

Real world criteria used to diagnose relapsed/refractory status of patients with multiple myeloma in Germany

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BACKGROUND

- The International Myeloma Workshop (IMWG) guidelines provide definitions of patients with relapsed and/or refractory multiple myeloma (RRMM) and key criteria to classify their disease status^{1,2}
- Both clinical and IMWG criteria for the assessment of progressive disease are important to guide the choice of treatment at relapse, which can be complicated by many factors, such as the timing of disease progression, its aggressiveness, response to prior therapy, and performance status^{3,4}
- The application of these disease criteria in clinical practice is unclear and has been evaluated in this real-world study in Germany

OBJECTIVES

- To identify key criteria used in routine practice in Germany to classify RRMM in patients experiencing progressive disease
- Secondly, to understand how these classifications and applied progressive disease criteria align with the IMWG guidelines^{1–3}

METHODS

- An online anonymized cross-sectional study with a questionnaire was sent to physicians and a Delphi panel of MM experts in 2021
- Eligibility criteria included:
 - Phase 1 (Survey):
 - MM-treating physicians who had actively treated at least 4 patients in the last 6 months prior to the survey, and
 - were responsible for treatment decisions for patients with MM
 - Phase 2 (Delphi panel):
 - MM-treating physicians who had actively treated at least 4 patients in the last 6 months prior to the Delphi panel, and
 - had fulfilled at least 2 of the following 3 criteria in the field of MM: investigator in clinical trials, author in peer-reviewed journals, speaker at conferences
- Physicians were excluded if they had 2 or more colleagues from the same institution already participating in the survey or Delphi panel
- The questionnaire used in the survey and Delphi panel had two parts (**Table 1**)

Table 1. Content of questionnaire used in the survey and Delphi panel

Part 1: Collection of information about 8 key IMWG criteria indicative of progressive disease	<ol style="list-style-type: none">Serum M-protein electrophoresisUrine M-protein electrophoresisFree Light Chains-quotientBone marrow plasma-cell percentageSoft tissue plasmacytomas or bone lesionsCalcium levelAnemiaCreatinine level or creatinine clearance
Part 2: MM disease assessment of 18 case scenarios describing the disease status of 7 fictive patient cases at different lines of therapy, in accordance with IMWG criteria ¹ (Figure 1 and Figure 2)	<ol style="list-style-type: none">'primary refractory' (n=7)*'relapsed only' (n=2)'relapsed and refractory' (n=6)'neither relapsed only nor relapsed and refractory' (n=3)

*Included n=1 'primary refractory' and n=6 'not primary refractory'

- Online Delphi panel:
 - In the 1st wave conducted in June 2021, the experts were asked to complete an online questionnaire
 - In the 2nd wave conducted in September 2021, the same experts were asked again to respond to the same questions and to re-assess their previous answers after review of the answers given in wave 1 by other experts
- Consensus was considered to be reached when 85% of physicians (survey) or 80% of experts (Delphi panel) had identical answers

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DISCLOSURES OF INTEREST

- BT and SP are employees of IQVIA who received funding from Amgen to conduct this research
- TS, FE and CF are employees of Amgen GmbH and hold Amgen stocks
- This study was funded by Amgen (Europe) GmbH

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Figure 1. Definitions of ‘primary refractory MM’, ‘relapsed and refractory MM’ and ‘relapsed MM’ based on the IMWG criteria¹ and used in the survey and Delphi panel

Primary refractory <ul style="list-style-type: none">Patient with MM that is non-responsive at any time, i.e., did not achieve a minimal response or better at any time during the complete treatment history (from diagnosis to present day)
Relapsed and refractory MM <ul style="list-style-type: none">Patient with MM achieving a minimal response or better during prior or current treatment (any therapy line including first line) and progressing either during current treatment or within 60 days after end of last treatment. This includes all treatments, including first line and maintenance therapyPatient with MM that is non-responsive while on 2nd or later therapy line, but achieving a minimal response or better and then progressing at some point previously
Relapsed MM <ul style="list-style-type: none">Patient with MM achieving a minimal response or better and then progressing more than 60 days after end of last treatment

Figure 2. Example of a hypothetical patient treatment history which includes 2 case scenarios matching the IMWG criteria,¹ one for ‘not primary refractory MM’ and one for ‘neither relapsed only nor relapsed and refractory MM’ at start of 2nd line therapy

Patient 4 <ul style="list-style-type: none">Age at MM diagnosis: 70 yearsGender: MaleDate of MM diagnosis: 11/2016
First line therapy <ul style="list-style-type: none">12/2016: Start of therapy1 Therapy: Bortezomib + dexamethasone + cyclophosphamide 2 cycles01/2017 (after 6 weeks): No response to therapy; end of therapy due to ongoing symptomatic progression while on treatment
Second line therapy <ul style="list-style-type: none">02/2017: Start of therapy2 Therapy: Lenalidomide + dexamethasone 5 cycles07/2017 (after 5 months): End of therapy due to toxicity (acute renal insufficiency); status at end of therapy: partial response
Third line therapy <ul style="list-style-type: none">08/2017: Start of therapy due to symptomatic progression occurred 45 days after stop of second line therapy3 Therapy: Panobinostat + bortezomib + dexamethasone

RESULTS

Physician demographics and characteristics – survey & Delphi panel

Phase 1: Survey participants

- In total, 49 physicians fulfilled all screening criteria and partly or completely answered the online survey between November 2020 and January 2021
- The majority of them (83.7%, n=41) completed the questionnaire, including the 18 hypothetical case scenarios
- Questions on progressive disease were answered by 43 physicians
- The survey physicians were mainly males (n=39, 80%), 88% were ≥40 years. Their median experience in MM was 16 years (**Table 2**)
- Almost half of them were office-based (47%), followed by hospital inpatient and outpatient practice (27%), hospital outpatient practice (14%), both an office and hospital practice (10%), and one worked in a hospital inpatient practice (2%; **Table 2**)

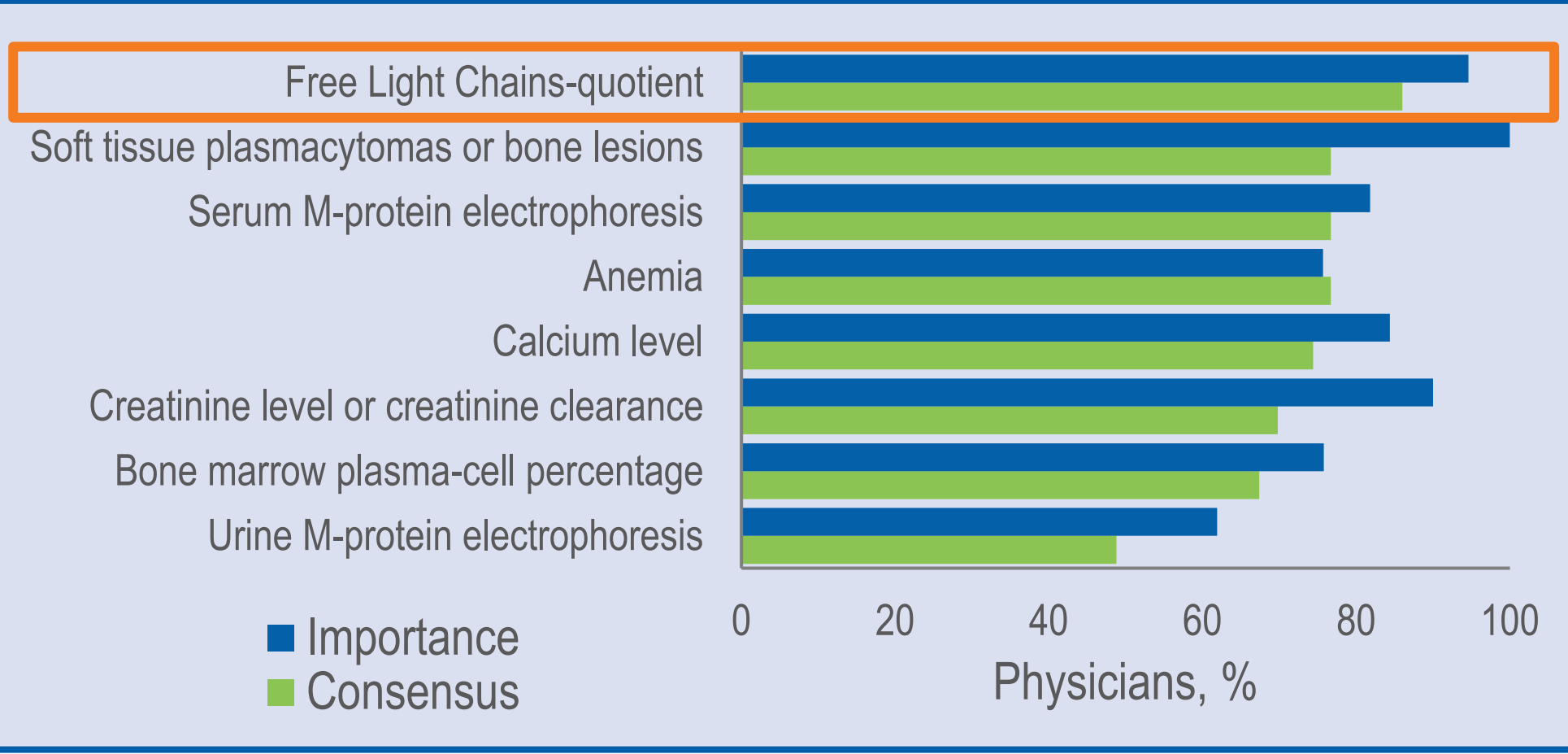
Table 2. Physician demographics and characteristics – survey participants & Delphi panel

	Survey (n=49)	Delphi panel (n=11)
Male, n (%)	39 (80)	9 (82)
Age (years) at participation, n (%)		
≤30	0 (0)	0 (0)
31–39	6 (12)	1 (9)
40–49	22 (45)	4 (36)
50–59	17 (35)	6 (55)
≥60	4 (8)	0 (0)
Setting, n (%)		
Office based	23 (47)	4 (36)
Hospital inpatient practice	1 (2)	0 (0)
Hospital outpatient practice	7 (14)	2 (18)
Hospital both, inpatient and outpatient practice	13 (27)	4 (36)
Both, office and hospital	5 (10)	1 (9)
Physician's main medical specialty, n (%)		
Internal medicine specialized in hematology / oncology	49 (100)	11 (100)
Other	0 (0)	0 (0)
Physician's experience in the specialty (years), median (range)	16 (6–30)	17 (9–23)

Phase 2: Delphi panel

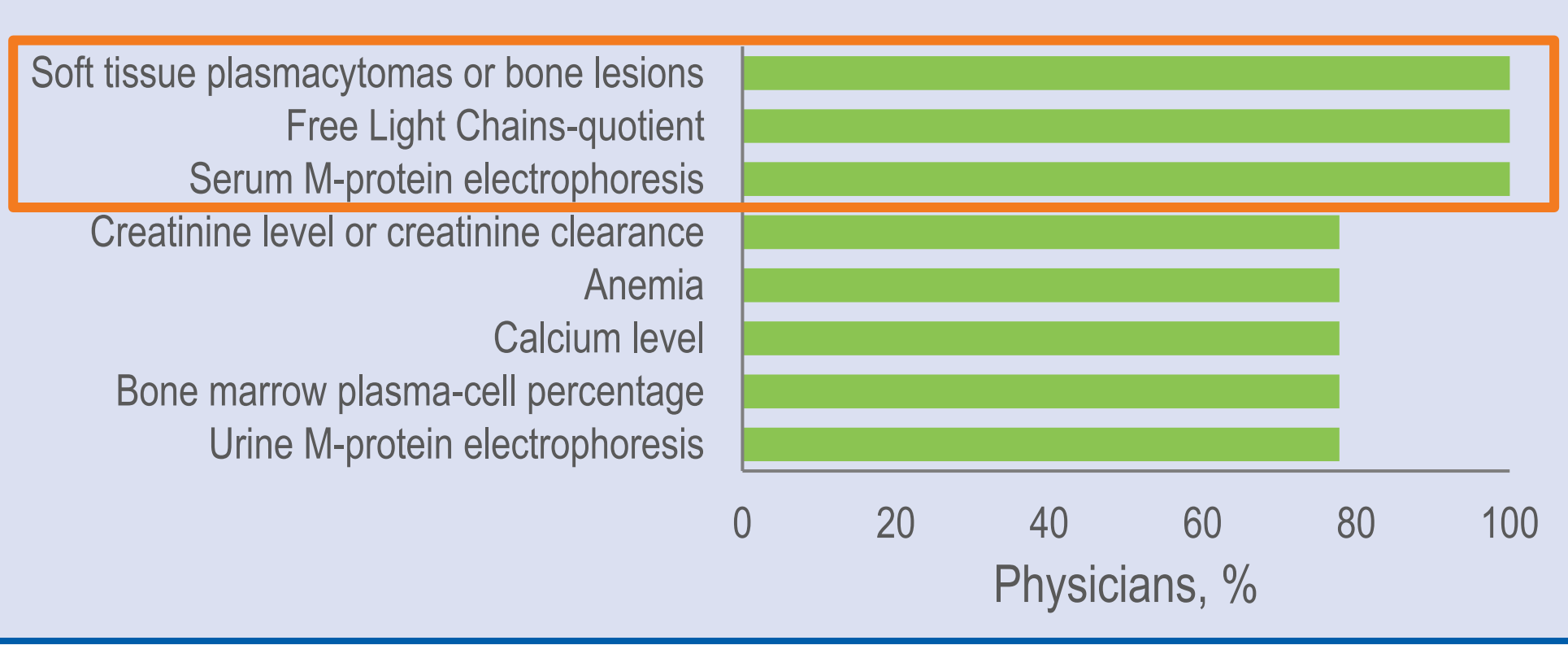
- In total, 11 experts completed the questionnaire in wave 1, and 9 completed the questionnaire in both waves
- Experts were mainly males (n=9, 82%); all but one were ≥40 years. Median experience in MM was 17 years (**Table 2**)
- An equal proportion of experts (36%) worked in a private office or a hospital inpatient and outpatient practice, two worked in a hospital outpatient practice (18%) and one in both an office and hospital practice (9%) (**Table 2**)

Figure 3. Consensus* and importance# for key factors indicative of progressive disease – survey (n=43 physicians)



*Consensus was considered to be reached when 85% of physicians (survey) had identical answers
#Either important or very important

Figure 4. Consensus* for key factors indicative of progressive disease – Delphi panel (n=9 experts)



*Consensus was considered to be reached when 80% of experts (Delphi panel) had identical answers

Consensus in key criteria of progressive disease

- Among the 43 hemato-oncologists answering the questions about progressive disease, a consensus was reached for 1 of the 8 (13%) key criteria: free light chain (FLC)-ratio (**Figure 3**)
- Most physicians ranked the progressive disease criteria as either important or very important for this assessment (**Figure 3**)
- In the Delphi panel (n=9), consensus was reached for 3 (38%) of the progressive disease criteria: FLC-ratio, serum M-protein electrophoresis, and soft tissue plasmacytomas/bone lesions (**Figure 4**)

Consensus in hypothetical case scenarios

- Of the 18 case scenarios, consensus among physicians or the expert panel was reached for 6 (33%) and 9 (50%) cases, respectively (**Table 3**)
- The classification of ‘primary refractoriness’ cases generally matched the IMWG criteria¹ (survey: 5 of 7; Delphi panel: 6 of 7; **Table 3**)

Table 3. Consensus reached on disease classifications irrespective of IMWG definitions in the survey and Delphi panel out of a total of 18 hypothetical case scenarios, including 7 scenarios assessing primary refractoriness and 11 scenarios assessing relapsed and/or refractory MM*

Consensus reached out of	Phase 1: Survey (n=41)	Phase 2: Delphi panel (n=9)
18 hypothetical case scenarios	6 scenarios# (33%)	9 scenarios ^{5, #} (50%)
7 ‘primary refractory’ case scenarios	6 scenarios# (86%)	7 scenarios# (100%)
<i>Including one consensus on patient case 4 that was at odds with the IMWG definition*</i>	39 physicians (95%)	9 MM experts (100%)
11 ‘relapsed only or relapsed and refractory’ case scenarios*	No consensus (0%)	2 scenarios ⁵ (18%)

*Scenarios for relapsed and/or refractory MM included: ‘relapsed only’ (n=2), ‘relapsed and refractory’ (n=6) or ‘neither relapsed only nor relapsed and refractory’ (n=3)
#In both the survey and the Delphi panel, a consensus was reached on one case identified as ‘primary refractory MM’ instead of ‘not primary refractory MM’ (Patient 4 described in Figure 2)
⁵The consensus among Delphi panel experts includes one case scenario which was at odds with the IMWG guidelines¹ as it was classified as ‘relapsed only’ instead of ‘relapsed and refractory’

CONCLUSION

- In this study, a German panel of MM experts identified three criteria as key diagnostic criteria of progressive disease
- Consistency in the classification of RRMM was found predominantly for primary refractory MM
- The lack of alignment on the RRMM status observed in this study may be due to the complexity of RRMM diagnosis and treatment schemes which make it difficult to evaluate with hypothetical patient cases
- Future studies are needed to identify relevant factors used to classify RRMM in practice. For example, comorbidities and frailty status are important factors for obtaining a more objective evaluation of patients’ real constitution and treatment endurance⁵
- The recent 2021 IMWG guidelines aim to provide more practical guidance for disease stage assessment and choice of appropriate treatment in RRMM⁶