Updated IMWG/IMS Response Criteria 2025

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International Myeloma Society

Workshop on Assessment of Response and Progression Criteria in Multiple Myeloma

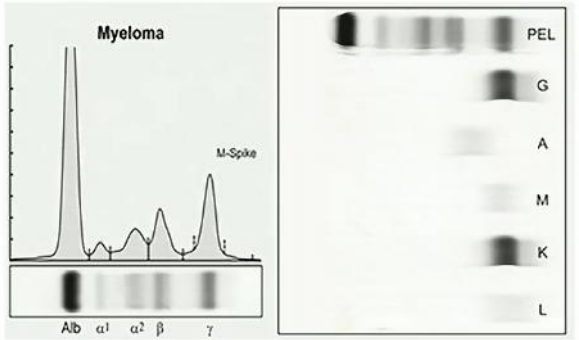
PARIS, FRANCE | NOVEMBER 16-17

M protein

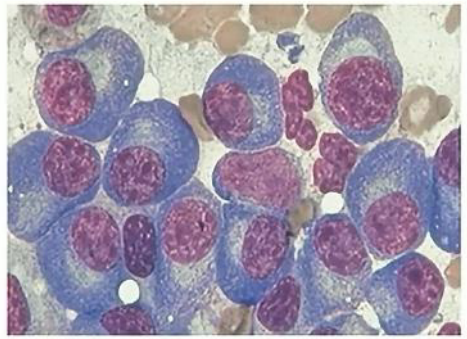
Serum, Urine

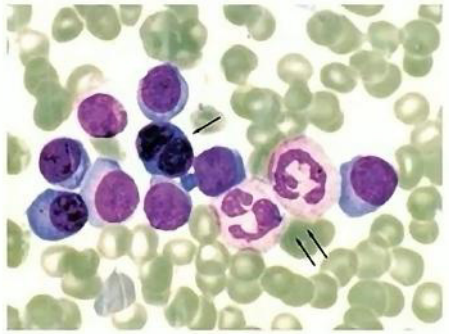
Plasma cells

Marrow, Blood, Extramedullary

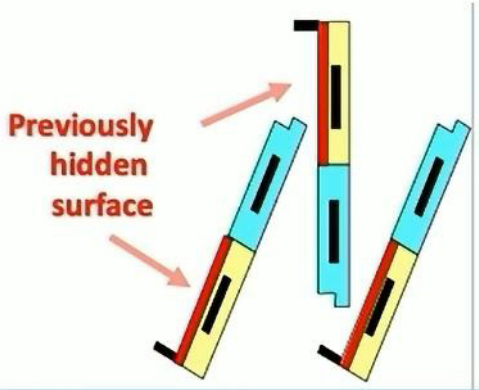


Protein electrophoresis

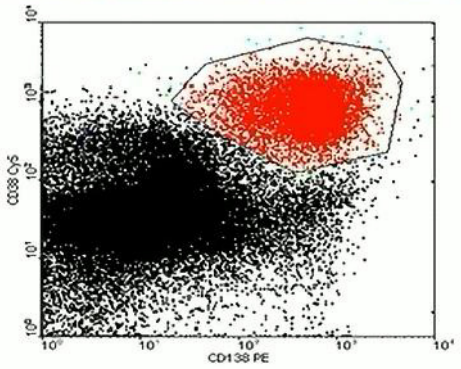


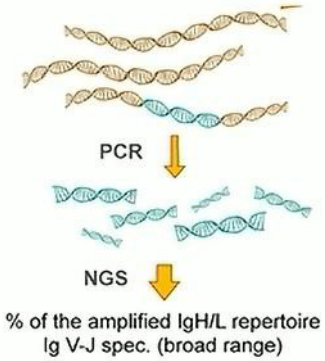


Microscopy

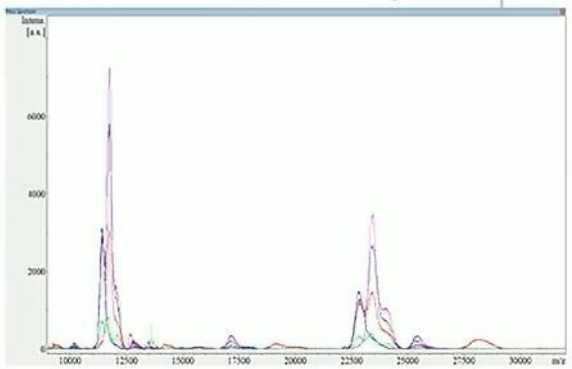


Light Chain Assay

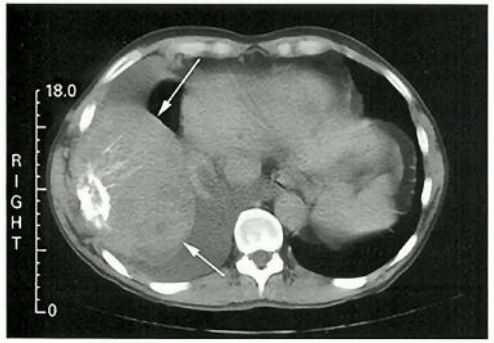




Flowcytometry/ NGS



Mass Spectrometry



CT/PET-CT/MRI

Measurable Disease

שרשראות לפני שתן

- SPEP ≥ 1g/dl (≥0.5 allowed in relapsed disease)
- Serum iFLC ≥10 mg/dL with an abnormal ratio
- 24-hour urine UPEP ≥200 mg/24 hours can be used in place of FLC assay if not available
  - If selected should be followed for response

If none of the above, then -

- BMPC≥30%
- Soft tissue mass (para-skeletal or EMD) with one dimension ≥2 cm

Response categories

- **Stable disease** - Not meeting criteria for complete response, very good partial response, partial response, or progressive disease
  - Nor recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates.

- **Minor Response** - ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%.

לא רואים טעם
לדווח MR
במחקרים קלינים

Response categories

Partial Response

- If serum is measurable by SPEP - ≥50% reduction of serum M-protein
  - If baseline Serum M spike was ≥0.5 and <1, then a reduction to ≤0.2 gm/dL
- If serum FLC is measurable - ≥50% decrease in the difference between involved and uninvolved FLC levels
- If 24 h urinary M-protein is used as measurable disease, a reduction by ≥90% or to <200 mg per 24 h
- If serum and urine M-protein and serum-free light assay are unmeasurable, ≥50% reduction in plasma cells (provided baseline PC% is ≥ 30%)

הקריטריונים לא השתנו, האיררכיה השתנתה

Response categories

Very Good Partial Response (VGPR)

- If serum is measurable by SPEP - ≥90% reduction of serum M-protein or immunofixation positive only
  - If baseline Serum M spike was ≥0.5 and <1, then a reduction to 0 gm/dL
- If serum FLC is measurable - ≥90% decrease in the difference between involved and uninvolved FLC levels or immunofixation positive only
- If 24 h urinary M-protein is used as measurable disease, a reduction to <100 mg per 24 h or immunofixation positive only

הקריטריונים לא השתנו, האיררכיה השתנתה

Response categories

- **Complete Response**
  - Negative immunofixation on the serum
  - normal FLC ratio or iFLC < ULN
  - Negative immunofixation on the 24-hour urine
  - and <5% plasma cells in bone marrow aspirates

מספיק ששרשרת מעורבת פחות מ- ULN ולא צריך יחס תקין

- **sCR (stringent**
  - Complete response a FLC ratio iFLC < ULN and absence of clonal cells i

כששיטות לקביעת קלונליות כך רגישות אין טעם בהגדרת sCR

** Bone marrow results from within +/- 6 weeks of the M protein/FLC assessment can be included for CR assessment*

כאן נעשה שינוי משמעותי- אחד האתגרים במיאלומה לנתר במיוחד בהשנות-הרבה EMD פעמים הפט כבר לא קולט אבל עדין יש מסה שארית

Imaging Based Response

Standard IMWG response criteria[f]	
Stringent complete response	Complete response as defined below plus normal FLC ratio[g] 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).[h]
Complete response[i]	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 (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)[j] 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 25%–49% reduction in SPD[j] of soft tissue plasmacytomas is also required.

Imaging Principles

- Recommendation for functional imaging (PET/CT or DWI-WBMRI) *and move away from SPD*
- For PSD/EMD functional imaging mandatory to allow response evaluation. MRI preferred for CNS.
- Same technique recommended pre and post therapy.
- Measures of the lesion(s) needed only if no other disease parameters to be quantified available
- 3 months window (+ or -) allowed to match with other tests (BM/PB)

MY-RADS (Myeloma Response Assessment and Diagnosis System)

MY-RADS RAC	Summary of Criteria
RAC 1 **(Imaging MRD-Negative)** **Highly likely to be responding**	• Return of normal fat containing marrow in areas previously infiltrated by focal or diffuse myelomatous infiltration • Unequivocal reduction in size/number of lesions/soft tissue • Decreasing soft tissue associated with bone disease • Previously evident lesion shows increase in ADC from ≤1400 μm^2/sec to >1400 μm^2/sec (≥40% increase in ADC from baseline with corresponding decrease in normalized high b-value signal intensity; morphologic findings consistent with stable or responding disease • For soft-tissue disease, RECIST version 1.1 criteria for PR/CR
RAC 2 **Likely to be responding**	• Evidence of improvement but not enough to fulfil criteria for RAC 1Slight reduction in size/number of focal lesions • Previously evident lesions showing increases in ADC ≥1000 μm^2/sec to <1400 μm^2/sec (≥25%, but <40%, increase in ADC from baseline) • For soft-tissue disease, RECIST version 1.1 not meeting requirements for PR
RAC 3 **No Change**	• No observable change
RAC 4 **Likely to be progressing**	• Evidence of worsening disease, but not enough to fulfill criteria for RAC 5 • Equivocal appearance of new lesions: No change in size but increasing signal intensity on high b-value images (with ADC values <1400 μm^2/sec) consistent with possible disease progression • For soft-tissue disease, RECIST version 1.1 criteria not meeting requirements for PD
RAC 5 **Highly likely to be progressing**	• New critical fracture(s)/cord compression requiring radiation therapy/surgical intervention; only if confirmed as malignant with MRI signal characteristics • Unequivocal new focal (0.5–10 mm)/diffuse area(s) of infiltration in regions of previously normal marrow • Unequivocal increase in number/size of focal lesions • New lesions/regions of high signal intensity on high b-value images with ADC value between 600–1000 μm^2/sec • For soft-tissue disease, RECIST version 1.1 criteria meeting requirements for PD

Messiou et al, Radiology 2019; 291:5–13

Imaging response categories
(with no plasmacytomas)

PET/CT/DWI-MRI response	Definition
CR (MRD)	Uptake ≤ liver pool (**Deauville scale < 4**) by PET or **RAC-1** by DWI-MRI in all locations (*Marrow and focal lesions*)
PR	**Decrease** of either number of focal lesions + stable SUV **(DS 4-5),** OR Decrease in activity, with stable number of focal lesions, OR both OR **RAC-2 on MRI,** compared to baseline
SD	**No significant change** of BM/FL FDG uptake or at MRI RAC-3 compared with baseline
PD	**New lesion (FL/EMD/PSD)** compared with baseline imaging, both in the functional imaging (PET DS > 4 or MRI RAC 4 or 5) or on CT

Imaging response categories
(with plasmacytomas: paraskeletal or extramedullary)

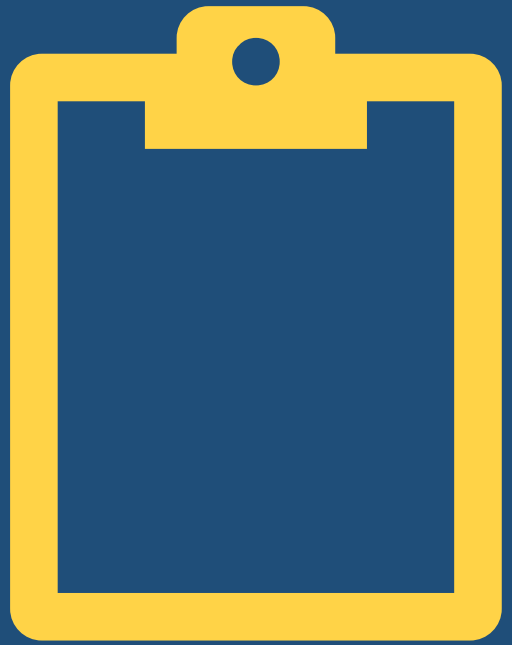
PET/CT/DWI-MRI response	Definition
CR (MRD)	Uptake ≤ liver pool (**Deauville scale < 4**) by PET or **RAC-1** by DWI-MRI in all locations (**BM/FL/PSD/EMD**) ***irrespective*** of the reduction of soft-tissue plasmacytomas size
PR	**Decrease** of either number of FLs/PSD/EMD + stable SUV **(DS 4-5),** OR Decrease in activity, with stable number of FLs/PMD/EMD, OR both or **RAC-2 on MRI,** compared to baseline ***irrespective*** of the reduction of soft-tissue plasmacytomas size.
SD	**No significant change** in BM/FL/EMD/PSD uptake or at MRI (RAC-3) compared with baseline, irrespective of soft-tissue plasmacytoma size
PD	**New lesion (FL/EMD/PSD)** compared with baseline imaging, both in the functional part (PET DS > 4 or MRI RAC 4 or 5) or on CT

First evaluation after 3 months from the start of therapy (to avoid as much as possible background influence/tumor flare after CART/ bone regeneration). If PR/SD: repeat imaging every 3-6 months until CMR/RAC-1. Once CR established, no other evaluation requested until suspect of progression

MINIMAL RESIDUAL DISEASE

Response categories - MRD

- **MRD negative CR** - Absence of aberrant clonal plasma cells by NGF or NGS on bone marrow aspirates with a minimum sensitivity of at least 1 in 10^5 nucleated cells
  - MRD rate at 10^{-6} rates should be reported when feasible designated as **MRD negative CR 10^{-6}**
  - If MRD negative as defined above but no negative immunofixation, should be defined as NGF/NGS negative (without CR) at either threshold
- **Imaging negative MRD neg** – MRD as defined above at either threshold with a functional imaging (PET-CT or WB-DWI MRI) negative
- **Sustained MRD negative CR**– MRD negative CR as defined above at either threshold with two negative MRD tests at least 24 months apart, and without any positive test in between



Conceptual – Deep/Stringent MRD

- MRD at 10^{-6} by NGS
- Negative by functional imaging (PET-CT or WB-DWI MRI)
- No monoclonal protein by mass spec
- No circulating plasma cells

- ***This will form the building block for a cure definition in future, when sustained for 5 years without therapy***

Disease Progression

PD based on M protein measurements

- ≥25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/l
- ≥25% increase in the difference between involved and uninvolved FLC levels. The absolute increase must be ≥10 mg/dl
- ≥25% increase in the 24 h urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h

לרוב החולים יהיה צריך איסוף שתן רק בבסיס, ואם חיובי בבסיס, פעם נוספת להגדרת CR

שוב, הקריטריונים לא השתנו, האיררכיה השתנתה

PD based on plasma cells/ plasmacytoma

- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas (Deauville score> 4 (increase of SUV > liver) in (or MRI DWI RAC >= 3) in one or more existing lesion)

- ≥25% increase in plasma cells in a bone marrow, which must also be an absolute increase of at least 10% only in patients without measurable disease by serum and urine

- Development of new bone lesions or soft tissue or para-skeletal plasmacytomas

- ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease

Additional considerations

- For IgA or IgD myeloma, quantitative measurement of the immunoglobulin should be used in place of SPEP measurements
  - Baseline measurable disease remains 1 g/dL
  - VGPR would require 90% decrease or reduction to normal range and CR would require negative IFE
  - Progression requires 25% increase -minimum increase of 0.5 g/dL

- If mass spectrometry is used in lieu of IFE, it should be specified

Additional points

בעיקר עם אימונוטרפיה
לפעמים עליה ב--FDG
uptake וצריך לחזור על
הדמיה לודא שזה לא
tumor flare

- Confirmation of monoclonal protein measurements are required, but sequential confirmation can be replaced by simultaneous confirmation-two markers at any given time point meeting threshold
- 24-hour urine measurements are required at baseline, and if M protein present, will need retesting only to confirm CR or higher
- Patients should be categorized as SD until they meet criteria for any response category or have PD
- One can elect to repeat and confirm an imaging study suggestive of PD if other disease markers suggest response.
- Patients can be considered to have PD if they meet the criteria for PD by a variable that was not considered measurable at baseline

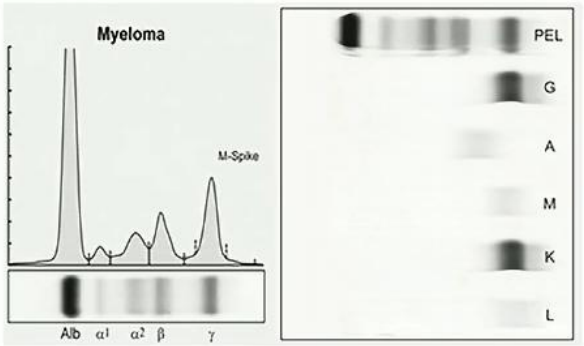
חשוב, כי הרבה פעמים יש LC ESCAPE
בהשנות

Summary of important changes

- Reliance on serum FLC measurements over 24-hour urine assessments with 24-urine only assessed when serum FLC is not available and for confirmation of negative immunofixation if positive on baseline evaluation
- Ability to use concurrent confirmation of two different blood or urine based measurements in place of sequential confirmation of the same marker,
- Elimination of minimal response and stringent CR as levels of response
- Normalization of the involved light chain being sufficient for categorizing a CR among those with light chain disease provided serum IFE is negative
- Specifications of techniques used – mass spec vs. SPEP/IFC, MRD sensitivity level 10^{-5} vs 10^{-6}, MRD negative CR or MRD negative ITT, when used
- Dependence on functional imaging for assessment of para-skeletal/ extramedullary lesions

M protein

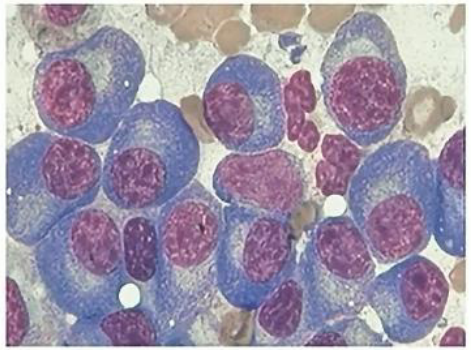
Serum, Urine

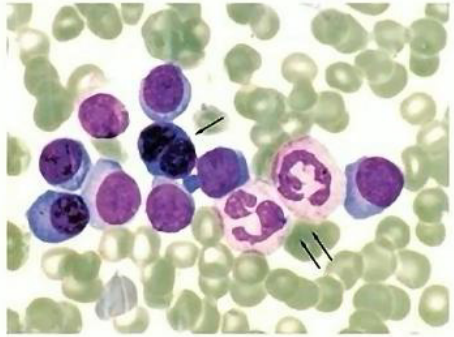


More sensitive mass spectrometry (*using expected protein sequence*)

Plasma cells

Marrow, Blood, Extramedullary



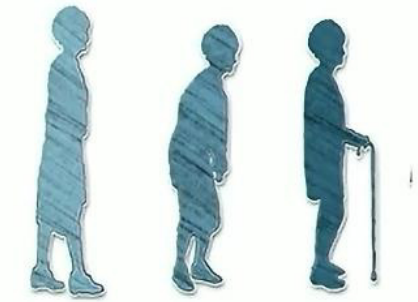


Circulating tumor/free DNA

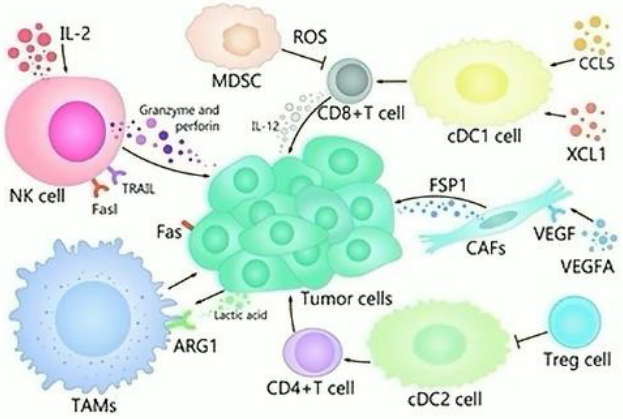
Novel imaging techniques

Host Measurements

Functional status



Tumor microenvironment



דוגמאות

מחקרים קליניים

יעל נמירובסקי

M-M, 74 Y
MM 2020

R-ISS I (normal FISH - standard risk)
IGG lambda M protein, FLC lambda – bone lesions.

LOT:
1) VRD + ASCT - Len maintenance - CR
PD: IGG lambda M protein 13.8 g/l, FLC L 226 mg/l, K 41.1 mg/l, R 0.18
BM: 7% PC, bone lesions, Para skeletal plasmacytoma, R-ISS I standard risk

2) Clinical study: Tri specific (BCMA-CD3-GPRC5D) + Dara

Date	M protein	Plasmacytoma	Response
JAN 2025	13.2 g/l IGG/L	Ribs T6, T7, L4	
JAN 2025	13.8 g/l IGG/L		
MAR 2025	10.9 g/l IGG/L		SD
APR 2025	4.2 g/l IGG/L		SD
APR 2025	3.2 g/l IGG/L	Deauville scale<4 PET, SPD 76% reduction	PR
MAY 2025	2.7 g/l IGG/L		PR
JUL 2025	0 g/l FLC L	Deauville scale<4 PET, SPD 77% reduction	VGPR, before PR

R-B 74 Y
MM 2022

M protein 0 g/l
Urine BJ – FLC L
FLC L
Bone lesions

LOT:
1. VCD – PR
2. VRD – VGPR – PD FLC + bone lesions
3. DPD – PD FLC
4. Clinical study ABBV383 (CD3 – BCMA) SC → IV

Date	Urine M mg/24 hs	FLC mg/l	Response
JUL 2024	261 FLC L	998.5 dFLC	
AUG 2024	0 FLC L	65.8 dFLC	VGPR
SEP 2024	0 negative	64.8 dFLC	VGPR
OCT 024	0 FLC L	94 dFLC	VGPR
NOV 2024	0 FLC L	136.12 dFLC	VGPR
DEC 2024	0 FLC L	204 dFLC	PD, before VGPR
DEC 2024	0 FLC L	192 dFLC	PD, before VGPR