab

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Options…

- Selinexor
- Panobinostat
- Belantamab
- ? Carfilzomib
- ? Pomalidomide
- ? Elotuzumab (No data of efficacy post-daratumumab)
- Venetoclax [for t(11;14)]

- CLINICAL TRIALS

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Some Real-World Findings…

- PI/IMiD combinations are most frequently used.
- Daratumumab utilization quite high
- Triplet use on the rise, but still at least a third of patients receive doublets
- Duration of therapy and TTNT much lower than in clinical trials
- SCT utilization lower than expected for eligible patients

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1. Ailawadhi, et al. ASH 2019. 2. Sanchez, et al. ASH 2020

Clinical Pearls in RRMM…

- Carfilzomib resistance = bortezomib/ixazomib resistance
- Pomalidomide resistance = lenalidomide resistance
- Whether daratumumab resistance = isatuximab resistance is not yet known
  - Activity in cross-trial comparisons very similar

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Conclusions

- Therapeutic advances have led to prolonged survival in MM, but it remains a chronic disease
- Treatment of myeloma requires a long-term strategy
- Key is delivering the best “package” of treatment at a given stage
- Optimal combinations and sequencing is key
- Risk stratified approach in clinic
- Future will be in developing more individualized approaches

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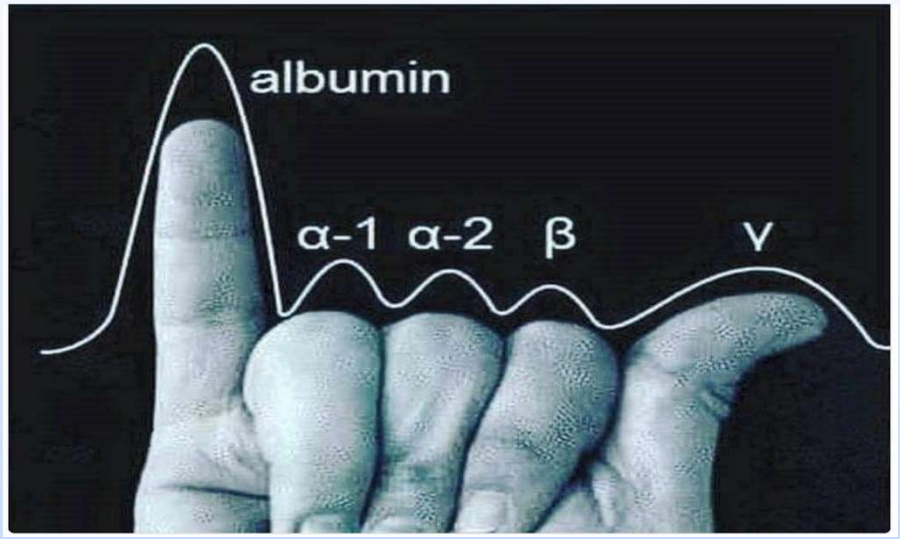

Thank You!