Table 1

IMWG criteria of response for patients with MM

Response SubCategory	Response Criteria
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

Table 2 Comparison between different techniques to detect MRD in MM-BM

	Multidimensional flow cytometry (phenotype detection)					Molecular techniques (genotype detection)	
	First generation	**Second generation and third generation**				**Second generation**	**Third generation**
	2008 EMN consensus (4-6 colors)	**Euroflow (6 colors)**	**2016 ICCS consensus (8 or more colors)**	**DURAClone RE PC (9 colors)**	**MKSSC32 (10 colors)**	ASO-qRT-PCR	Next generation sequencing
Number of cells required		20×10^6 leukocytes	$2\text{-}5 \times 10^6$ leukocytes	5×10^6 leukocytes	20×10^6 leukocytes	500 ng, 1× 106 PCs for triplicate analysis	1400 ng, 2× 106 PCs for triplicate analysis
Theoretical LOD/LOQ	0.004	$4 \times 10^6/1 \times 10^5$	0.0004	$8 \times 10^6/2 \times 10^5$	$2 \times 10^6/5 \times 10^6$ (10×10^6 cells staining capacity)	0.0001	0.00001
Applicability (% cases)	95	99	95	99	99	50-90	80-90
Pre-treatment evaluation ansample quality assurance	Required	Not required	Not required	Not required	Not required	Required	Required
Required sample at diagnosis	No	No	No	No	No	Yes	Yes
Required fresh sample	Yes	Yes	Yes	Yes	Yes	No	No
Turnaround	60-90 min	60-90 min	60-90 min	60-90 min	60-90 min	Days	Days
Cost	+	++	++	++	++	+	++++
Availability	Widely available	Specialised labs				Intermediate	Specialised labs
Harmonization	Yes (EMN)	Yes (EMN)	Yes (ICCS/ESCCA)		ongoing	Yes	ongoing (EuroMRD)

Supplementary Table 1
Impact of MFC/MRD status on cytogenetic risk

Study	Method, LOD	Outcome in MRD$^+$patients			
		PFS in high-risk cytogenetics	**PFS in standard-risk cytogenetics**	**OS in high-risk cytogenetics**	**OS in standard-risk cytogenetics**
Hu, 2019[60]	MFC, 10^{-4}	mPFS 19 mo	mPFS 24 mo	not reported	not reported
Li, 2019[14]	MFC, 10^{-4}	mPFS 22 mo	mPFS 34 mo	4-yrs OS 54%	4-yrs OS 84%
Chakraborty, 2017[59]	MFC, 10^{-4}-10^{-5}	mPFS 22 mo (in del17p pts)	not reported	mOS 50 mo (in del17p pts)	not reported
Paiva, 2012[107]	MFC, 10^{-4}-10^{-5}	3-yrs TTP 0%	3-yrs TTP 32%	3-yrs OS 57%	3-yrs OS 90%
Rawstron, 2013[58]	MFC, 10^{-4}	mPFS 8.7 mo	mPFS 33.7 mo	not reported	not reported
Liu, 2012[115]	MFC, 10^{-5}	mPFS 13.2 mo	mPFS 22.6 mo	mOS 22.7 mo	mOS 18.2 mo
Paiva, 2016[26]	MFC, 10^{-5}	mTTP 12 mo	mTTP 15 mo	median OS not reached	median OS not reached

Abbreviations: MFC: multiparametric flow cytometry; mPFS: median progression free survival; mOS: median overall survival; mTTP: median time to progression; mo: months.