High Risk Multiple Myeloma Patients Management

A case presentation

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12/12/1401

- A 54 -years old -gentleman referred to hematology clinic with severe generalized bone pain since 2 months
- PMH: neg
- DH: neg
- Lab tests:

CBC-diff

WBC = 4100 /ml

Hgb = 9.2 gr/dl

PLT = 143000/ml

ESR = 98 mm/hr

Ca = 12 mg/dL

Alk-p = 212 IU/L (nl)

Cr = 2.6 mg/dL

SPEP = 4gr/dL m-peak

SIEP = IgG /Kappa

TP =7.2 gr/dl

- **BMB/A** : suboptimal sample, but a sheet of PC in interlobular marrow was seen suggestive of plasma cell dyscrasia
- **IHC**: CD38 + / CD56 + / CD138 + strong positive in almost all PCs
- **FLOWCYTOMETRY**: 10 to 15 % PC was seen that according to specific expression markers on PCs, MM is diagnostic

SKULL X ray : multiple punched out lytic lesions

Question 1:

You are a Hematologist & Oncologist in Mashhad ,Esfahan ,Kermanshah ,Sari,….

- Which of the following tests is your choice In routine practice?

1- **LDH, B2M, ALb -- whole bone x ray survey**

2- Cytogenetic + FISH study from BM ---PET-ct scan or Thoraco lumbosacral MRI

3- Non of them (initial tests are enough for diagnosis and treatment)

4- Both of them +/_ PET or MRI

- Result!

- Result!

Question?

- How do you stratify the Risk in MM patient in clinic
- In patient without any symptoms in bone , with lytic lesions in skull x Ray do you recommend whole body MRI or PET-Ct scan in routine practice?
- Role of flowcytometry in diagnosis?
- Review of new risk stratification by FISH study

IMWG Criteria for Diagnosis of MM

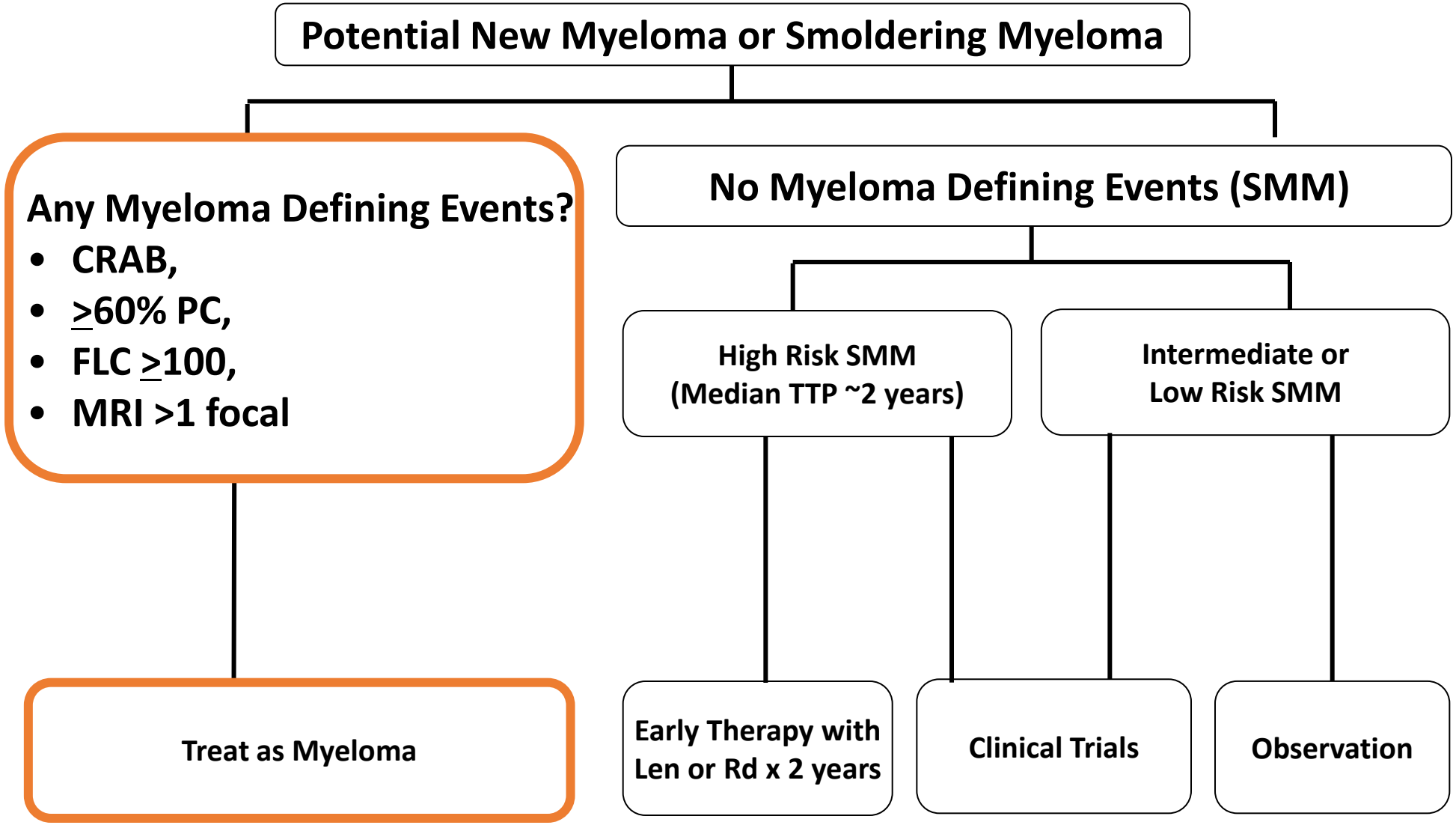
MGUS	Smoldering Myeloma	Active or Symptomatic Multiple Myeloma
▪ M protein < 3 g/dL ▪ Clonal plasma cells in BM < 10% ▪ No myeloma-defining events	▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) ▪ Clonal plasma cells in BM ≥ 10% to 60% ▪ No myeloma-defining events	▪ Underlying plasma cell proliferative disorder ▪ AND ≥ 1 SLiM-CRAB* features

*S: ≥60% clonal bone marrow plasma cells
Li: Serum free light chain ratio ≥100 (involved kappa) or ≤0.01 (involved lambda)
M: MRI studies with >1 focal lesion (≥5 mm in size)

C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (CrCl <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hb <10 g/dL or 2 g/dL less than LLN)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET/CT)

Rajkumar. Lancet Oncol. 2014;15:e538.

MAYO CLINIC



Rajkumar SV. 2022

Current Role for Imaging in MM

	Skeletal X-Ray	Low-Dose Whole Body CT	Whole Body MRI	^{18}F-FDG PET/CT
Diagnosis	✓	✓	✓	✓
Monitoring			✓	✓
Detection of lytic lesions	✓	✓	✓	✓
Detection of focal lesions			✓	✓
Detection of extraosseous lesions			✓	✓
Advantages	Low cost; widely available	Higher sensitivity; short imaging time	High sensitivity; detects early bone damage; focal and diffuse lesions can be prognostic	High sensitivity; ^{18}F-FDG SUV prognostic; determine response to treatment and evaluate relapse/progression
Disadvantages	Lower sensitivity	Limited use for diffuse or non-lytic lesions; some limited availability	Higher cost; longer imaging time; limited availability	Higher cost; potentially limited availability
Use	Not recommended	Recommended for routine clinical practice	Recommended if CT is negative; for suspected cord compression	Recommended to detect EMD

Zamagni. Blood. 2019;133:644.

Clinical Case and Question?

- Patient fulfills criteria for active MM
- Spine MRI showed multiple lytic lesions without FX (requested just because of patient symptom)
- ↑ B2M= 4,2 mg/L, ↓ ALb= 3.3 mg/dL , LDH = 243 IU/L (NL)
- The patient was diagnosed with ISS stage 2, R-ISS stage2 MM
- Was considered to have **high-risk cytogenetics due to gain(1q).**

- **According to the last updated guidelines,which induction therapy, is optimal for this patient?**

1- **VCD X 4 course** then early ASCT

2- frontline**, VCD** and after recovery of kidney ,**change to VRD** (total 4 to 6 course)+ early ASCT

3- **Dara+VTD** 4 to 6 course then early ASCT

4- Dara + KTD 4 to 6 course then early ASCT

Result

Result

International Staging System (ISS) for Multiple Myeloma

Stage	VALUES (β2M = Serum β2 microglobulin; ALB = serum albumin
I	Sβ2M < 3.5 mg/L; serum albumin ≥ 3.5 g/dL
II	Sβ2M < 3.5 mg/L; serum albumin < 3.5 g/dL; or β2M 3.5 to 5.5 mg/L, irrespective of serum albumin
III	Sβ2M > 5.5 mg/L

Revised International Staging System (R-ISS)

Stage	Criteria
I	Sβ2M < 3.5 mg/l Serum albumin ≥ 3.5 g/dl Standard-risk chromosomal abnormalities (CA) by iFISH Normal LDH
II	Not R-ISS stage I or III
III	Sβ2M ≥ 5.5 mg/L and either High-risk CA by FISH OR High LDH

MAYO CLINIC

msmart.org

mSMART 3.0: Risk Stratification of Active MM

High-Risk Myeloma

- FISH
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - 1q gain

- Double-Hit Myeloma = any 2 high risk abnormalities
- Triple-Hit Myeloma = 3 or more high risk abnormalities

- **Relapse within 12 months of stem cell transplantation or progression within first year of diagnosis**

- **Extramedullary disease and/or plasma cell leukemia (PCL)**

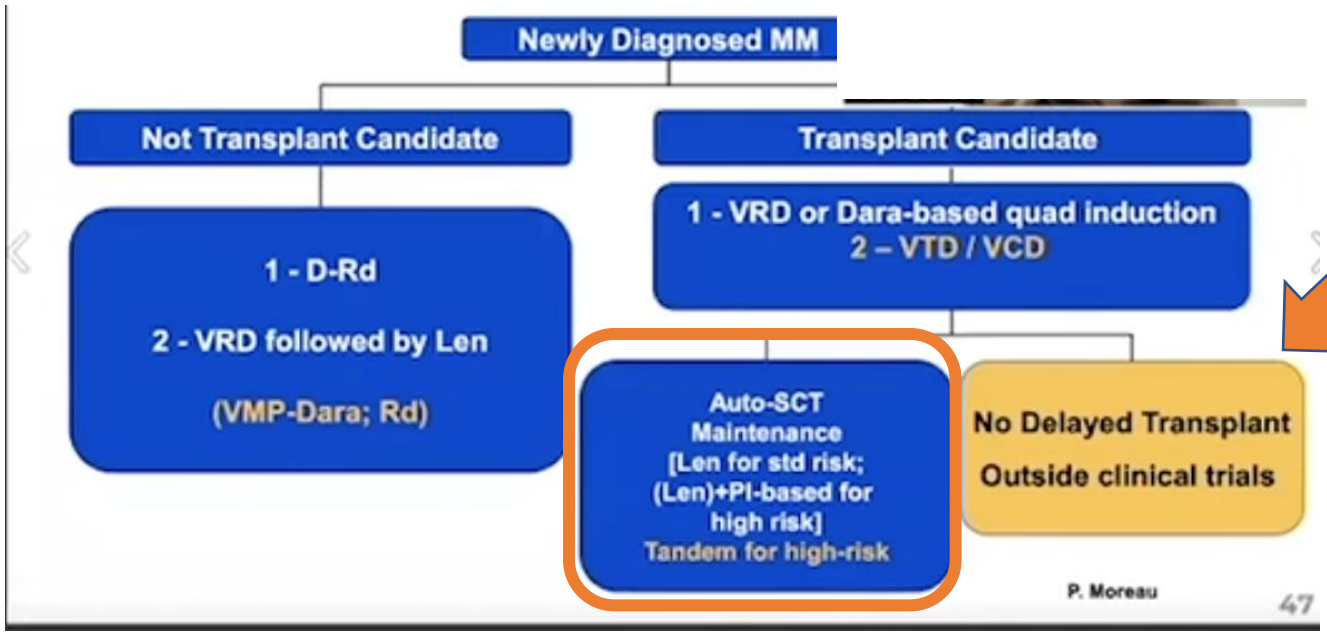
Standard-Risk Myeloma

All others including:

- Trisomies
- t(11;14) ← VENETOCLAX
- t(6;14)

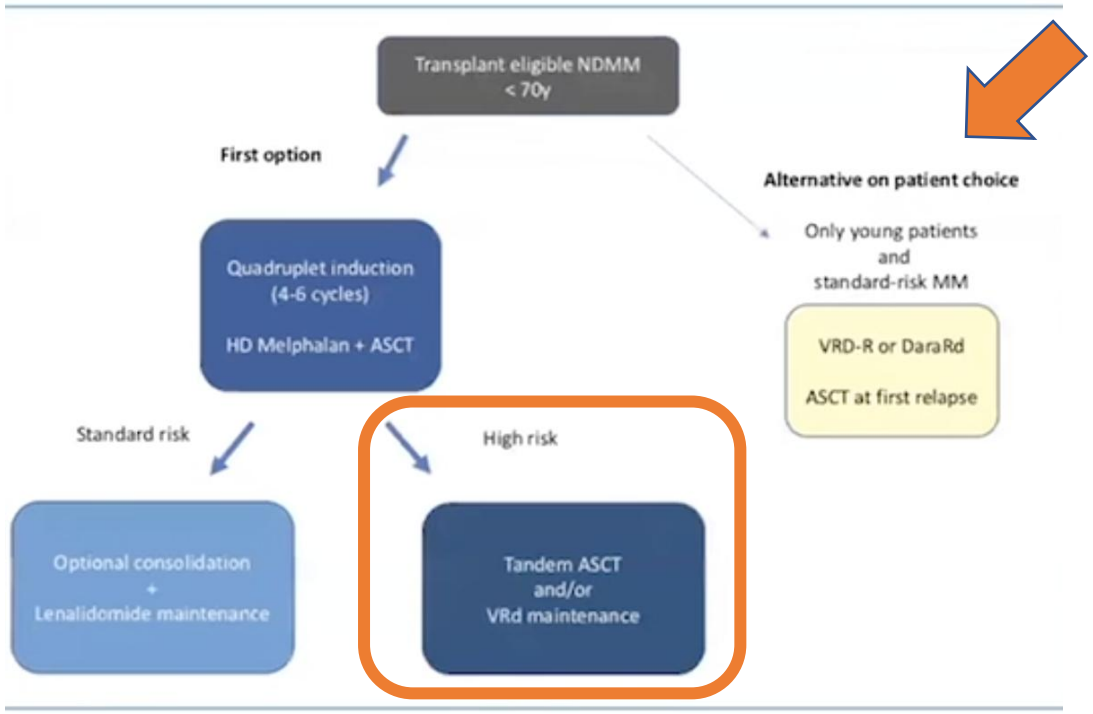
EHA-ESMO guidelines 2021:first line treatment

P.Moreau EHA 2021
Myeloma: frontline treatment



ASH guidelines 2021:first line treatment

Perrot Blood 2021
How I treat Frontline MM

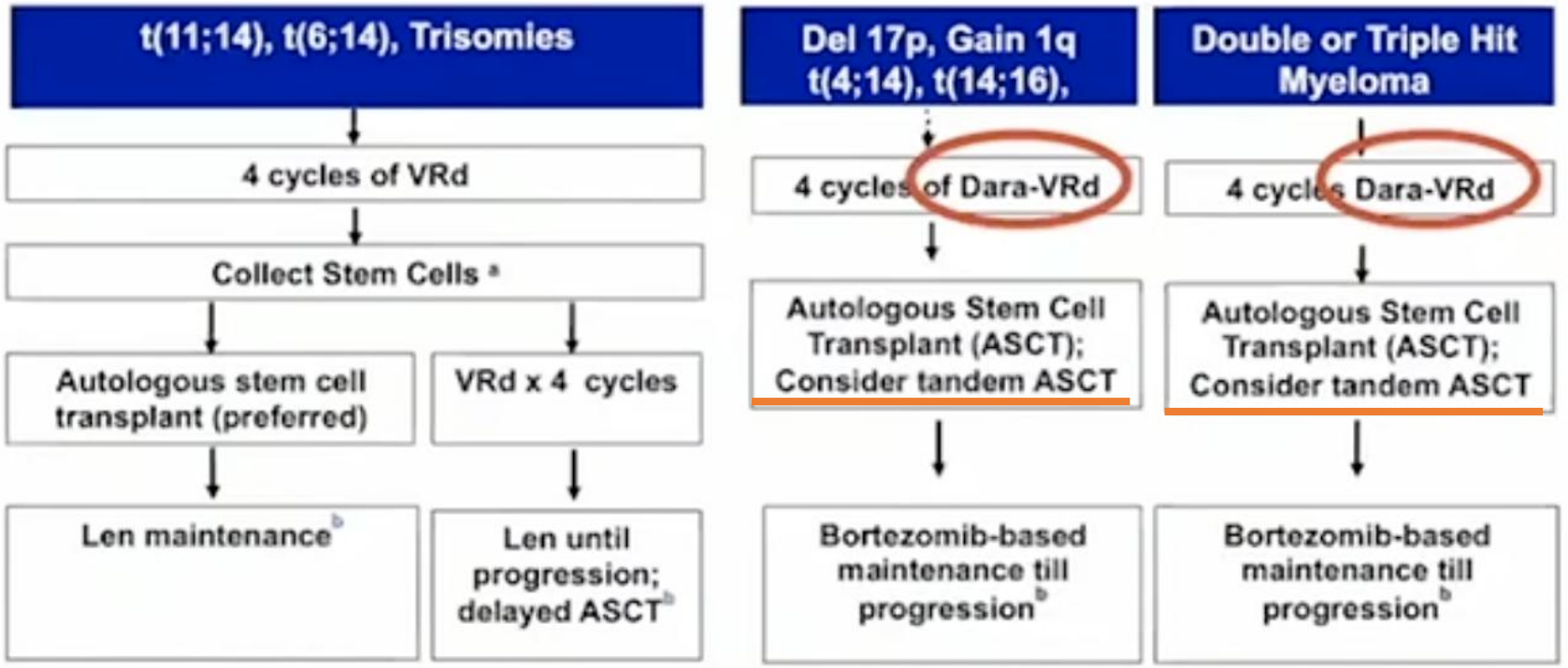


MAYO CLINIC

2021

mSMART – Off-Study

Transplant Eligible



a If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor; b Duration usually until progression based on tolerance

VRd, Bortezomib, lenalidomide, dexamethasone; Dara, daratumumab

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v19 //last reviewed Feb 2021

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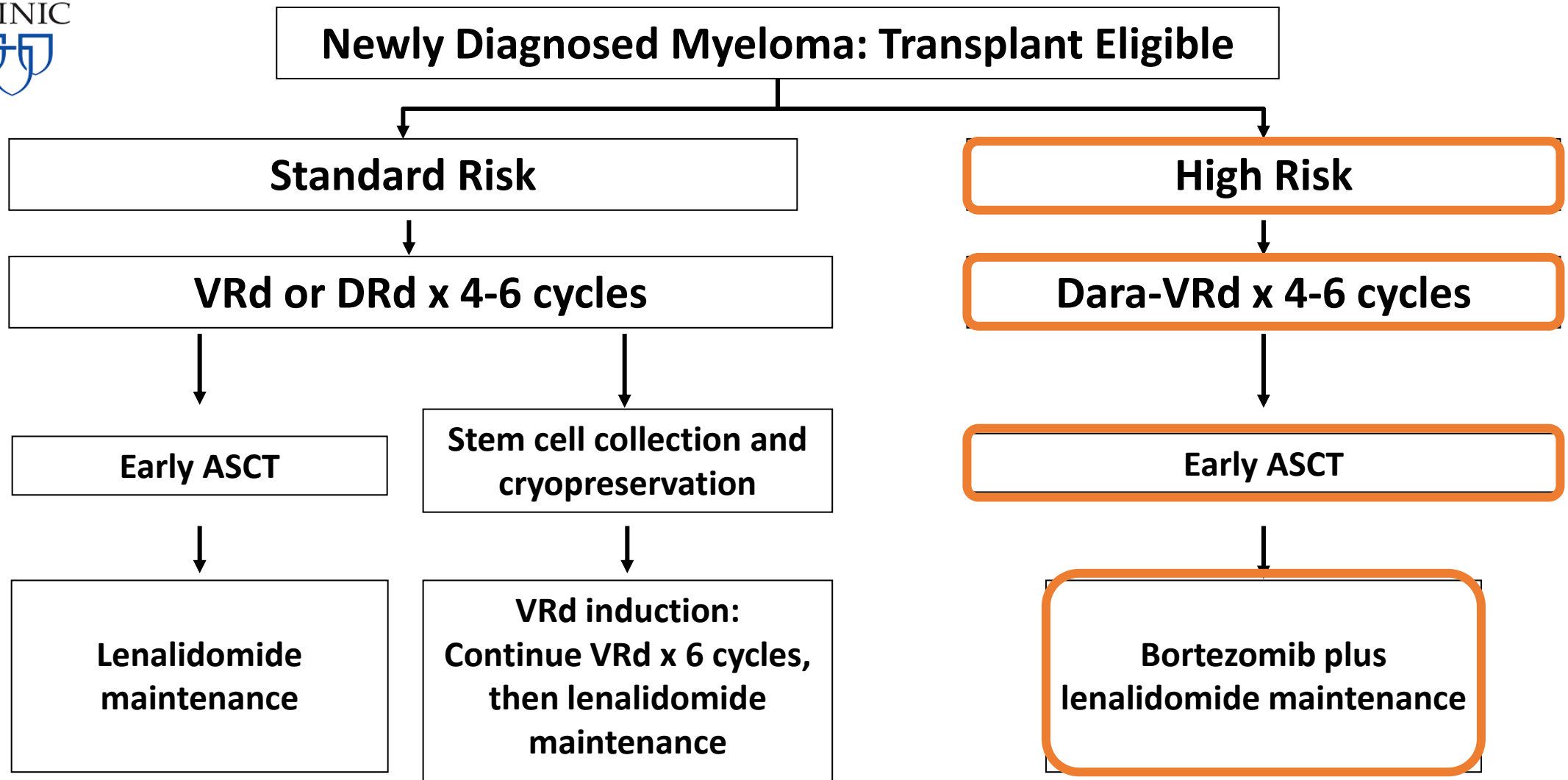
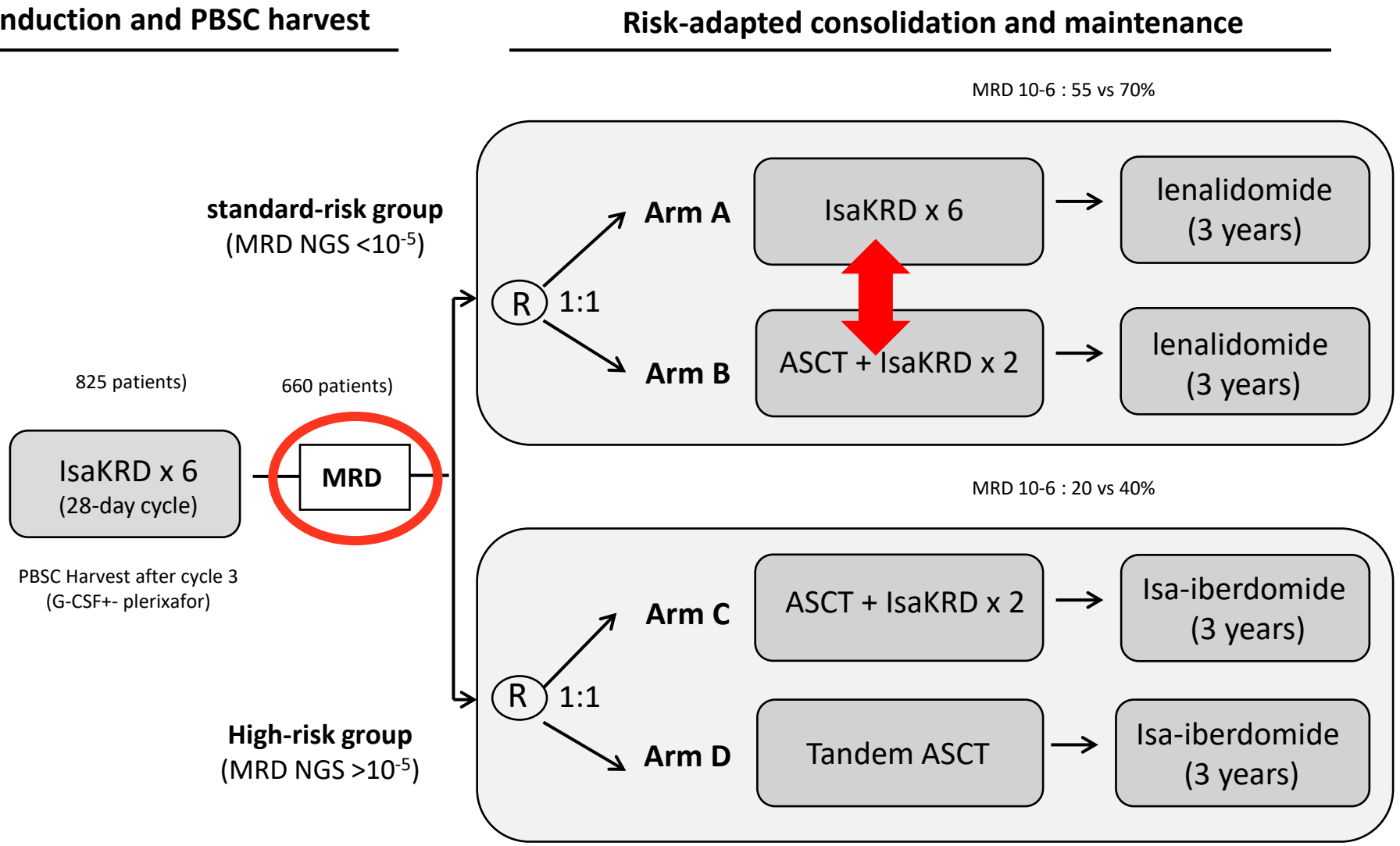
MAYO CLINIC



Rajkumar SV. 2022:

Initial therapy. The 3 main choices are VRd, DRd, and Dara-VRd. I prefer VRd. But the other options are reasonable. Transplant eligible patients need 3-4 cycles, then stem cell collection

MIDAS study : MInimal res Disease Adapted Strategy



NCT04934475

CLINICAL CASE

- VCD X 2 course was started then changed to VRD X 4 course after recovery of kidney and response to treatment

- At the End Of induction ,CBC ,ESR ,Ca ,BUN , Cr,B2M,ALB,SPEP ,were normal. **(VGPR)**

Some questions ?

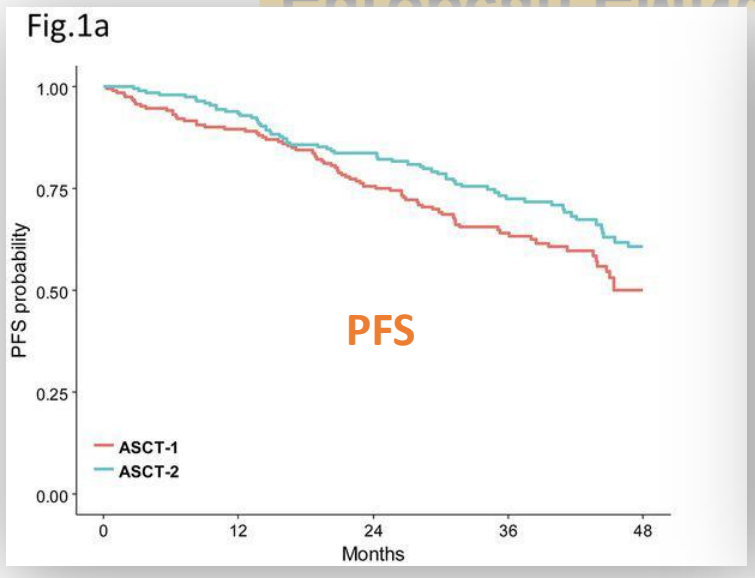
- Your opinion about imaging study for response assessment
- Do you recommend BMB/A after induction to confirm CR or sCR?
- What’s your opinion about Tandem ASCT?
- Role of MRD in multiple myeloma

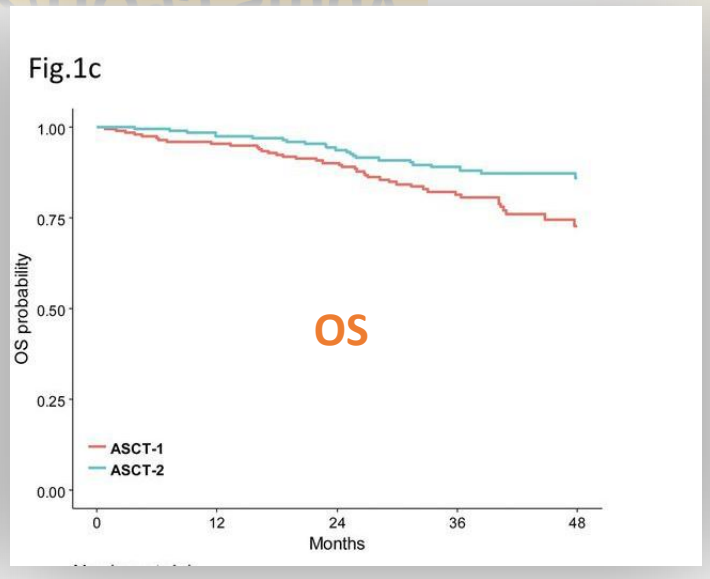
https://www.myeloma.org/videos/conversation-myeloma-experts-making-sense-evolving-treatment-landscape

SINGLE VERSUS TANDEM ASCT

- Some of the discrepancies between the **European** and **North American studies** have been attributed to variations in both the types and duration of induction therapies
- **PFS was superior in the tandem transplant arms** in all studies, whereas the OS rates were superior in only a few of them

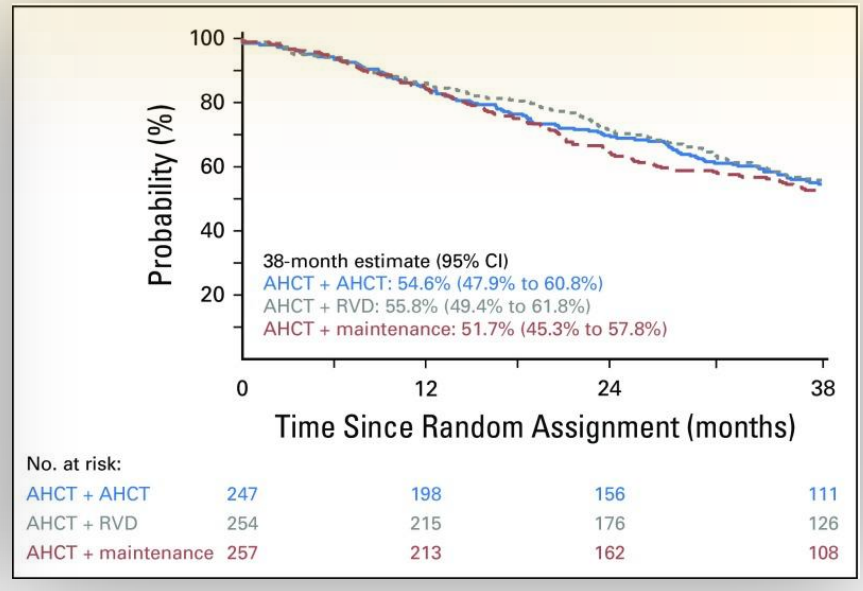
European EMN02/HO95 study





Significantly higher 3-year PFS

Results of the BMT CTN 0702 Trial



No differences between the 3 groups in terms of either PFS or OS

INTERNATIONAL MYELOMA FOUNDATION
Improving Lives Finding the Cure®

https://www.myeloma.org/resource-library/international-myeloma-working-group-imwg-uniform-response-criteria-multiple

HOME > INTERNATIONAL MYELOMA WORKING GROUP (IMWG) UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma

- The Difference between :
  - Progressive disease:
  - Clinical Relapse
  - Relapse from CR (To be used only if the end point studied is DFS)

	Response criteria*
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

(Table 4 and footnotes continue on the next page)

IMWG 2016

(Continued from previous page)

Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia)

*Globally, about 60 MRD laboratories are EuroMRD members and participate twice per year in the external quality assurance rounds.

https://sci-hub.3800808.com/10.1016/S1470-2045(16)30206-6

Review

LANCET ONCOL 2016

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé,

- Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression.(MGUS-Like)
- For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease.
- Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.
- In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.
- All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

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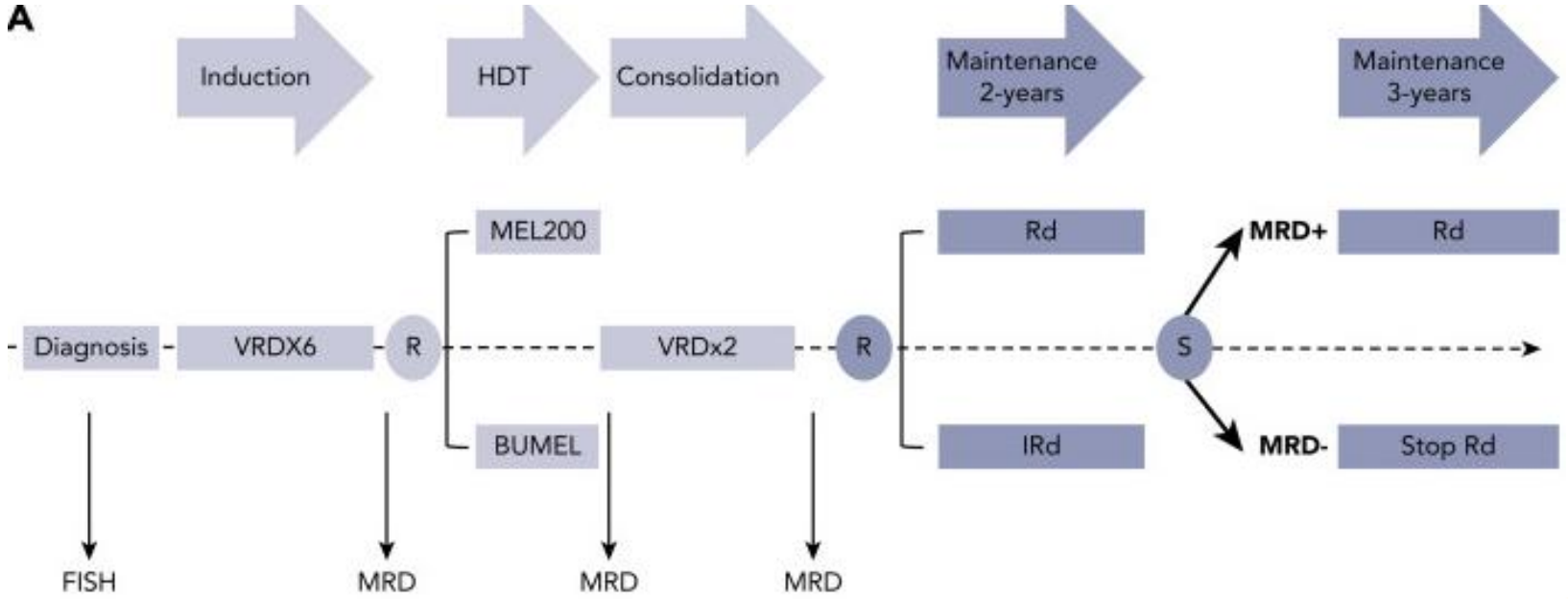
Validation of conventional IMWG response criteria is expired? or not yet ?

Blood. 2021 Nov 11; 138(19): 1901–1905.
doi: 10.1182/blood.2021012319

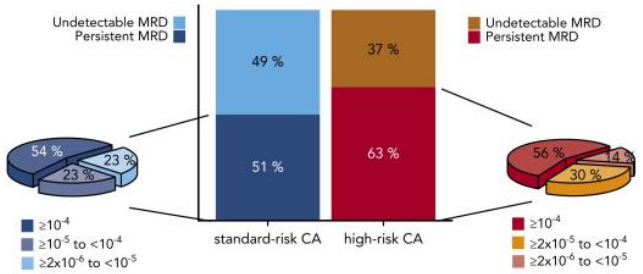
IS IT REPLACED BY MRD?

Validation of the International Myeloma Working Group standard response criteria in the **PETHEMA/GEM2012MENOS65 study**: **are these times of change?**



Dynamic risk stratification

it is now recognized that achievement of MRD negativity is a powerful prognostic factor—and in fact, multiple studies have shown that this is a more important prognostic factor than cytogenetic abnormalities



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Blood. 2021 Nov 11; 138(19): 1901–1905.
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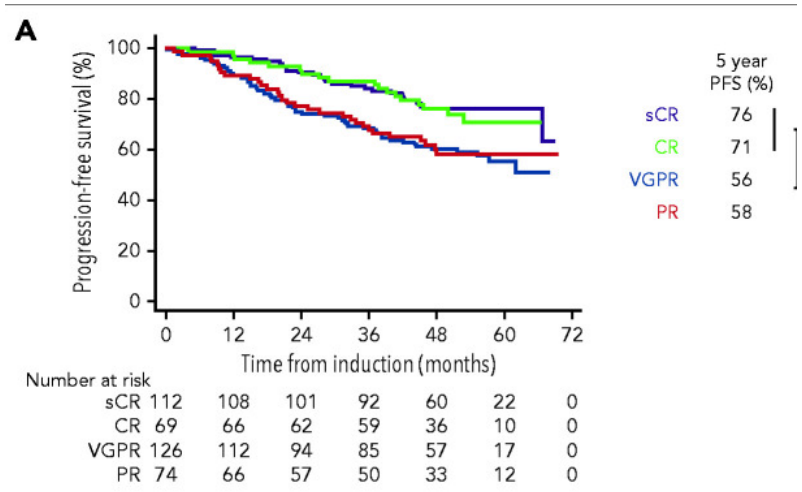
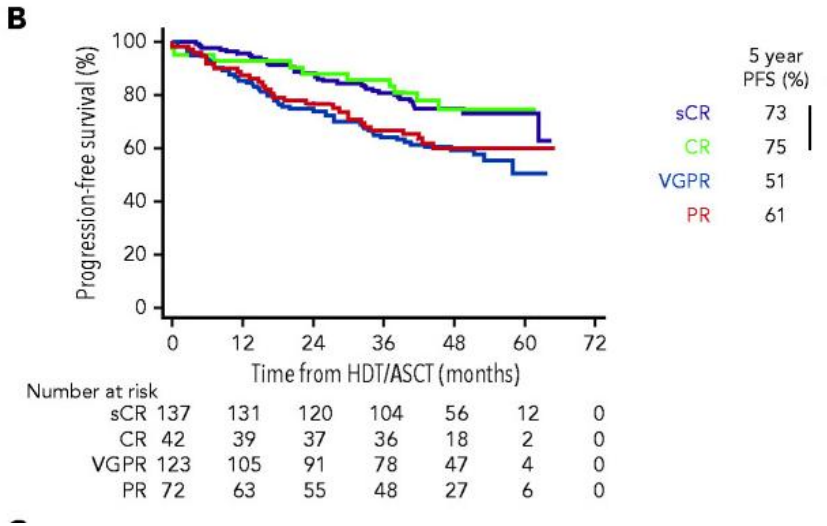
Validation of the International Myeloma Working Group standard response criteria in the PETHEMA/GEM2012MENOS65 study: are these times of change?



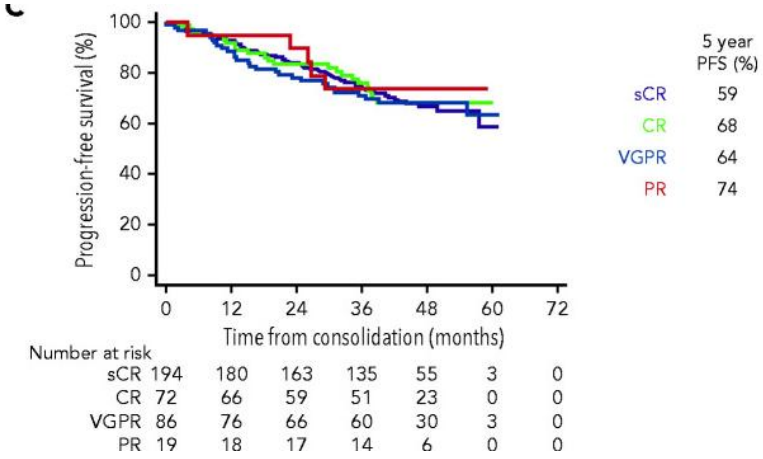
5Y PFS

after 6 induction cycles of VRD



5Y PFS

after ASCT conditioned with Bu-Mel or Mel-200 HDT



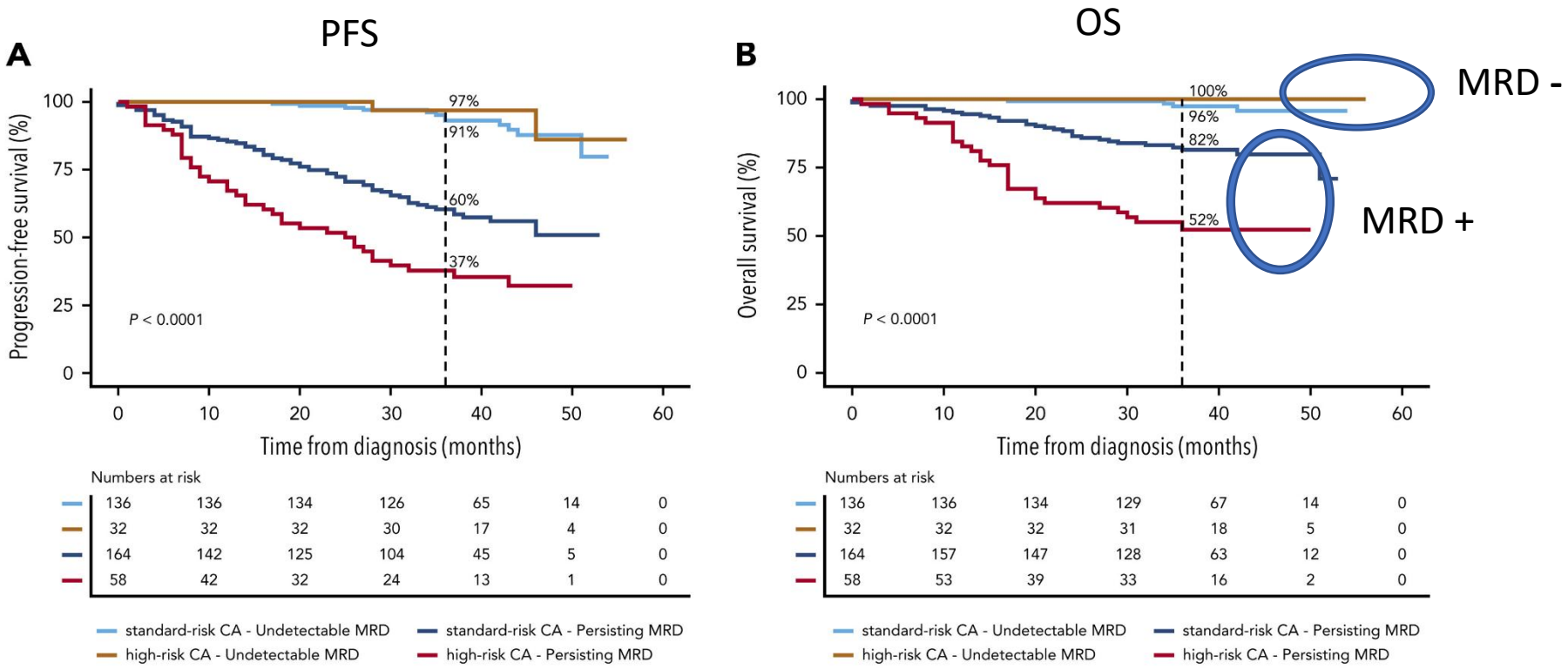
5Y PFS

After 2 consolidation cycles of VRD

blood®
Volume 137, Issue 1, 7 January 2021, Pages 49-60

Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma

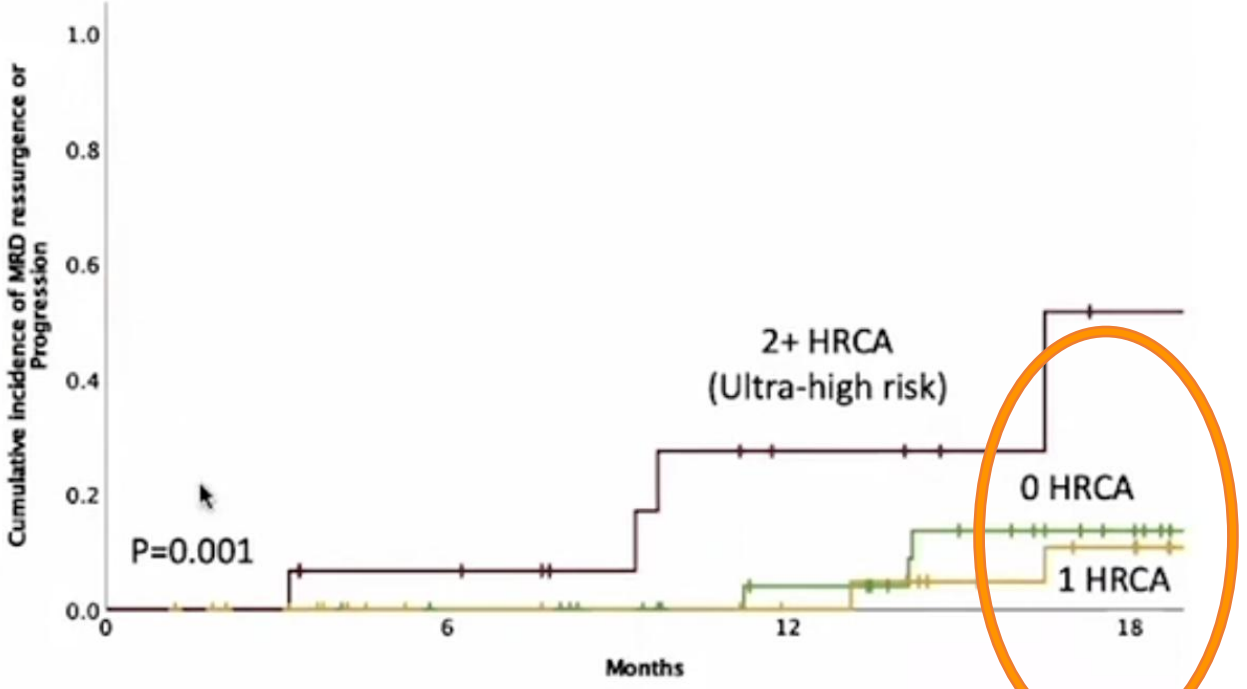
PETHEMA/GEM2012MENOS65 study



MRD-SURE

- 84 patients achieved MRD-SURE
  - 0 HRCA – 62%
  - 1 HRCA- 78%
  - 2+ HRCA – 63%
- Median follow up in MRD-SURE: 14.2 mo.
- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA – 4%
  - 1 HRCA- 0%
  - 2+ HRCA – 27%
- **None** of patients entering MRD-SURE died from MM progression

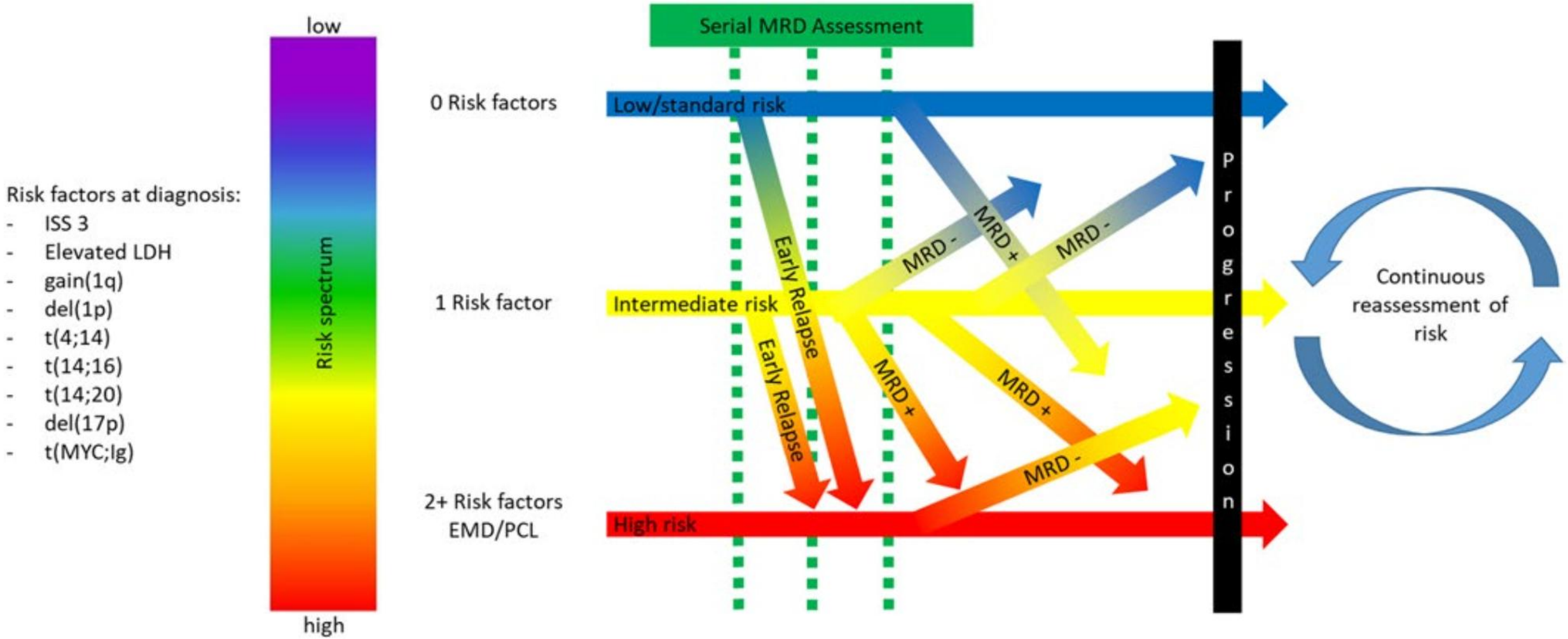
Cumulative incidence of MRD resurg



No. at risk:				
0 HRCA	33	31	23	12
1 HRCA	36	24	21	14
2+ HRCA	15	23	5	0

MASTER trial

HRCA = t(4;14)/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)



ASH 2022 Education Book MM

Care should be taken:

- Not to abandon the context provided by risk stratification at diagnosis.

- Some patients with standard-risk disease experience years of survival without MRD negativity—
  - as seen for those with a monoclonal gammopathy of undetermined significance-like expression profile and many of the “exceptional responders” to lenalidomide therapy

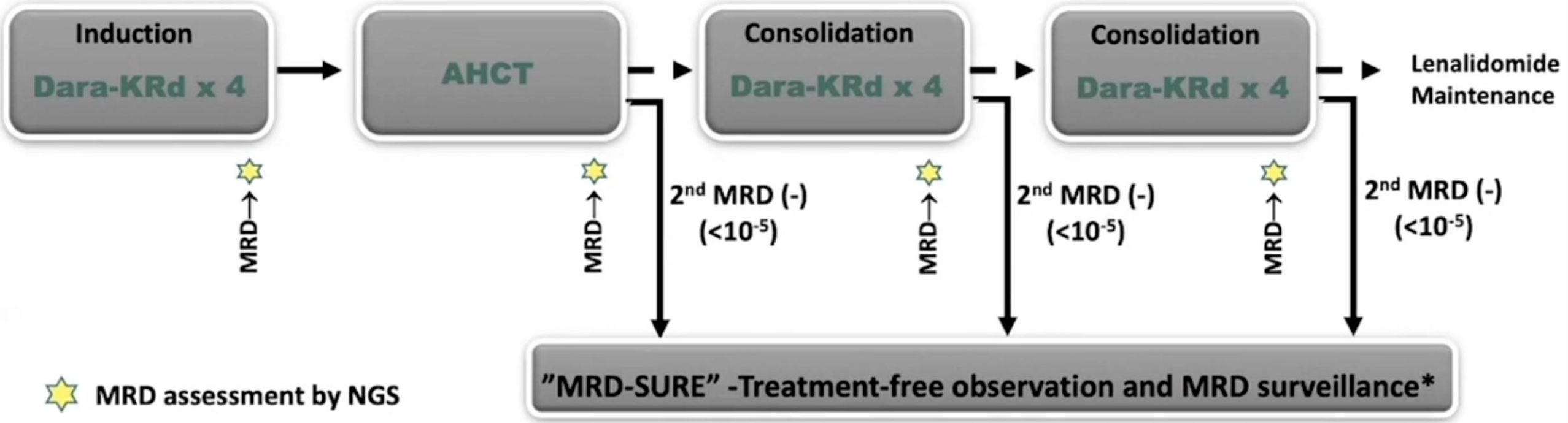
Rodríguez-Otero P, Mateos MV, Martínez-López J, et al. Predicting long- term disease control in transplant-ineligible patients with multiple mye- loma: impact of an MGUS-like signature. *Blood Cancer J*. 2019;9(4):36.

- By contrast, despite sustained MRD negativity in the MASTER trial, much higher rates of MRD resurgence or progression were seen after treatment discontinuation among patients with ≥2 high-risk FISH abnormalities

Treatment

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

MASTER trial

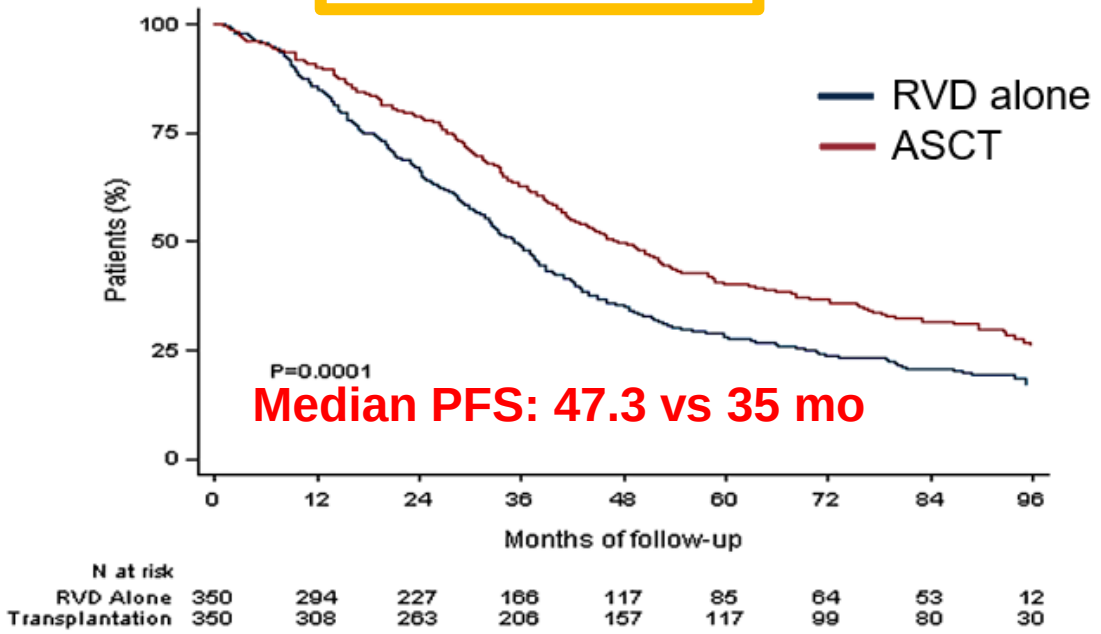
Clinical Case

- VCD X 2 course was started then changed to VRD X 4 course after recovery of kidney and response to treatment
- At the End Of induction CBC, ESR, Ca, BUN, Cr, B2M, ALB, SPEP, SIEP were normal. **(VGPR)**
- Lenalidomide maintenance + 2-3 mg Bortezomib ,SC , every 2 weeks, was started !!
- Early ASCT was considered and for tandem ASCT adequate stem cell was harvested
- After 2 months he received first high dose melphalan and stem cell transplantation was done but he refused tandem ASCT
- After 3 months of ASCT ,suboptimal hematologic recovery was occurred and maintenance with 10mg lenalidomide was started(due to poor compliance he can't received treatment dose)
- He refused injection of Bortezomib

Question ?

What should the ideal duration of therapy be for first-line MM?

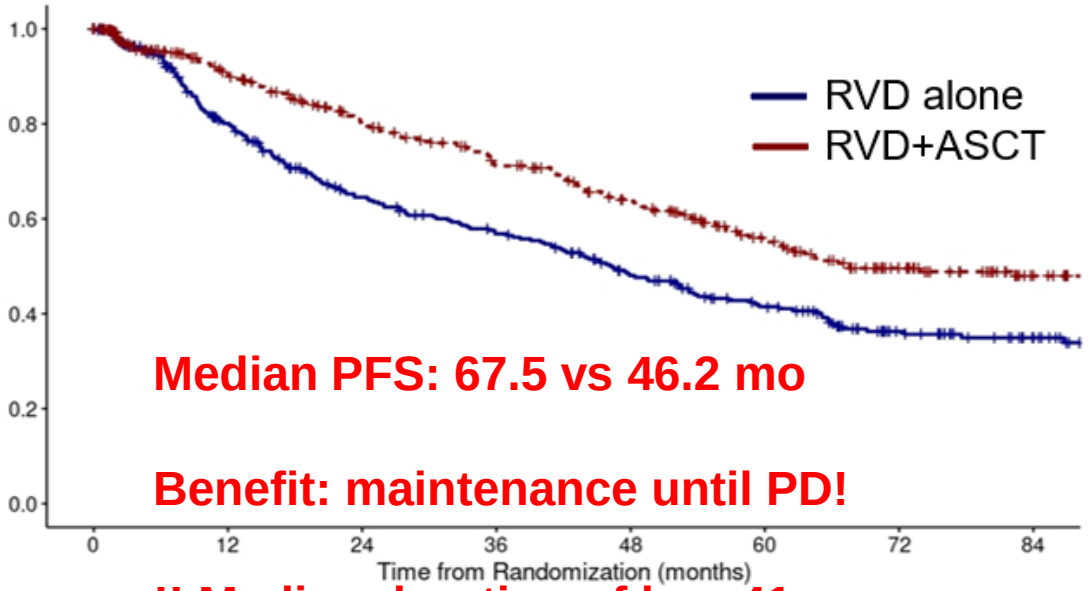
1 year Lenalidomide



Attal et al. N Engl J Med 2017
Perrot et al. ASH 2020

open-label, phase 3 trial conducted at 69 centers in France, Belgium, and Switzerland.

Until progression Lenalidomide



Median PFS: 67.5 vs 46.2 mo

Benefit: maintenance until PD!

!! Median duration of len: 41 mo

Richardson et al. N Engl J Med 2022

3 DETERMINATION trial, which was originally designed as a parallel study to the IFM 2009 trial but was amended to include the use of lenalidomide maintenance therapy until disease progression in both the RVD-alone group and the RVD-plus-ASCT (transplantation) group.

Clinical Case

- After 6 months of ASCT, he came to clinic with new M-Peak in SPEP but without any symptom and sign:

Mini peak in gamma region = 1 gr/dl

Other lab tests:

- **WBC** =3400 /ml
- **Hgb** =10,9
- **PLT** =178000/ml
- **Ca** =8,2 mg/dL
- **ESR** = 23 mm/hr
- **Cr** =0.9 mg/dL
- **B2M** =2.2 mg/L
- **LDH** =227
- **Alb** = 4.4

Question?

- What’s your next approach in routine practice?

BMB/A

1- **YES**

2- **NO**

Result

Result

Question?

- WHAT'S YOUR NEXT TREATMENT CHOICE?

1- **VRD** FOLLOWED BY ASCT

2- **Dara+Rd** OR **Dara+Vd** followed by ASCT

3- Treatment dose of **lenalidomide(25 mg) and weekly dexamethasone**

4- **VRd** OR **DRd** or **KRd** or **Pomalidomid +Vd** then followed by **allo-SCT** in case of available HLA-match sibling donor

5- **DRd until progression**

6- 3 , 4 , 5

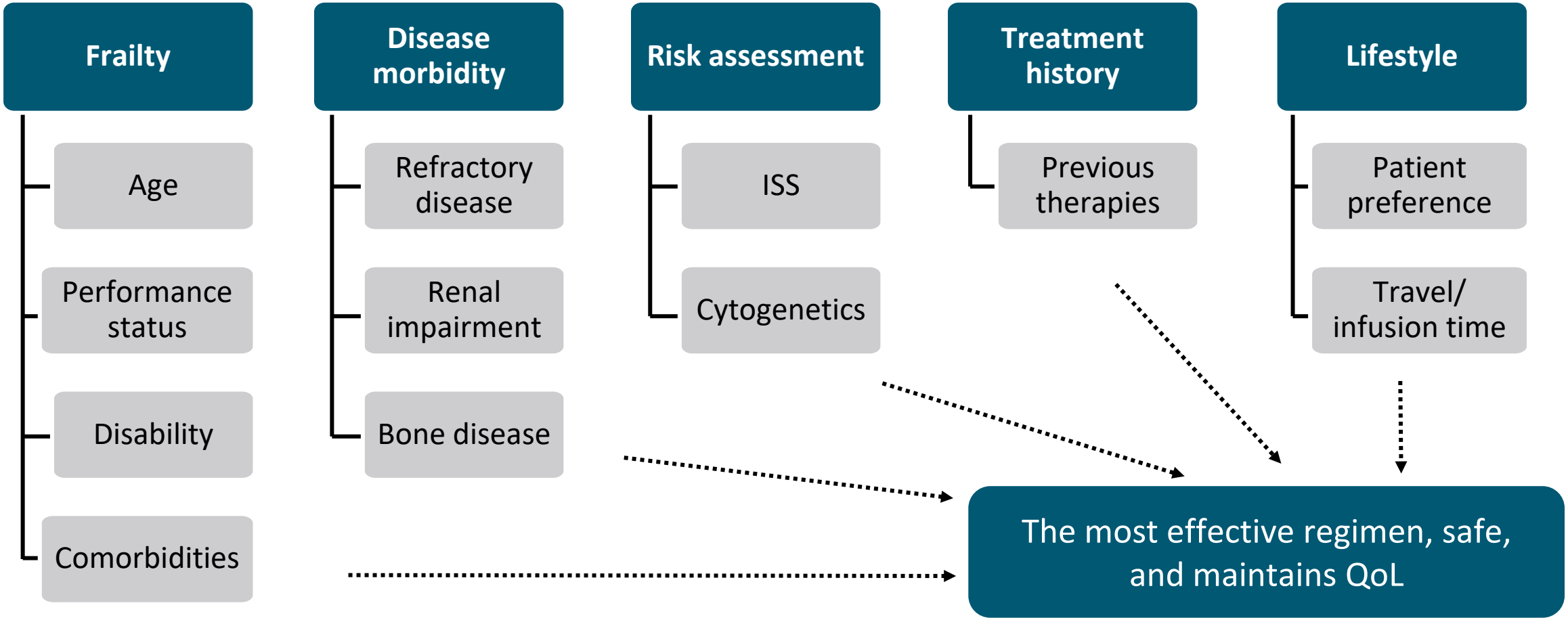
Result

Result

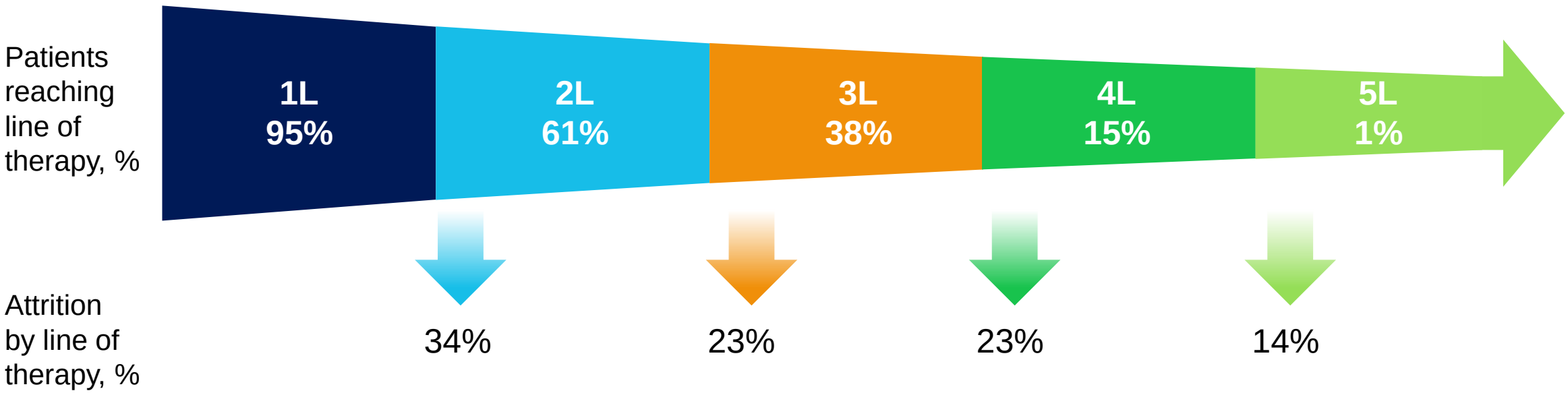
Question?

- What strategy do you use to select therapy at first relapse?
- Role of FISH STUDY in relapse

Disease and Patient Factors Influence Treatment Choices in Relapsed/Refractory Myeloma



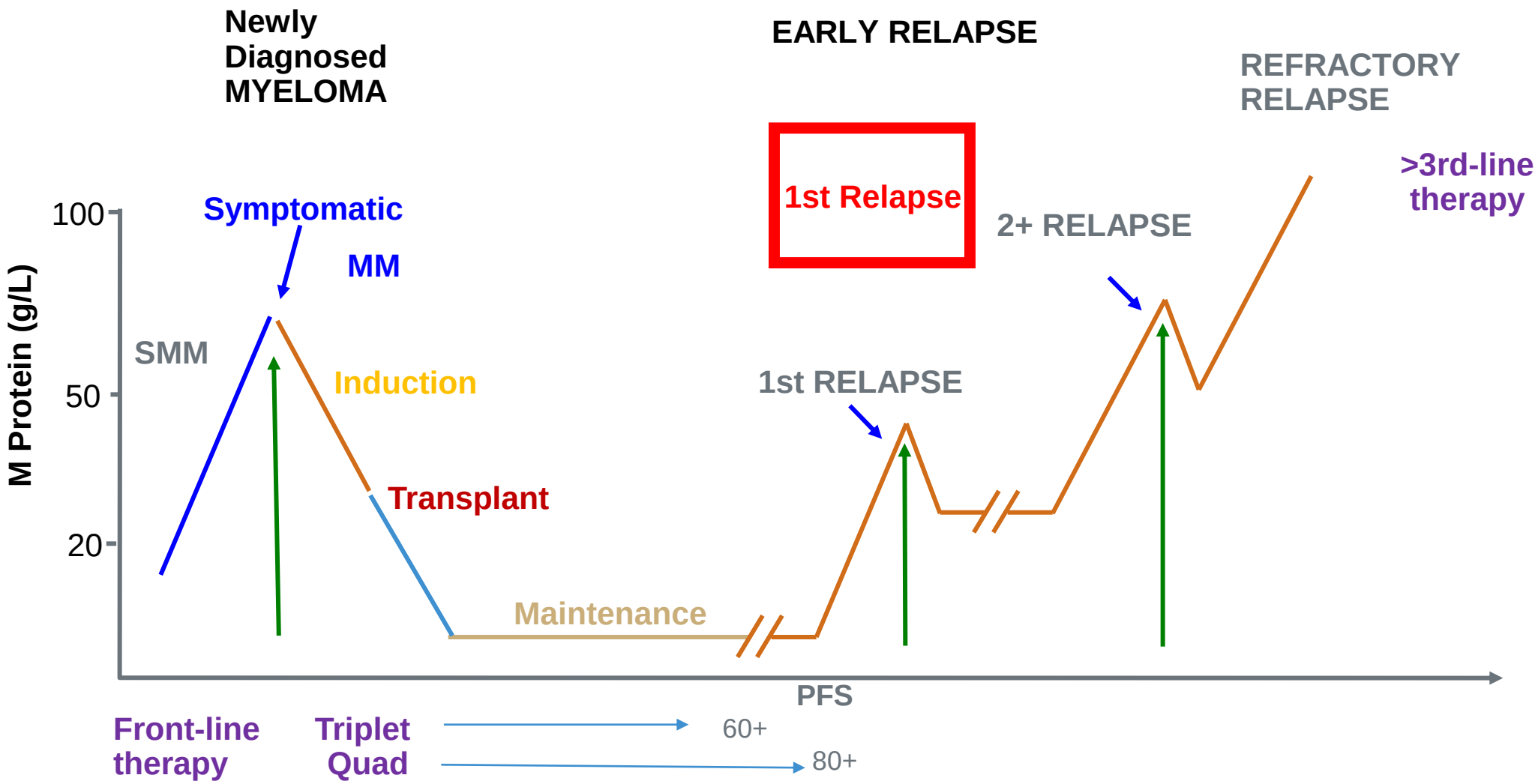
Treatment Attrition in Multiple Myeloma



In every new line of therapy, 15%-35% of patients are lost

Yon K et al. Br J Haematol. 2016;175:252.
Fonseca R et al. BMC Cancer. 2020;20:1087

Natural History in Multiple Myeloma



MAYO CLINIC

Selection of Regimen in Relapse

- Timing of the relapse
- Response to prior therapy
- Aggressiveness of the relapse
- Performance status

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Indications for Therapy at First Relapse

Clinical Progression

- Symptomatic
- Asymptomatic

Biochemical Progression

- Significant paraprotein relapse (any of the following in 2 consecutive measurements separated by ≤2 months)
  - Doubling of M spike
  - Increase in serum M protein by ≥1 g/dL
  - Increase in urine M protein by ≥500 mg/24 hours
  - Increase in involved FLC level by ≥200 mg/L

High-risk patients:

- any progression

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PRINCIPLES

- Prefer triplets
- At least two new drugs
- Consider transplant in eligible patients
- Clinical trials

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Results of Recent Phase III Randomized Studies in Relapsed Myeloma

Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (median in months)	P value for progression free survival
Dimopoulos et al (APOLLO)	Pd	153	46	20	7	0.002
	Dara-Pd	151	69	51	12	
Attal et al (ICARIA)	Pd	153	35	9	6.5	<0.001
	Isa-Pd	154	60	32	11.5	
Dimopoulos et al (CANDOR)	Kd	154	75	49	16	0.003
	Dara-Kd	312	**84**	**69**	NR	
Moreau et al (IKEMA)	Kd	123	83	56	19	<0.001
	Isa-Kd	179	**87**	**73**	NR	

Rajkumar SV. Am J Hematol 2022;97(8):1086.

Active Drugs in Multiple Myeloma

- Alkylators
- Steroids
- Anthracyclines

IMiDs
- Thalidomide
- Lenalidomide
- Pomalidomide

Proteasome Inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib

Anti-SLAMF7 moAb
- Elotuzumab

Anti-CD38 moAbs
- Daratumumab
- Isatuximab
- Felzartamab (MOR202)
- TAK 079
- SAR 442085

Anti-BCMA antibody drug conjugate
- Belantamab

- Selinexor (XPO1 inhibitor)
- Venetoclax (BCL-2 inhibitor) only in t(11-14)

CELMoDs
- Iberdomide
- Mezigdomide

Anti-BCMA CAR-T
- Cilta-cel
- Ide-cel
- JCARH125

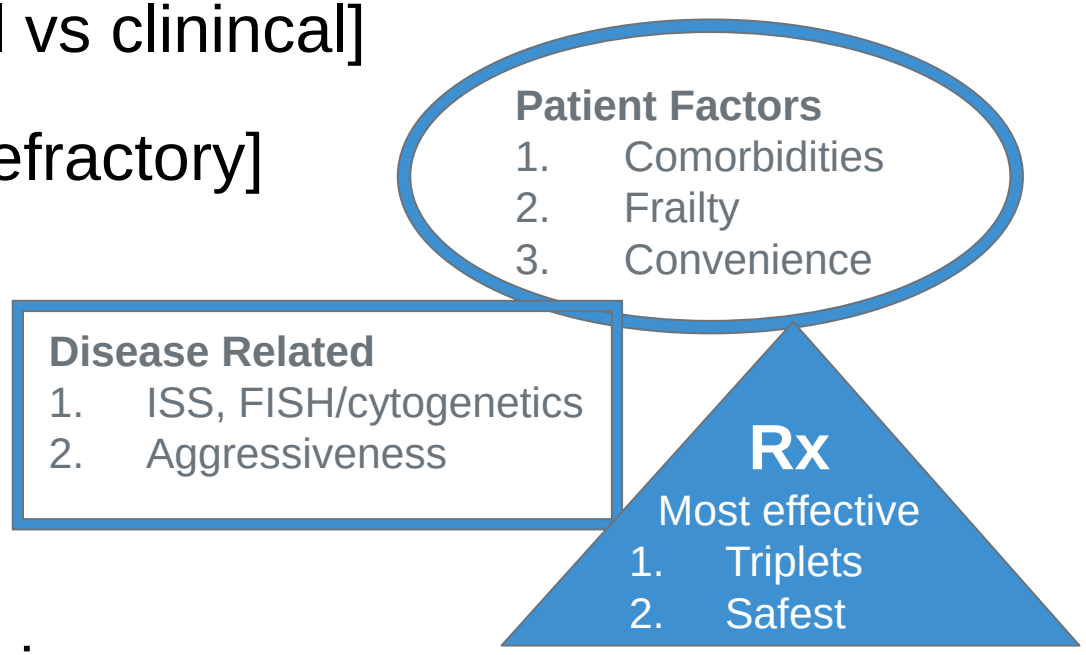
Anti-BCMA bispecifics
- Teclistamab
- REGN-5458
- Alnuctamab
- Elranatamab
- TNB 383B
- AMG 701

Novel bispecifics
- Talquetamab (GPRC5D/CD3)
- Cevostamab (FcRH5/CD3)

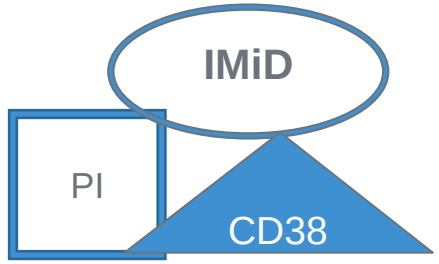
moAB: monoclonal antibody

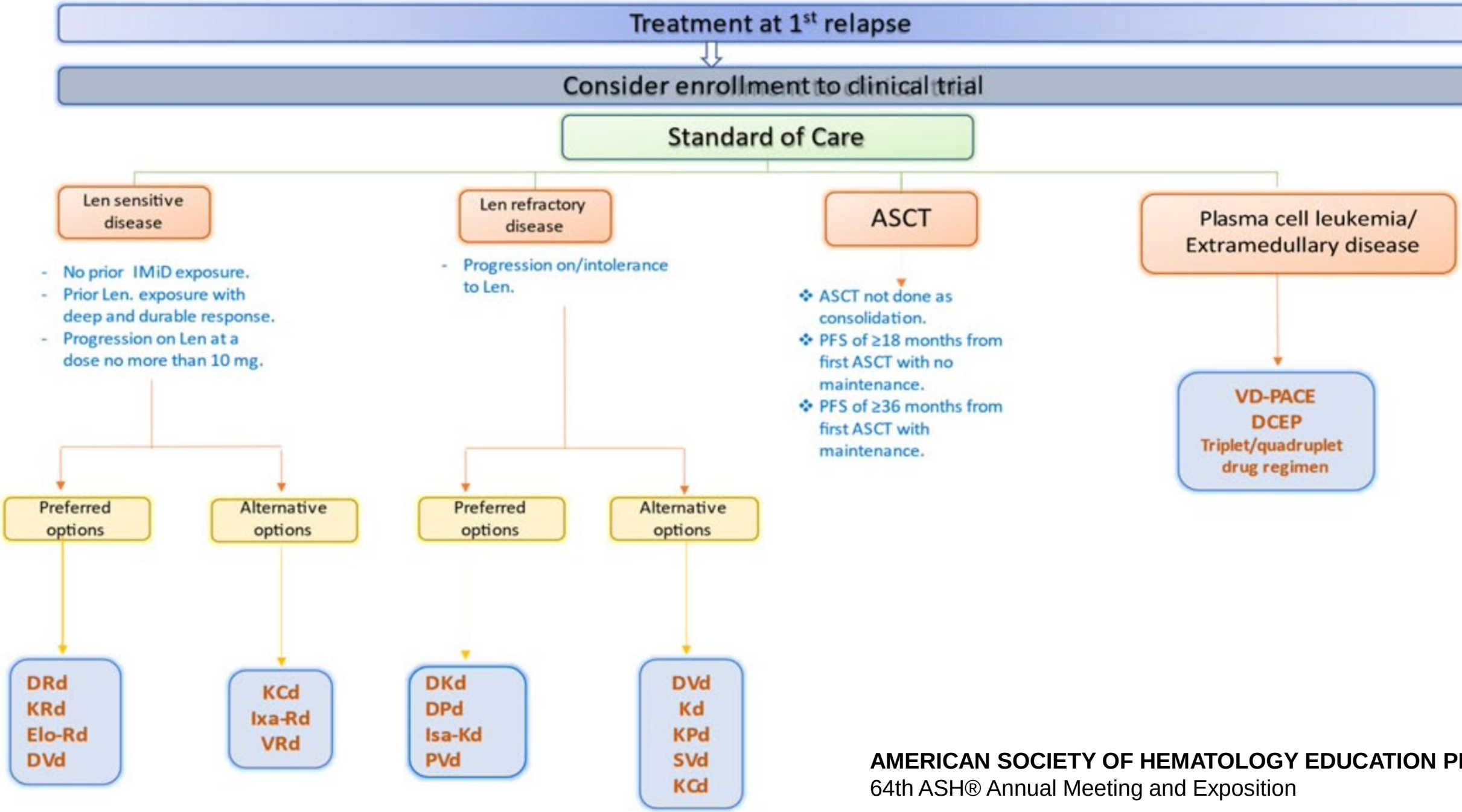
Relapse MM: Selecting Therapy

- Timing of the relapse. [Type: biochemical vs clinincal]
- Response to prior therapy [sensitive vs refractory]
- Aggressiveness of the relapse
  - Biochemical only
  - Hypercalcemia
  - Renal failure
  - Cytopenias/high-risk cytogenetics
- Performance status/comorbidities/convenience
  - What can't they receive (allergy/intolerance, PN, HTN, etc)?
  - What support do they have?
  - Help patient choose



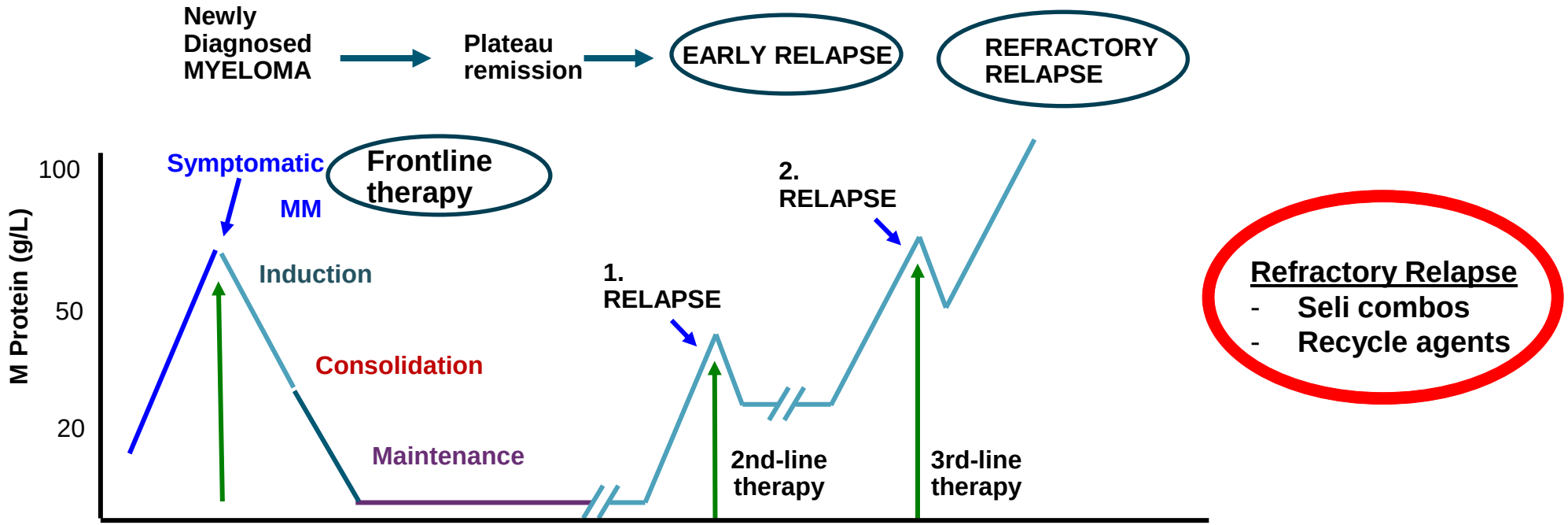
Class switching➔




Treatment at 1st relapse
Consider enrollment to clinical trial
Standard of Care
Len sensitive disease
- No prior IMiD exposure.
- Prior Len. exposure with deep and durable response.
- Progression on Len at a dose no more than 10 mg.
Preferred options
DRd
KRd
Elo-Rd
DVd
Alternative options
KCd
Ixa-Rd
VRd
Len refractory disease
- Progression on/intolerance to Len.
Preferred options
DKd
DPd
Isa-Kd
PVd
Alternative options
DVd
Kd
KPd
SVd
KCd
ASCT
❖ ASCT not done as consolidation.
❖ PFS of ≥18 months from first ASCT with no maintenance.
❖ PFS of ≥36 months from first ASCT with maintenance.
Plasma cell leukemia/ Extramedullary disease
VD-PACE
DCEP
Triplet/quadruplet drug regimen

Natural History of MM

What Are the Options for Relapsed and Refractory Multiple Myeloma?



Frontline
QUADS
- Dara-RVd

Early Relapse (1-3 Prior Lines)
Isa/Dara + Pd/Kd

Late Relapse (4+)
BCMA (CAR, BsAb>>Bela)

Outline and Agents for R/R MM

- **Approved agents for early relapse**
- **Which combinations and sequence may be best?**

Steroids	Conventional Chemotherapy	IMiDs	Proteasome Inhibitors	HDAC/XPO/ Bcl-2 Inhibitors	Immunologic Approaches
Prednisone	Melphalan	Thalidomide	Bortezomib	Panobinostat	Isatuximab
Dexamethasone	Cyclophosphamide	Lenalidomide	Carfilzomib	Selinexor	Daratumumab
	Liposomal doxorubicin	Pomalidomide	Ixazomib	[Venetoclax]	Elotuzumab
	DCEP/D-PACE/CVAD				Cilta-Cel
	Bendamustine				Ide-Cel
					Teclistamab
					~~Belantamab~~

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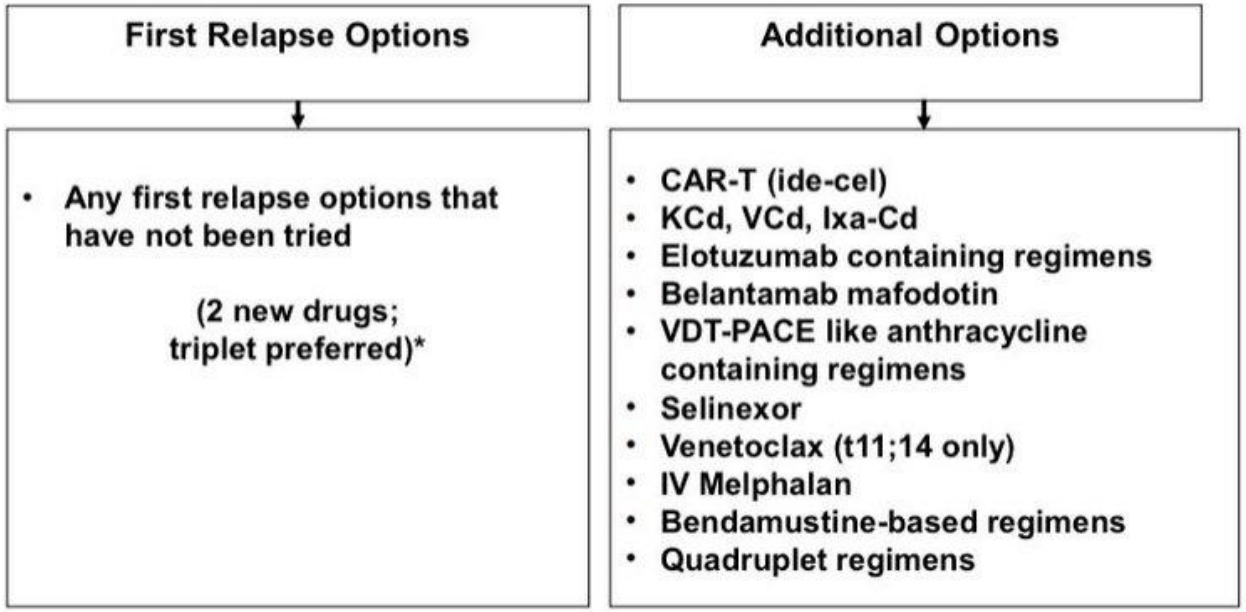
Second or higher relapse



*Consider ixazomib instead of carfilzomib or bortezomib if an all oral regimen is needed

Rajkumar Comment :

Second or higher relapse. Thankfully the first relapse regimen can usually work for a long time. This is also improving. There are a number of treatment options available for second or higher relapses.

Clinical case

- Patient’s economic condition is poor
- He received 25 mg lenalidomide daily (□) + 40 mg dexamethasone weekly
  - (due to MGUS-Like relapse)
- After 6 months of follow up ,ESR,B2M and M-peak were increased and anemia was progressed but Ca and Cr ,PLT ,WBC were NL
- PBS also was NL
- BMB/A was not performed because of highly suspicion of disease progression
- He was started on VCD ,after 4 cycle, anemia and ESR were near to normal and he received bortezomib SC every 2 weeks +DEXA weekly + Zometa every 3 months
- He is under follow up until now(about 8months) with a mini M-peak and normal ESR ,Ca ,Cr without any bone pain and mild anemia(Hgb=10-11 mg/dL)