EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

Self-assessment case 1

Session on MM

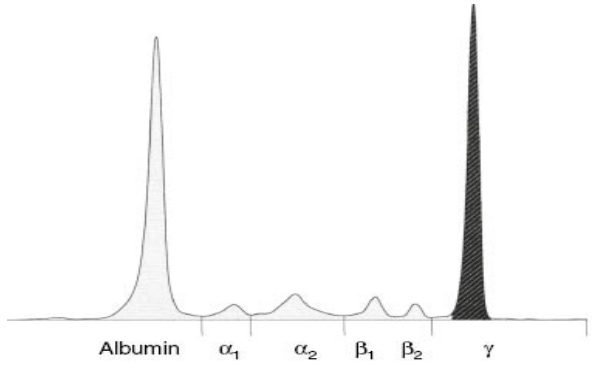
October 19, 2024 – Dr. Roberto Mina

Case presentation

- 47-year-old male patient presents with fatigue and intense, diffuse bone pain, located in the pelvic area, ribs and dorsal spine since 2 months.

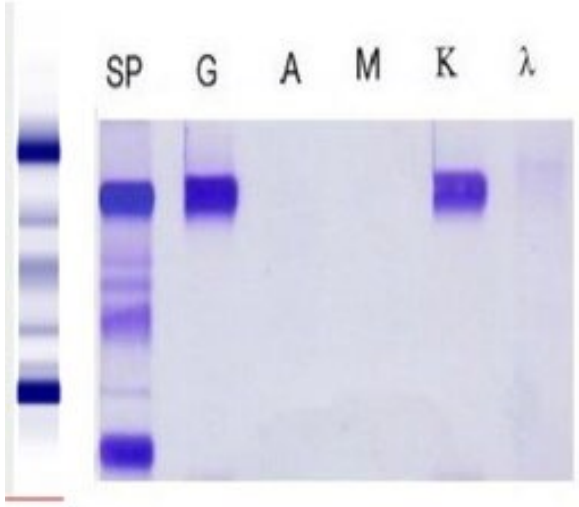
- Lab tests: Hb 11.3 g/L - creatinine 1.26 mg/dL - calcium 2.25 mmol/L

- **Quantitative serum protein electrophoresis (QPE):** IgG-Kappa M-Protein, 3.46 g/dL; free-light chain Kappa 1200 mg/l, Lambda 3 mg/l, k/L ratio 400



Total protein: 9.7 g/dL (6.0–8.3)
A/G: 0.83

Fractions	%	g/dL		Ref. g/dL
Albumin	45.4	4.40		3.43–4.84
α_1	3.4	0.33		0.21–0.44
α_2	8.4	0.81		0.54–0.97
$\beta_{1\,\&\,2}$	6.2	0.60	L	0.65–1.03
γ	36.6	3.55	H	0.70–1.47
M-Spike	35.7	3.46		

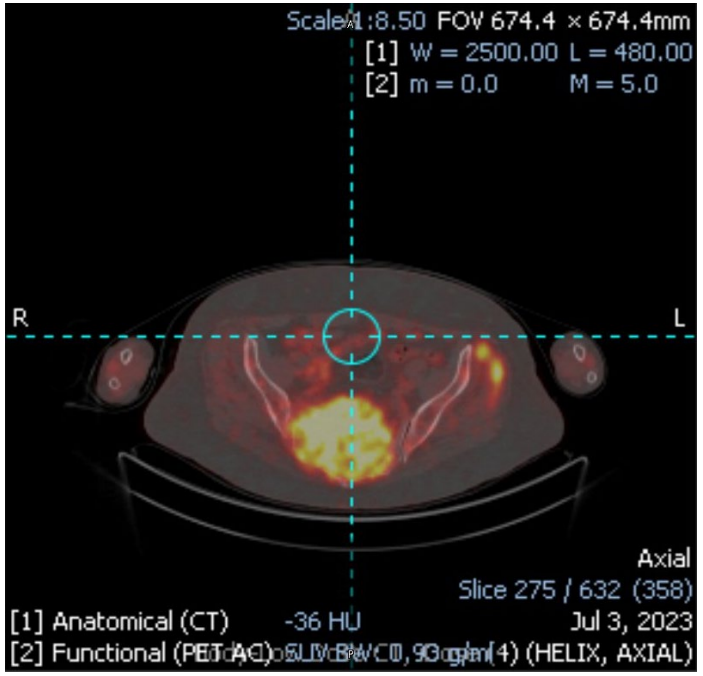


(b)

Case presentation

PET-CT shows:

- diffuse increased FDG uptake in the skeleton
- focal lesions in the thoracic spine vertebra, the sternum with underlying lytic lesions
- abnormal uptake in the sacrum where a 12x9 cm extramedullary tissue is detected.



Bone marrow aspirate shows:

- 40% clonal plasma cells IgG-restricted on smear
- Flow cytometry shows CD138+ CD45- CD56+
- FISH analysis on purified plasma cells:
  - t(4;14) positive
  - del17p positive (50% of the nuclei)
  - del13q+

Q1) What is the most likely diagnosis?

1. Solitary plasmocytoma with minimal marrow infiltration
2. Multiple myeloma
3. Solitary plasmocytoma
4. Smoldering myeloma
5. NHL with bone involvement

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Multiple Myeloma Risk Stratification

Baseline Risk Factors	
Albumin	4.6 g/dL
B2M	3.9 mg/dL
LDH	elevated
FISH	del13q+, del17+, t(4;14)+, 1q gain/amp -
Bone marrow plasma cells	40%
Extra-medullary disease	present
PET/CT focal lesions	>3

D'Agostino M. J Clin Oncol. 2022 Oct 10;40(29):3406-3418. doi: 10.1200/JCO.21.02614. Epub 2022 May 23. Erratum in: J Clin Oncol. 2022 Dec 1;40(34):4032. doi: 10.1200/JCO.22.02228. PMID: 35605179.

Q2) Which factors are included in the current IMWG risk stratification system (R-ISS)?

1. Albumin, LDH, bone marrow plasma cells %
2. LDH, B2M, Albumin and FISH chromosomal abnormalities
3. LDH, B2M, Albumin, FISH chromosomal abnormalities and number of bone lesions
4. Number of Bone lesions, LDH and B2M
5. B2M, LDH, FISH chromosomal abnormalities and extramedullary disease

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5. B2M, LDH, FISH chromosomal abnormalities and extramedullary disease

Q3) 47 y.o. patients, diagnosed with R-ISS 2 MM, symptomatic for bone lesions (+ EMD) and anemia.

What frontline treatment would you recommend?

1. DaraVTD/VRd induction followed by ASCT
2. VTD/VRd induction followed by ASCT
3. DaraVTD/VRd induction followed by maintenance
4. VTD/VRd induction followed by maintenance
5. Non-transplant approach with DRd or DVMP

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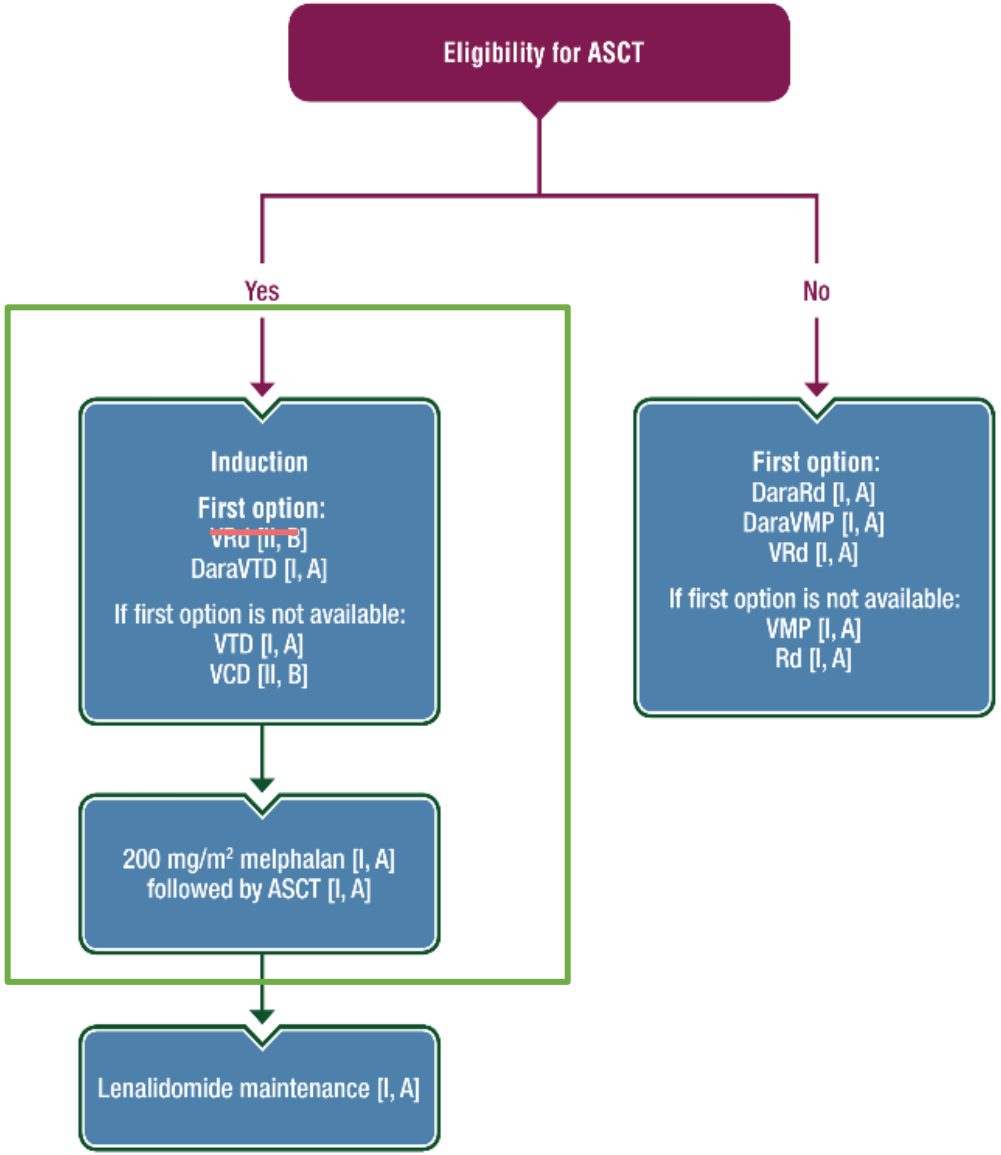
FRONTLINE TREATMENT
WHAT IS THE BEST STRATEGY?

Young patient (< 70 years)
No relevant comorbidities
High-risk disease

TRANSPLANT-ELIGIBLE

ESMO 2021



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Dimopoulos MA et al. Ann Oncol. 2021 Mar;32(3):309-322.

Q4) How do you proceed after induction therapy?

1. ASCT regardless of the response to induction
2. ASCT only if <CR after induction
3. ASCT only if <PR after induction
4. Allogeneic stem cell if available donor
5. Maintenance therapy

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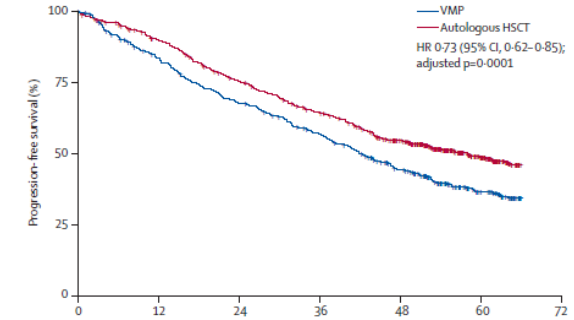
The role of ASCT: PFS benefits

EMN-02/HO95

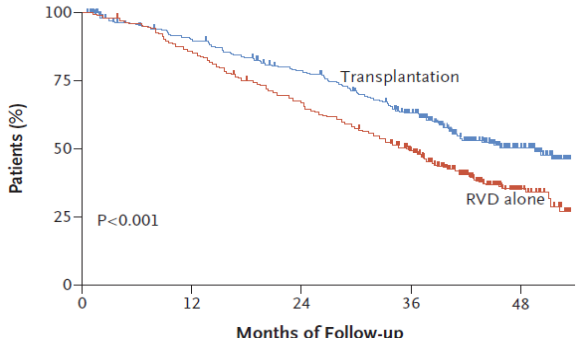
Median follow-up: 60 months



mPFS: **56.7 months** in the ASCT group vs. **41.9 months** in the VMP group

IFM-2009

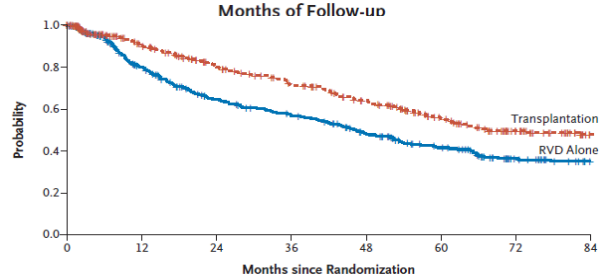
Median follow-up: 43-44 months



mPFS: **50 months** in the ASCT group vs. **36 months** in the RVD-alone group

DETERMINATION

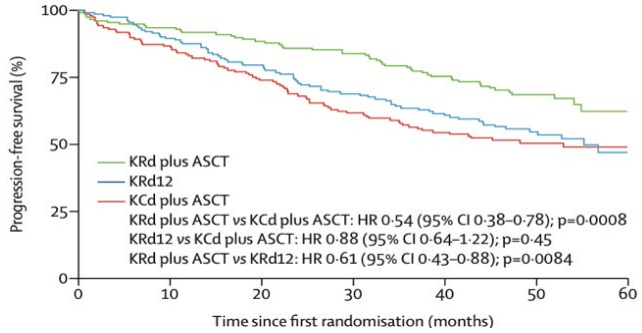
Median follow-up: 76 months



mPFS: 67.5 months in the ASCT group and **46.2 months** in the RVD-alone group

FORTE

Median follow-up: 51 months



4-y PFS: **69%** in the ASCT group and **56%** in the KRD12 group
mPFS: **NR** vs 55 months

HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; d, dexamethasone; C, cyclophosphamide; R, lenalidomide, V, bortezomib, KRd plus ASCT, 4 KRD induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; ; KRd12, 12 KRd cycles; HR, hazard ratio; CI, confidence interval; p, p-value; Nr, not reached; PFS, progression free survival

Cavo et al., EMN02, Lancet 2020; Gay F et al., FORTE trial, Lancet Oncol 2021; Attal M et al., IFM-2009, N Engl J Med 2017; Richardson P et al., DETERMINATION study, N Engl J Med 2022

Q5) How to assess response to treatment in this patient?

1. Serum/urine M-protein + free-light chains, bone marrow for residual plasma-cells if suspected CR and imaging for EMD assessment

2. Serum/urine M-protein + free-light chains and bone marrow for residual plasma-cells if suspected CR

3. Free-light chains

4. PET/CT for EMD assessment

5. Bone marrow for residual plasma-cells

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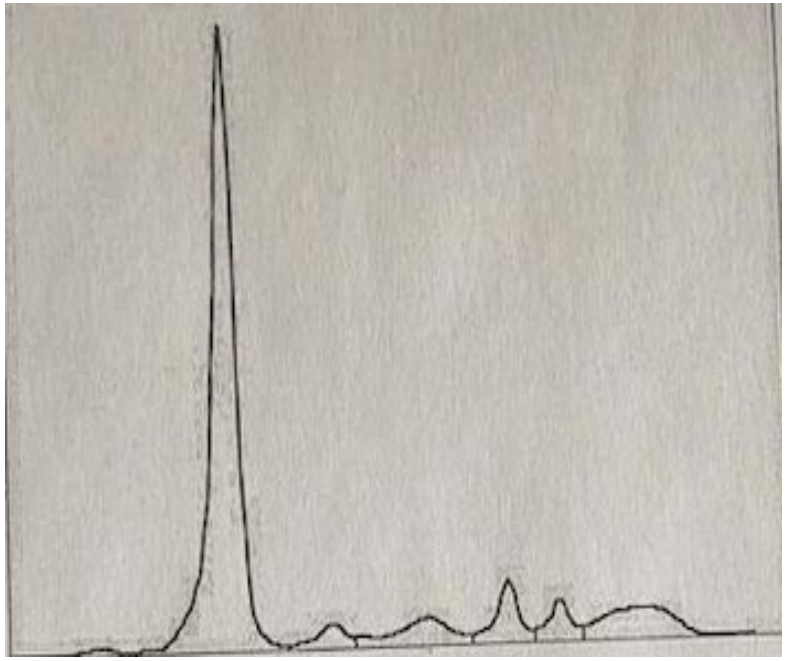
5. Bone marrow for residual plasma-cells

	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 plus 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

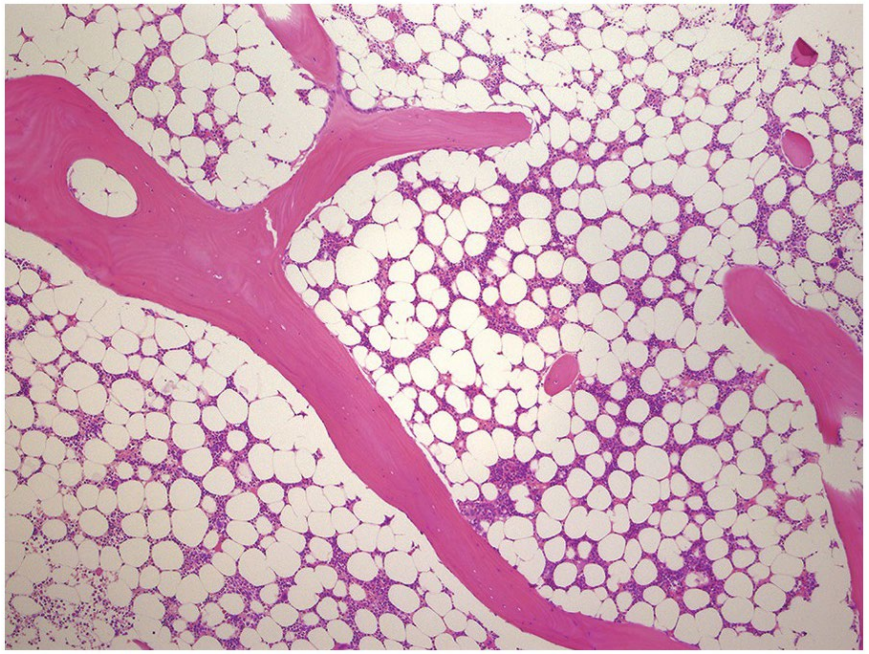
(Table 4 and footnotes continue on the next page)

Kumar S, et alInternational Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-e346. doi: 10.1016/S1470-2045(16)30206-6. PMID: 27511158.

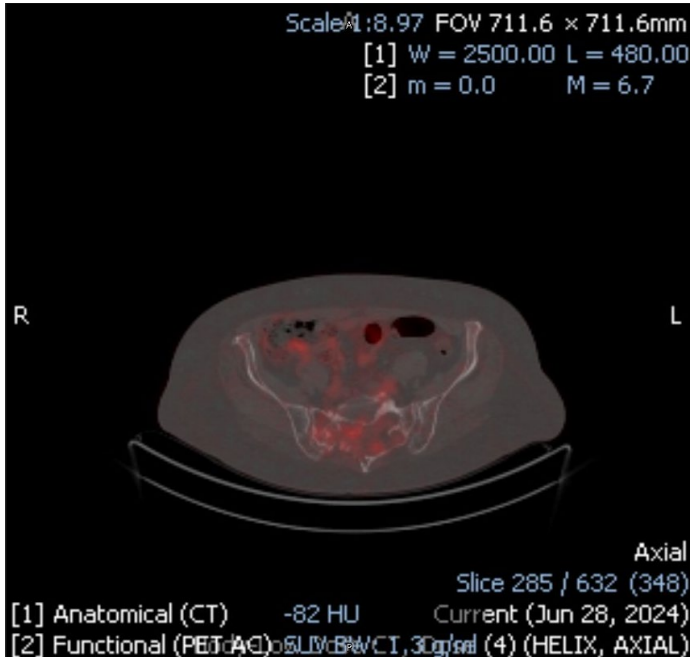
Response Assessment after induction and transplant



No monoclonal protein detected by serum protein electrophoresis



No clonal plasma cells in the bone marrow



No significant uptakes at PET/CT scan

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Q6) Post transplant maintenance: What would you recommend?

1. No maintenance and follow-up
2. Maintenance with lenalidomide only if <CR after transplant
3. Maintenance with bortezomib
4. Maintenance with lenalidomide for 2 years
5. Maintenance with lenalidomide until progressive disease

Q6) Post transplant maintenance: What would you recommend?

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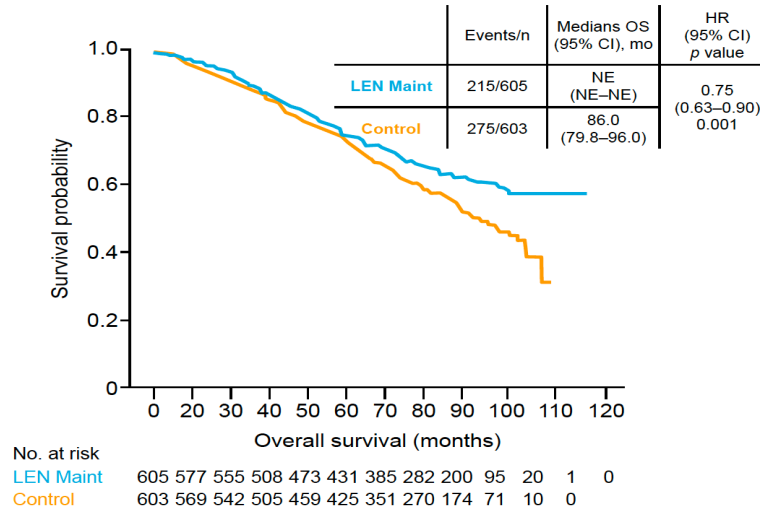
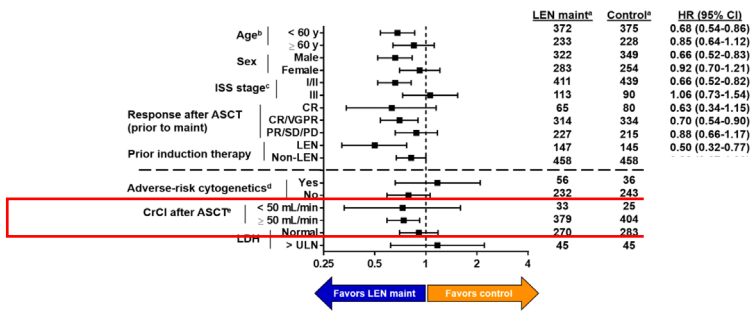
Maintenance therapy: can we do better?

Lenalidomide maintenance according to FISH risk

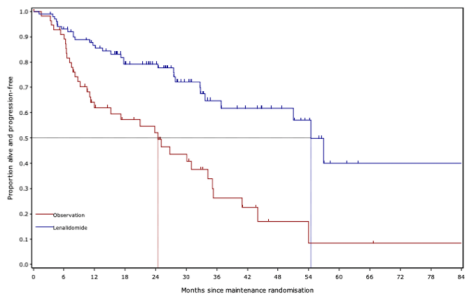
Overall survival





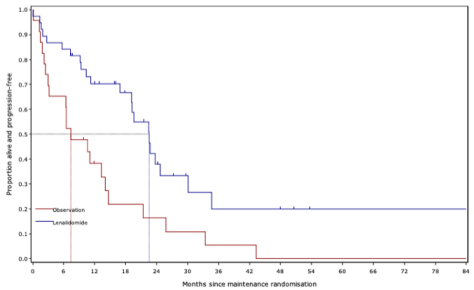
Myeloma XI study: lenalidomide versus observation

High risk
1 cytogenetic abnormality

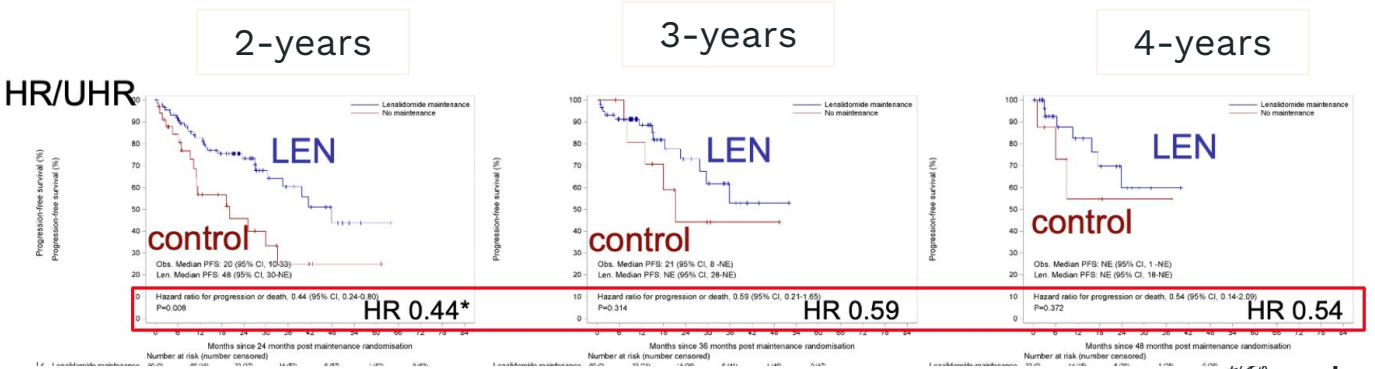


Len vs. Obs: 54 vs. 24 months

Ultra-high risk
≥2 cytogenetic abnormalities



Len vs. Obs: 24 vs. 7 months



McCarthy et al. J Clin Oncol 2017; 35(29):3279-3289; G. Jackson GH. Et al, Lancet Oncol. 2019 Jan;20(1):57-73. Pawlin C. et al ASH22

Discussion and conclusions

- Induction therapy in transplant eligible patients: quadruplets including anti-CD38 monoclonal antibodies, IMiDs (thalidomide and lenalidomide) and proteasome inhibitors (e.g. bortezomib) are a standard for induction and consolidation

- High-dose chemotherapy and autologous stem cell transplant is a standard among transplant eligible patients
  - Shorter PFS with non-transplant approaches.

- Maintenance:
  - Lenalidomide maintenance until progression is the standard for post-transplant/consolidation treatment

EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

Self-assessment case 2

Session on MM

October 19, 2024 – Dr. Roberto Mina

Clinical report N.2

- 82 year-old female patient presents with anemia and mild lumbar pain not requiring analgesics
- Medical history: hypertension, myocardial infraction, type II diabetes, colorectal cancer surgically treated 4 years ago without adjuvant radio-chemotherapy.
- Independent for self-care activities, requires assistance to manage health and finance-related issues
- Lab Tests: Hb 11 g/L – serum creatinine 1.34 mg/dL - calcium 2.24 mmol/L
- QPE: IgA-k M-protein, 0.46 g/dL; Free light-chain K 740 mg/l; Lambda 8 mg/l; serum free light chain ratio (FLCr) 93; Bence-Jones proteinuria 195 mg/die

Q1: What radiological assessment would you request?

1. Targeted conventional skeletal X-Ray
2. Conventional whole-skeletal X-Ray
3. Whole body computed tomography
4. Targeted body computed tomography
5. Whole-body MRI

Imaging for MM

Suspicion of Bone Disease
- Perform LDCT Scan

No apparent lesions
- Perform MRI

Assess Bone leisions >5 mm
- If Bone lesion <5mm consider PET

analysis, presence of more than one focal lesion remained a significant predictor of progression. In patients with more than one focal lesion on MRI, if such lesions are small (<5 mm) or equivocal, additional imaging with CT or PET-CT should be considered before making the diagnosis of multiple myeloma.

Kumar S, et al International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-e346. doi: 10.1016/S1470-2045(16)30206-6. PMID: 27511158.

- CT-Scan results: no bone lytic lesions nor vertebral collapses detected

- MRI is performed: T1 hypointense, T2 and STIR hyperintense L4 vertebral lesion (d=8 mm)

- Bone marrow aspirate:
  - 35% atypical plasma cells, CD138+, CD45- and CD56+
  - FISH: t(11;14) positive, negative for del17p, 1q gain/amplification, del1p
- Bone marrow biopsy: 80% of IgA-k clonal plasma cells

Q2) What is the diagnosis?

1. Smoldering Myeloma
2. MGUS
3. Multiple Myeloma
4. MGRS
5. Multiple Myeloma with AL-amyloidosis

MGUS, Monoclonal gammopathy of undetermined significance; MGRS, Monoclonal gammopathy of renal significance

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Q3) The diagnosis of MM is based on which Slim-CRAB criteria?

1. Serum creatinine
2. Anemia
3. Focal lesion detected by MRI
4. Bone marrow plasma cells %
5. Serum free light-chains

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IMWG diagnostic criteria

Panel: **Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma**

Definition of multiple myeloma

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

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Rajkumar VS et al. Lancet 2014

Q4) What are the elements included in the IMWG frailty score?

1. Chronological age, Charlson comorbidity index, ADL and IADL
2. Karnofsky's performance status, ISS and chronological age
3. ECOG Performance status and serum albumin levels
4. C-reactive protein, renal and pulmonary function
5. ECOG Performance status, C-reactive protein and chronological age

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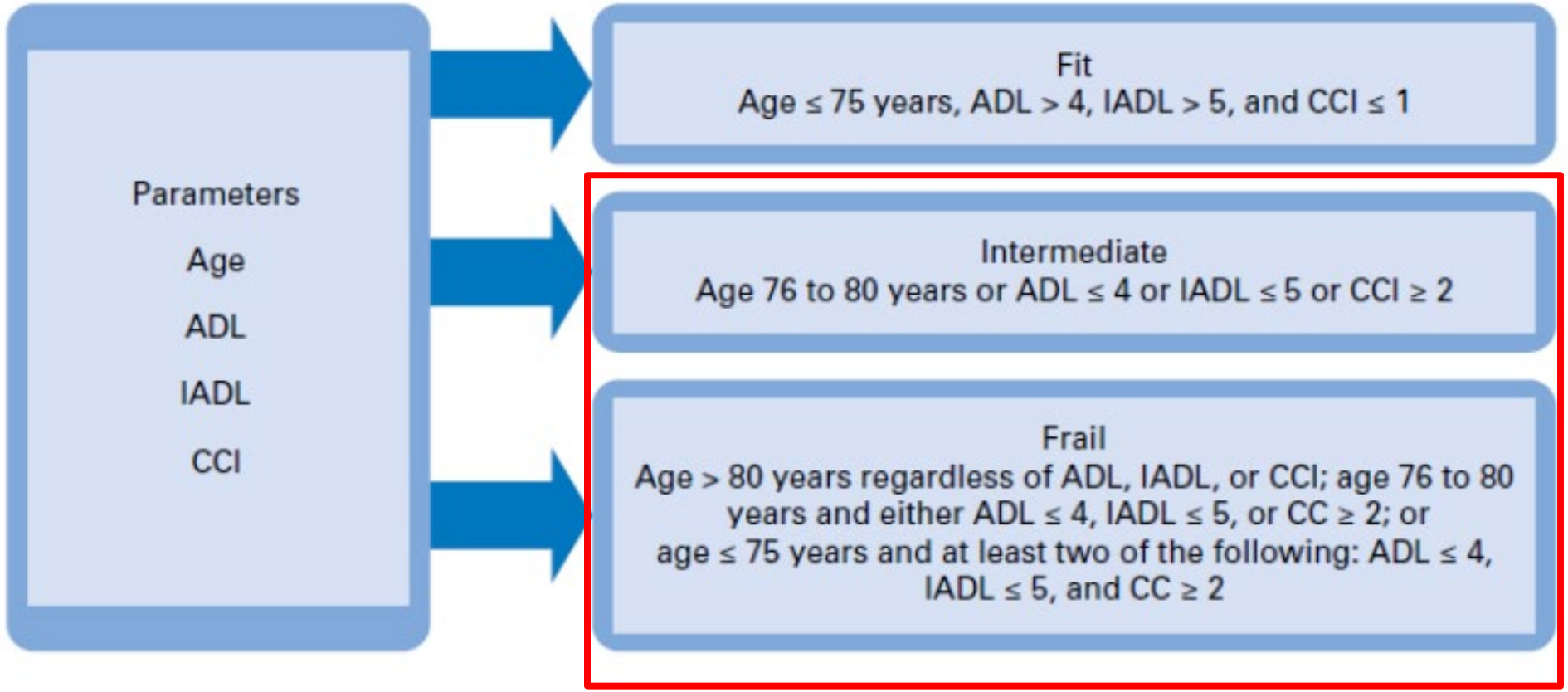
Frailty Assessment



Palumbo A, et al, Blood 2015;125(13):2068-74; Larocca A & Palumbo A. J Clin Oncol 2016;34(30):3600-3604

Q5) What is your first-line treatment option for this frail patient?

1. Daratumumab-Rd until progression or intolerance
2. Daratumumab-VTd
3. Single agent lenalidomide
4. Lenalidomide-dexamethasone (Rd)
5. Daratumumab-Rd for 12 cycles followed by Rd maintenance

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Q6) In which study a quadruplet, IsaVRd, proved to be superior to VRd as frontline treatment for older patients?

1. MAIA
2. Alcyone
3. Perseus
4. IMROZ
5. DREAMM-3

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Discussion and conclusions

- Older, transplant ineligible patients are a heterogeneous population and geriatric assessment allows to identify patients at higher risk of treatment-related toxicity, treatment discontinuation and worse survival outcomes

- Treatment goals and strategies can be modulated based on disease risk and patient's frailty

- Triplets including a monoclonal antibody targeting CD38 are currently a standard of care for the initial treatment transplant ineligible patients, while in the future quadruplets may become a new standard for old, fit patients