Published	Median time to progression (months) [CI]		Risk for progression at 2 years (%) [CI]	
	BMPCs ≥ 60 %	*BMPCs < 60 %*	*BMPCs ≥ 60 %*	*BMPCs < 60 %*
Early publications	9.20 [6.02-15.56]	101.47 [89.90-NA]	86.21 [65.74-94.45]	21.19 [18.15-24.12]
Recent publications	30.31 [18.71-62.93]	80.46 [70.97-115.48]	45.45 [20.12-62.75]	20.32 [15.18-25.14]
Combined data	15.48 [10.93-21.93]	96.73 [87.01-NA]	68.63 [52.92-79.09]	20.97 [18.37-23.48]
	FLCratio ≥ 100	*FLCratio < 100*	*FLCratio ≥ 100*	*FLCratio < 100*
Early publications	15.33 [9.38-19.10]	58.59 [52.78-65.80]	73.00 [62.39-80.62]	26.58 [22.89-30.09]
Recent publications	48.06 [40.51-64.91]	115.15 [105.96-118.81]	31.61 [25.30-37.39]	16.79 [14.91-18.64]
Combined data	30.40 [25.43-38.69]	93.19 [81.37-105.96]	43.82 [38.14-48.97]	19.45 [17.75-21.12]
	> 1 lesion	*≤1 lesion*	*> 1 lesion*	*≤1 lesion*
Early publications	15.07 [10.49-32.98]	102.42 [69.67-102.42]	67.30 [48.97-79.05]	16.14 [11.10-20.90]

≥100 and an involved FLC concentration of ≥100 mg/dl or > 1 MRI-defined ≥5mm focal lesion. The main reason for revising the diagnostic criteria was the data available at that time, which showed a very short time to progression (TTP) to CRAB positive MM (between 9.2 and 15.3 mos), leading to the recommendation to initiate anti-MM therapy in these pts.

Objective: To determine whether the prognosis (median time to progression □TTP□ and 2-year risk of progression) of biomarker-defined early MM or "SliM CRAB" positive MM pts has changed over the past decade compared with data previously available for the consensus group. Recent clinical experience suggests that a substantial proportion of pts meeting SliM CRAB MM criteria do not progress to MM within a short period of time.

Methods: We performed a comprehensive literature search and meta-analysis, including studies listed in Embase and PubMed (01/01/2010 - 01/11/2022) on SliM CRAB positive pts, including digitizable progression curves that would allow generation of individualized data. We used WebPlotDigitizerTM to digitize published TTP curves and then applied the algorithm described by Guyot et al (2012) in R to obtain individualized patient outcomes. We generated Kaplan-Meier curves and forest plots using random-effects models from the digitized and published data and compared median TTP, 2-year risk of progression, and odds ratios (ORs) for the comparison of 2-year risk of progression between data published before and after the publication of the IMWG consensus.

Results: We found 11 recent studies in addition to the six previously available studies with a total of 3482 pts. Our analysis showed longer TTP (median: 30.3 vs. 9.2 mos) and a reduction in 2-year risk of PD (45.5% vs. 86.2%) in pts with ≥60% BMPCs and in pts with a FLCratio ≥ 100 (48.1 vs. 15.3 mos and 31.6% vs. 73.0%, respectively) in more recent compared with earlier studies. Such analyses were not possible for pts with focal lesions defined by MRI because no further studies were published after 2014 (table 1).

A meta-analysis using ORs for the 2-year risk of progression in pts with ≥ 60% BMPC showed a significantly higher OR in the two earlier (OR: 27.01, 95% CI 4.49-162.34, p=0.0003) compared to a later report (OR: 3.27, 95% CI 1.37-7.99, p=0.009). Testing for heterogeneity revealed that the two time periods differed significantly in their ORs (I2 =78.6%, p=0.009). Similar results were obtained for pts with a FLCratio ≥100 compared to those with a FLCratio < 100 in early (OR: 7.03, 95% CI 4.34-11.37, p < 0.0001) and recent publications (OR: 2.69, 95% CI 1.77-4.09, p < 0.0001), I2 = 67.8%, p = 0.005.

Conclusions and Relevance: We found an approximately 3-fold longer TTP and 50% lower 2-year risk of progression in SMM patients with ≥60% BMPC or FLC ratio ≥ 100 in recent compared to earlier studies. This phenomenon is likely due to improved diagnostic workup with modern skeletal imaging and exclusion of patients with bone lesions. Therefore, routine treatment of patients meeting SliM criteria CRAB (BMPC or FLC ratio) should be initiated only after careful evaluation and documentation of signs of progression.

P09 DARATUMUMAB PLUS LENALIDOMIDE AND DEXAMETHASONE (D-RD) VERSUS LENALIDOMIDE AND DEXAMETHASONE (RD) ALONE IN TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM): UPDATED ANALYSIS OF THE PHASE 3 MAIA STUDY

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Introduction: Daratumumab is a human IgGκ monoclonal antibody that is approved as monotherapy and in combination with standard-of-care regimens for relapsed/refractory multiple myeloma and in combination with standard-of-care regimens for NDMM. In the primary analysis of the phase 3 MAIA study (median follow-up, 28.0 months), D-Rd significantly improved progression-free survival (PFS) and the minimal residual disease (MRD)–negativity rate (10–5 sensitivity) versus Rd alone in transplant-ineligible patients with NDMM. With longer follow-up (median follow-up, 56.2 months), D-Rd significantly improved overall survival (OS) versus Rd. Here, we present an analysis of MAIA after a median follow-up of 64.5 months.

Patients and methods: Patients with NDMM ineligible for high-dose chemotherapy and autologous stem cell transplant were randomized 1:1 to Rd ± D. Randomization was stratified by International Staging System disease stage (I vs II vs III), region (North America vs other), and age (<75 vs ≥75 years). All patients received 28-day cycles of Rd (R: 25 mg PO on Days 121; d: 40 mg PO on Days 1, 8, 15, and 22). In the D-Rd arm, D (16 mg/kg IV) was given once weekly in Cycles 12, once every 2 weeks in Cycles 3-6, and once every 4 weeks thereafter. In both groups, patients were treated until disease progression or unacceptable toxicity. PFS was the primary endpoint; key secondary endpoints included MRDnegativity rate (10–5 sensitivity, clonoSEQ® version 2.0), overall response rate (ORR), OS, and safety.

Results: A total of 737 patients were randomized (D-Rd, n=368; Rd, n=369). At a median follow-up of 64.5 months, PFS was improved with D-Rd versus Rd (median, 61.9 vs 34.4 months; hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.45-0.67; P<0.0001). D-Rd reduced the risk of death by 34% versus Rd. Median OS was not reached with D-Rd versus 65.5 months with Rd (HR, 0.66; 95% CI, 0.53-0.83; P=0.0003), with estimated 60-month OS rates of 66.6% and 53.6%, respectively. ORR was higher for D-Rd versus Rd (92.9% vs 81.6%; P<0.0001), as were rates of MRD negativity (32.1% vs 11.1%; P<0.0001) and sustained MRD negativity lasting ≥12 months (18.8% vs 4.1%; P<0.0001). The most common (≥15% of patients in either arm) grade 3/4 treatment-emergent adverse events (TEAEs; D-Rd/Rd) were neutropenia (54.1%/37.0%), anemia (17.0%/21.6%), pneumonia (19.5%/10.7%), and lymphopenia (16.5%/11.2%); grade 3/4 infection rates were 42.6%/29.6%. Pneumonia was the most common serious

TEAE in both groups (18.7%/10.7%). Rates of treatment discontinuation due to TEAEs were lower with D-Rd (14.6%) versus Rd (23.8%).
Conclusions: In this analysis of MAIA after a median follow-up of >5 years, the addition of DARA to Rd continued to demonstrate PFS and OS benefits in transplant-ineligible patients with NDMM. D-Rd also achieved higher MRD-negativity and ≥12-month sustained MRD-negativity rates versus Rd alone. No new safety concerns were observed with longer follow-up. These results continue to support the frontline use of D-Rd in transplant-ineligible patients with NDMM. Additional OS results based on extended follow-up will be presented.

P10 AN ULTRA-SENSITIVE METHOD FOR SEQUENCING AND MONITORING OF M-PROTEIN IN PERIPHERAL BLOOD (M-INSIGHT)

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With the improvement of therapy (monoclonal antibody, CAR-T), detection of minimal residual disease (MRD) and early restart of therapy is of high importance to manage multiple myeloma disease (MM). Most sensitive MRD assays to date are based on quantification of clonal plasmocytes by next generation sequencing or flow cytometry in bone marrow aspirates. However, such methods have shown limitations such as being invasive with sample heterogeneity and lacking the possibility for frequent sampling. Frequent MM monitoring on blood at equivalent sensitivity than achieved with bone marrow could provide actionable information on disease activity and detect early signs of progression.
M-protein is a well-established biomarker used for MM diagnostic and monitoring. Mass spectrometry (MS) has been introduced as a possibility to monitor M-protein. Intact protein measurement by MS has the drawback of lacking in sensitivity with high interference from the polyclonal background. Clonotypic peptides originating from the variable region of the M-protein are unique for each patient. Their detection by MS, which circumvent interferences from other immunoglobulins, has been demonstrated to quantify M-protein at MRD level. Several studies from our group have been published showing the use of targeted mass spectrometry-based MRD blood-test (M-InSight) that detects clonotypic peptides.
In this study, M-InSight is used to sequence and select clonotypic peptides to allow highly specific and ultra-sensitive monitoring of the M-protein. Therapy response of 41 Multiple myeloma patients from the IFM-2009 clinical trial (NCT01191060) was used to evaluate the assay. M-InSight uses a novel de novo approach using Peaks Ab software to sequence the M-protein with mass spectrometry from serum that are further assembled into full length HC (Heavy Chain) and LC (Light chain) sequences. All 41 patients were sequenced by mass spectrometry, which was then compared to RNA sequencing data based on tala cDNA from all expressed genes. RNA assembly pipeline using Trust4 was used to construct clonotypes and to identify clonal molecular fingerprints and finally their clonotypic peptides based on transcriptomic datasets. Results showed a coverage of more than 90% of the entire LC and HC sequenced by mass spectrometry compared to the data obtain from RNA sequencing.
Once the M-protein sequence was obtained, several clonotypic peptides were further chosen with the use of an in-house bioinformatics algorithm to select the best candidate. Each peptide is chosen to be specific to the patients (CDR region) from both chains. Clonotypic peptides are used to quantitate M-protein in patients' serum after treatment. M-protein concentrations were determined by calibration on a sample with a known M-protein concentration quantified by an agarose gel electrophoresis system (Hydrasys 2, Sebia).
Results showed a very high sensitivity with M-protein still detectable by M-InSight despite a MRD negativity determined by next generation sequencing data on bone marrow aspirate. The best sensitivity achieved by M-InSight, detecting 0.2 mg/L of M-protein, was 1000- and 100-fold more sensitive compared to SPE and intact protein MS method, respectively.
In conclusion, the newly developed and validated M-InSight assay is presented as an ultra-sensitive fully blood based assay to sequence and monitor M-protein with the possibility for frequent non-invasive analysis.

P11 COMBINED DIFFUSION WEIGHTED WHOLE BODY MRI (DW-MRI) AND MULTIPARAMETRIC FLOW CYTOMETRY (MFC) EVALUATION FOR MINIMAL RESIDUAL DISEASE DETECTION IN MULTIPLE MYELOMA PATIENTS: CONCORDANCE ANALYSIS OF THE TWO TECHNIQUES AND PREDICTIVE ROLE AFTER TRANSPLANT

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Introduction: The increasing availability of functional imaging techniques has enabled the combined evaluation of MRD in MM within and outside bone marrow (BM). Diffusion-weighted whole-body MRI (DW-MRI) is increasingly used in the management of MM patients (pts) and criteria for Response Assessment Category (RAC) have been established by the Myeloma Response Assessment and Diagnosis System (MY-RADS), with a 5 point scale defining complete imaging response (i.e. RAC 1) or residual-progressive disease after treatment (i.e. RAC 2-5). We compared the results of MY-RADS with those of MRD assessment by flow cytometry (MFC) at different timepoints after autologous stem cell transplant (ASCT) in order to evaluate the agreement of the two techniques and to investigate the predictive role of a dual assessment of response on patients outcome.
Methods: we retrospectively assessed MRD in transplant eligible MM pts by performing combined evaluations of BM and DW-MRI at day +100 after ASCT and yearly thereafter. MY-RADS RAC criteria were applied for the evaluation of imaging residual disease, whereas 8-color MFC (sensitivity 10-5) was performed for BM MRD detection. The concordance between DW-MRI and MFC results was calculated and the level of agreement was expressed by Cohen's kappa statistics. The outcome according to the combined DW-MRI/MFC evaluation after ASCT was also investigated. Results: from 2016 to 2021 we performed 143 combined evaluations of DW-MRI and MFC in 79 pts. MFC was negative in 96 BM samples (67%); according to MY-RADS, a complete imaging response (RAC1) was observed in 107 cases (75%), whereas some residual disease was identified in 36 cases (25%) [RAC2: 24 (17%), RAC3: 6 (4%), RAC4: 3 (2%), RAC 5: 3 (2%) respectively]. The concordance between WB-MRI and BM MFC results was low (68.5%, kappa 0,067: 13% both positive, 55% both negative). MRD assessment at day +100 after ASCT (considering the second ASCT in case of double transplant) was available in 76 patients [27(35%) ISS-3, 29 (38%) high risk cytogenetics]. Pts were treated with the following induction regimens: VTD 56 (74%), DaraVCD 6 (8%), DaraVRD 6 (8%), VRD 6 (8%), KCD 1 (1%), KRD 1 (1%); 37 pts (49%) received double ASCT (MEL200). Response rates were sCR 25%, CR 45%, VGPR 21%, PR 9%. MFC was negative in 48 samples (63%), whereas RAC1 was observed in 52 (68%) pts.
Seventy pts (92%) received maintenance therapy with lenalidomide (58), daratumumab-lenalidomide (6), daratumumab-ixazomib (6). After a median follow up of 42 months, PFS was significantly better for patients with DW-MRI RAC1 and MFC negative after ASCT, compared to pts with RAC ≥2 and MFC positive results (PFS NR vs 22.3 months; p <0.0001, HR 0.10 - 95%CI: 0,02-0,43). Intermediate PFS was observed for pts with either imaging or BM positive results (PFS NR), with a significantly different outcome of the three subgroups (p <0.0001). A trend of different OS was also observed, although not statistically significant (3y OS: 95% for double negative pts, 89% for pts with either imaging or BM positive results, 60% for double positive pts, p 0.06). Conclusion: DW-MRI is a powerful tool to evaluate the prognosis of pts treated with ASCT; the low concordance between DW-MRI and MFC highlights the complementarity of the two techniques for the definition and monitoring of response in order to better refine the prognosis of pts achieving CR after ASCT