

# Psychometric Evaluation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Items and Myeloma 20-item Module



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# Disclosures

**Heather Romero:** Full time employee of Takeda Pharmaceuticals

**Flora Mazerolle:** Full time employee of Modus Outcomes, a division of THREAD, which received payment from Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

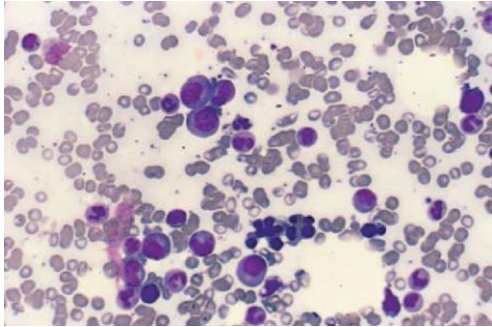
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# Introduction



- Multiple myeloma (MM), a neoplasm of malignant plasma cells in the bone marrow, is associated with high symptom burden and can result in extensive skeletal destruction with osteolytic lesions, and/or pathological fractures<sup>1-3</sup>
- Despite recent therapies that have improved overall survival and modified treatment side effects, MM remains incurable and negatively impacts patients' health-related quality of life (QoL)<sup>4-5</sup>
- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 item (QLQ-C30) and EORTC Quality of Life Questionnaire Myeloma 20-item module (QLQ-MY20) are standard patient reported outcomes (PRO) instruments included in clinical trials to capture the experience of patients with MM<sup>4-5</sup>
- Previous studies support the fitness for purpose of these instruments for use in clinical trials in MM<sup>6-8</sup>
- More recent psychometric data is required to establish their appropriateness

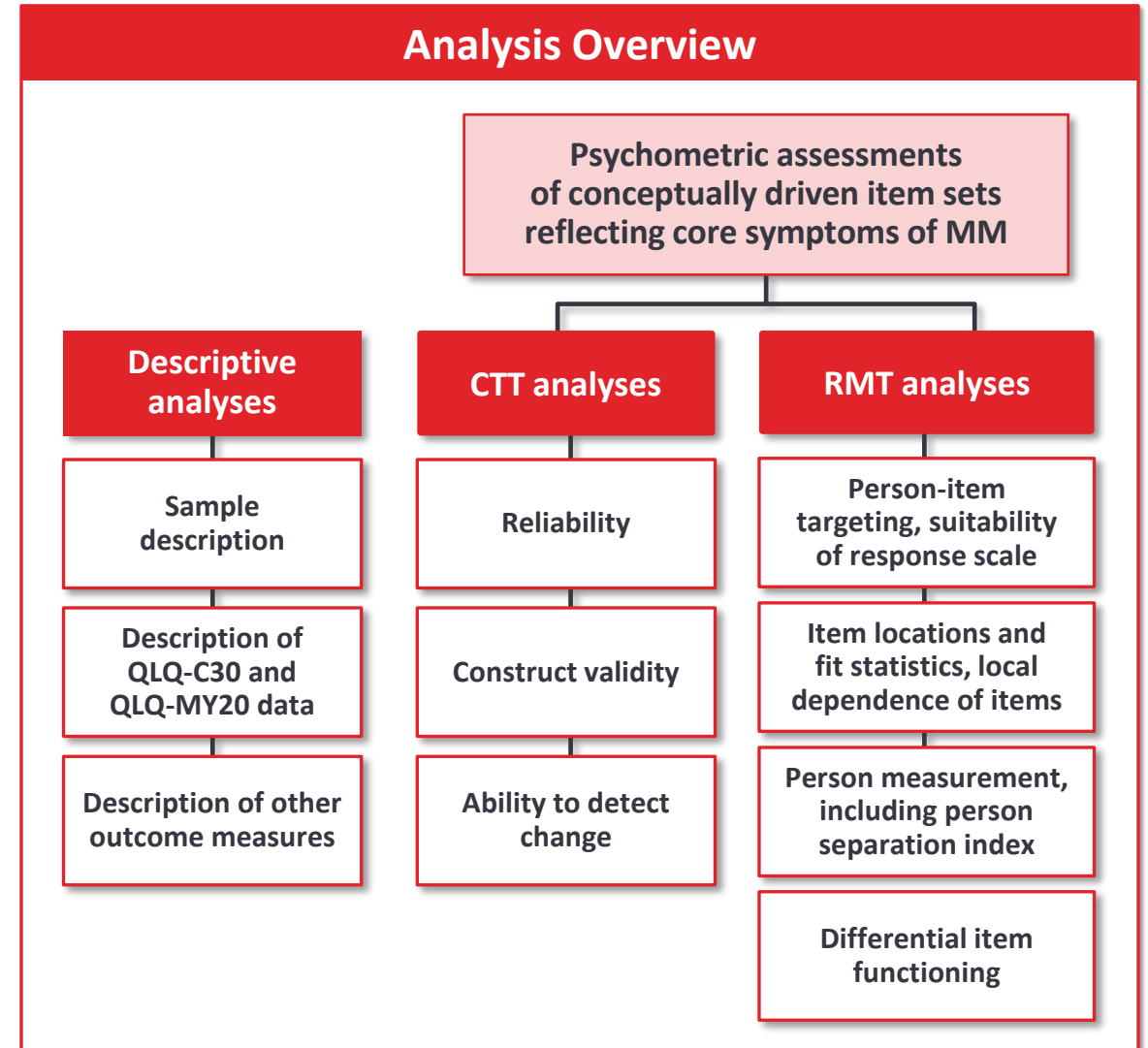
**Objective: To confirm the fitness for purpose of EORTC-QLQ-C30 and EORTC-QLQ-MY20 scores to demonstrate clinical benefit of MM therapies**

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520. 2. Rajkumar SV. Multiple myeloma: Every year a new standard? *Hematol Oncol*. 2019;37 Suppl 1(Suppl 1):62-65. 3. van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. *Lancet*. 2021;397(10272):410-427. 4. Seitzler S, Finley-Oliver E, Simonelli C, Baz R. Quality of life in multiple myeloma: considerations and recommendations. *Expert Rev Hematol*. 2019;12(6):419-424. 5. Baz R, Lin HM, Hui AM, et al. Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on health-related quality of life. *Support Care Cancer*. 2015;23(9):2789-2797. 6. Cocks K, Cohen D, Wisløff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. *Eur J Cancer*. 2007;43(11):1670-1678. 7. Kvam AK, Wisløff F, Fayers PM. Minimal important differences and response shift in health-related quality of life; a longitudinal study in patients with multiple myeloma. *Health Qual Life Outcomes*. 2010;8:79. 8. Sully K, Trigg A, Bonner N, et al. Estimation of minimally important differences and responder definitions for EORTC QLQ-MY20 scores in multiple myeloma patients. *Eur J Haematol*. 2019;103(5):500-509.

# Study Design

## Methods Overview

- Psychometric properties of the EORTC QLQ-C30 and EORTC QLQ-MY20 were evaluated using Classical Test Theory (CTT) and modern Rasch Measurement Theory (RMT) measurement theory frameworks
- CTT and RMT analysis were conducted using pooled blinded, dry-run data from 6 TOURMALINE-MM clinical trials of newly diagnosed MM (NDMM) and relapse/refractory MM (RRMM) patients:
  - C16010, C16014, C16019, C16021, C16029, C16047
- Measurements of key concepts for patients with MM, focusing on the core PRO concepts for cancer trials recommended by the FDA were investigated: physical function, role function, disease-related symptoms, and symptomatic adverse events



# Instruments Overview

## EORTC QLQ-C30

- Key functioning scales: physical functioning and role functioning
- Key symptoms scales: pain and fatigue
- Single items: Global health and quality of life scale
- All scores range from 0 to 100. Functioning and Global/QoL – higher score indicates better health. Symptom scales – lower score indicates better health

## EORTC QLQ-MY20

- Key symptom scales: disease symptoms and side effect of treatment
- Functioning scales/single items: future perspective and body image
- All scores range from 0 to 100. Functioning – higher score indicates better health. Symptom scales – lower score indicates better health

European Quality of Life 5 Dimensions 5/3 Level (EQ-5D-5L/3L)	Brief Pain Inventory - Short Form (BPI-SF)	Eastern Cooperative Oncology Group Performance Status (ECOG-PS)
<ul style="list-style-type: none"> <li>• PRO used to assess health status</li> <li>• Five items measuring mobility, self-care, usual activity, pain/discomfort, and anxiety/depression</li> <li>• Items of the 5L version are rated on a 5-point scale, from no problem to extreme problem</li> <li>• Items of the 3L version are rated on a 3-point scale</li> </ul>	<ul style="list-style-type: none"> <li>• PRO used to assess pain</li> <li>• Items on pain severity and impact of pain on patient's life</li> <li>• Items rated on a 11-point scale from 0 to 10</li> <li>• Pain severity items (4) used as single items</li> <li>• Pain interference score calculated as the mean of the 7 interference items</li> </ul>	<ul style="list-style-type: none"> <li>• Clinician-reported outcome</li> <li>• Assesses functional status</li> <li>• Six-point scale ranging from 0 (fully active) to 5 (dead)</li> </ul>

# Results: Select Sample Characteristics in the Pooled Analysis Set

Select variable	Study						Pooled Analysis Set N=2972
	C16010 N=722	C16014 N=705	C16019 N=656	C16021 N=706	C16029 N=122	C16047 N=61	
Age, mean (SD)	65.67 (9.41)	73.56 (6.22)	57.36 (8.10)	72.51 (6.83)	69.43 (8.58)	67.77 (7.80)	<b>67.53 (9.94)</b>
Male, %	56.6	50.2	63.1	53.4	50.0	52.5	<b>55.4</b>
<b>Race</b>							
White, %	85.2	81.7	80.5	78.6	90.2	86.9	<b>82.0</b>
Asian, %	8.9	13.6	14.5	14.4	0.8	0.0	<b>12.0</b>
Black or African American, %	1.8	3.4	1.5	2.8	0.8	4.9	<b>2.4</b>
Other, %	4.1	1.3	3.5	4.2	8.2	8.2	<b>3.6</b>
Type of MM	RRMM	NDMM	NDMM	NDMM	RRMM	RRMM	<b>NDMM: 70.0% RRMM: 30.0%</b>
Time from diagnosis to start of treatment, months, mean (SD)	51.73 (37.50)	1.85 (3.44)	10.22 (4.32)	10.70 (3.53)	69.52 (40.82)	46.46 (40.48)	<b>21.45 (30.31)</b>
ISS stage at screening	I or II: 88% III: 12%	I or II: 83% III: 17%	Missing	Missing	I or II: 76% III: 24%	I or II: 77% III: 18%	<b>I or II: 46% III: 8%</b>

ISS, international staging system; MM, multiple myeloma; NDMM, newly diagnosed MM; RRMM, relapse/refractory MM; SD, standard deviation.

# CTT Results: Reliability

Key QLQ-C30 and QLQ-MY20 scores and reconceptualized items demonstrated adequate psychometric properties: Good Cronbach's alpha reliability coefficients and good test-retest reliability (ICC)

		Pooled Analysis Set		Subsample of Stable Participants (QLQ-C30 item 29 "overall health")	
Instrument	Score	N	Cronbach's Alpha <sup>a</sup>	N	ICC <sup>b</sup>
QLQ-C30	Physical functioning	2899	0.86	969	0.88
	Role functioning	2906	0.89	967	0.81
	Fatigue	2900	0.87	969	0.81
	Pain	2899	0.88	971	0.80
QLQ-MY20	Disease symptoms	2838	0.82	958	0.85
	Side effects of treatment	819	0.81	956	0.82
	Future perspective	2887	0.84	955	0.78
	Body image	–	–	947	0.70

<sup>a</sup>Cronbach's alpha calculated at baseline. <sup>b</sup>Test-retest calculated between screening and baseline. Note: High Cronbach's alpha is >0.80; Adequate test-retest reliability (ICC) is (0.70-0.79) and good is >0.80  
CTT, classical test theory; ICC, intraclass correlation coefficient; QLQ-C30, Quality of Life Questionnaire – Core 30 items; QLQ-MY20, Quality of Life Questionnaire Myeloma 20-item Module.

# CTT Results: Construct Validity

Correlations between key QLQ-C30 and QLQ-MY20 scores and clinician rating of performance status and PRO measures support their construct validity

- QLQ-C30 physical functioning score: moderate correlation with ECOG-PS
- Key QLQ-C30 and QLQ-MY20 scores: moderate correlation with QLQ-C30 item #29 (Overall health)
- Key QLQ-C30: moderate to high correlations with EQ-5D-3L/5L

		Correlation Coefficients <sup>a</sup>			
Instrument	Score	ECOG-PS <sup>b</sup> N=2972	QLQ-C30 Item 29 <sup>b</sup> N=2972	EQ-5D-3L Usual Activities <sup>c</sup> N=2060	EQ-5D-5L Usual Activities <sup>c</sup> N=2060
QLQ-C30	Physical functioning	<b>-0.44</b>	<b>0.57</b>	<b>-0.70</b>	<b>-0.65</b>
	Role functioning	-0.36	<b>0.54</b>	<b>-0.72</b>	<b>-0.65</b>
	Fatigue	0.33	<b>-0.60</b>	<b>0.59</b>	<b>0.57</b>
	Pain	0.33	<b>-0.54</b>		
	Cognitive functioning	-0.24	0.38		
QLQ-MY20	Disease symptoms	0.27	<b>-0.51</b>		
	Side effects of treatment	0.27	<b>-0.46</b>		
	Future perspective	-0.14	0.33		
	Body image	-0.15	0.31		

<sup>a</sup>Spearman's rank-order correlation coefficient calculated at baseline. <sup>b</sup>Calculated in the pooled analysis set. <sup>c</sup>Calculated in participants from studies that included the 3L version of the EQ-5D (i.e., C16010, C16014, and C16019).

Note: Moderate ( $0.4 \leq r < 0.69$ ) to high ( $r \geq 0.7$ ) score correlations are marked in bold. CTT, classical test theory; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L/3L, European Quality of Life 5 Dimensions 5/3 Level Version; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire – Core 30 items; QLQ-MY20, Quality of Life Questionnaire Myeloma 20-item Module.

# CTT Results: Ability to Detect Change

QLQ-C30 and QLQ-MY20 scores demonstrated some ability to detect change over time:<sup>a</sup> baseline to cycle 4

- Effect sizes for key QLQ-C30 and QLQ-MY20 scores characterized as “improved” were between 0.2 and 0.5
- Effect sizes for QLQ-C30 role functioning, fatigue, and QLQ-MY20 side effect scores categorized as “worsened” were between 0.2 and 0.5

QLQ-C30 Score	Change in QLQ-C30 Item 29 “overall health”	N	Standardized Effect Size <sup>b</sup>
<b>Physical functioning</b>	Improved	823	<b>0.35</b>
	Stable	1021	0.09
	Worsened	671	-0.17
<b>Role functioning</b>	Improved	820	<b>0.37</b>
	Stable	1020	0.05
	Worsened	671	<b>-0.29</b>
<b>Fatigue</b>	Improved	823	<b>-0.38</b>
	Stable	1021	-0.01
	Worsened	672	<b>0.38</b>
<b>Pain</b>	Improved	823	<b>-0.43</b>
	Stable	1023	-0.11
	Worsened	675	0.19

QLQ-MY20 Score	Change in QLQ-C30 Item 29 “overall health”	N	Standardized Effect Size <sup>b</sup>
<b>Disease symptoms</b>	Improved	807	<b>-0.41</b>
	Stable	1005	-0.10
	Worsened	659	0.02
<b>Side effects of treatment</b>	Improved	805	-0.14
	Stable	1004	0.09
	Worsened	658	<b>0.35</b>
<b>Future perspective</b>	Improved	806	<b>0.39</b>
	Stable	1000	0.20
	Worsened	655	0.08
<b>Body image</b>	Improved	802	<b>0.21</b>
	Stable	993	0.01
	Worsened	653	-0.18

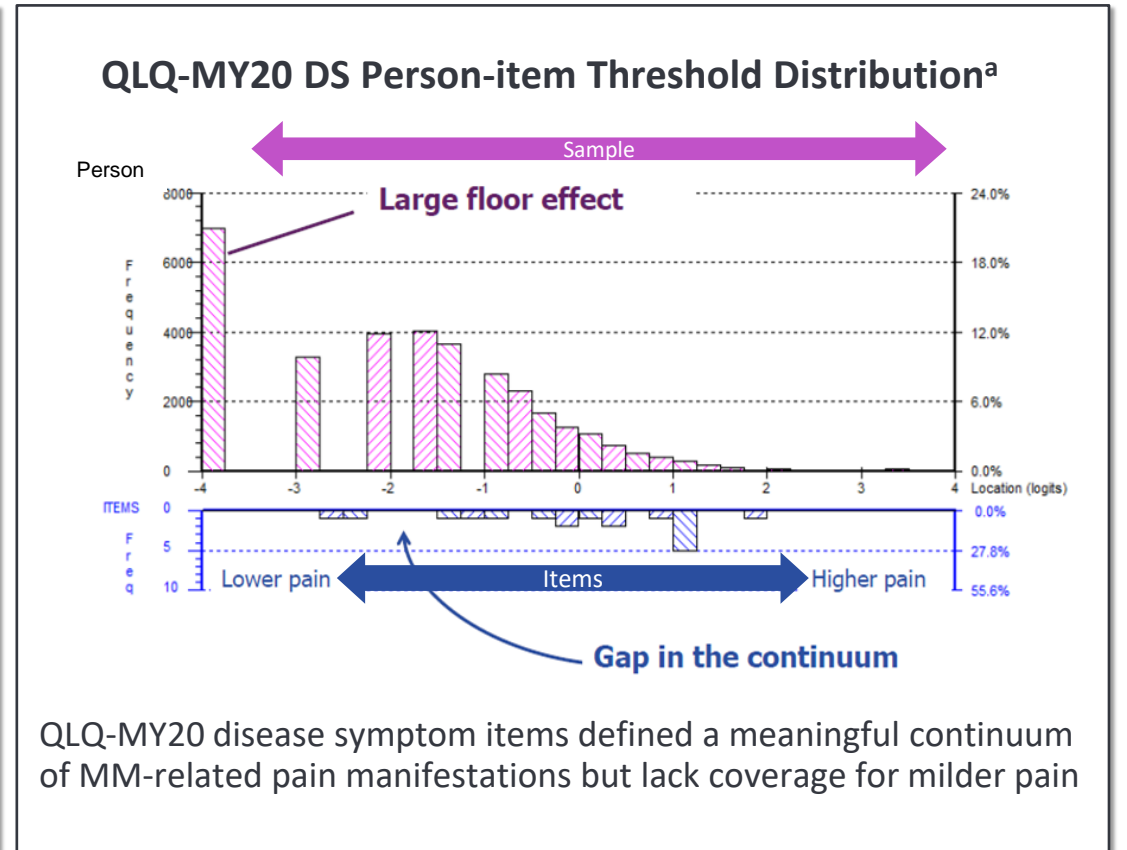
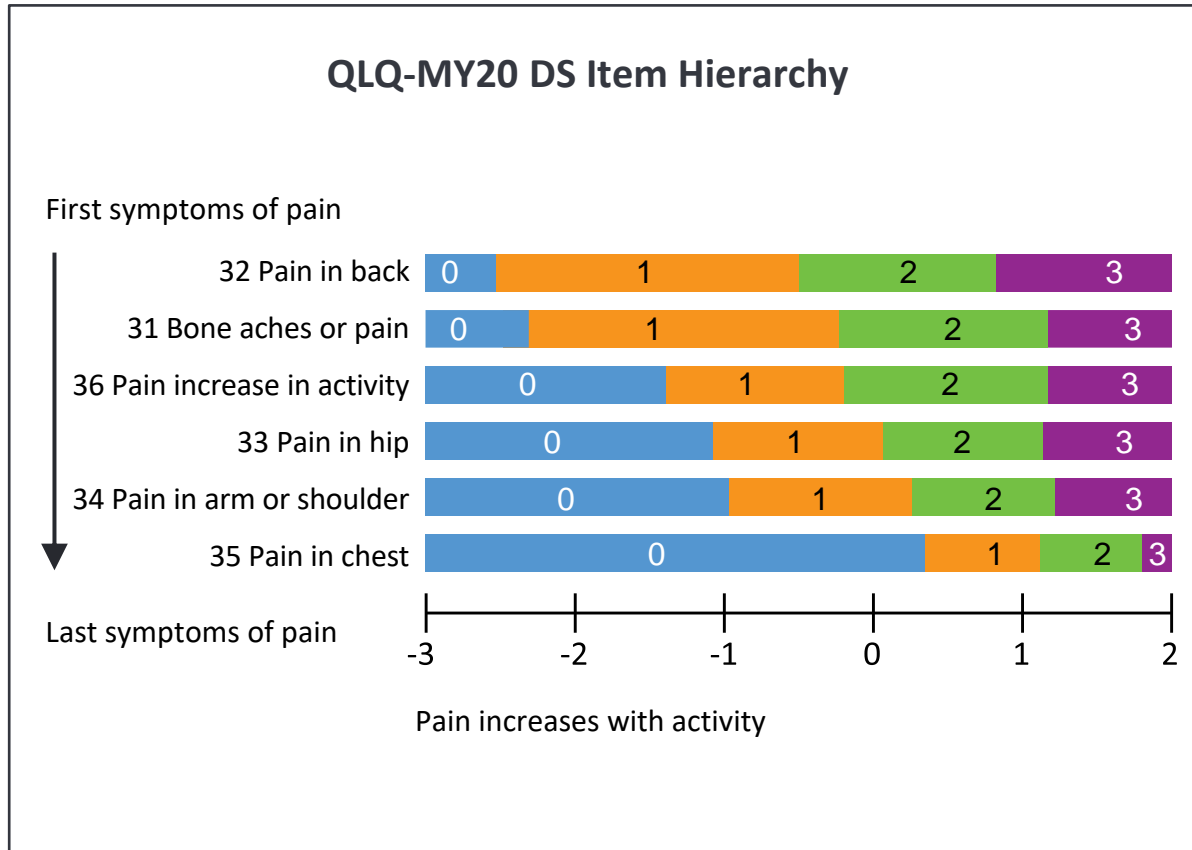
<sup>a</sup>Schedule of assessment of EORTC QLQ-C30 and EORTC QLQ-MY20 is different across trials. Key timepoints common to all trials included in this study were screening, baseline, and Cycle 4. <sup>b</sup>Calculated in the pooled analysis set.

Note: Absolute value of effect-size between 0.2 and 0.5 are marked in bold indicating “improving” or “worsening” scores. QLQ-C30, Quality of Life Questionnaire – Core 30 items; QLQ-MY20, Quality of Life Questionnaire Myeloma 20-item Module.

# RMT Results

RMT analysis identified a meaningful hierarchy in the QLQ-C30 physical functioning, pain and fatigue, and the QLQ-MY20 disease symptom items

For key scales except QLQ-MY20 SE, items composing a given scale defined a wide continuum of the measured concept with imperfect coverage, including gaps, floor and ceiling effects



QLQ-MY20 disease symptom items defined a meaningful continuum of MM-related pain manifestations but lack coverage for milder pain

<sup>a</sup>Grouping set to interval length of 0.25 making 32 groups.

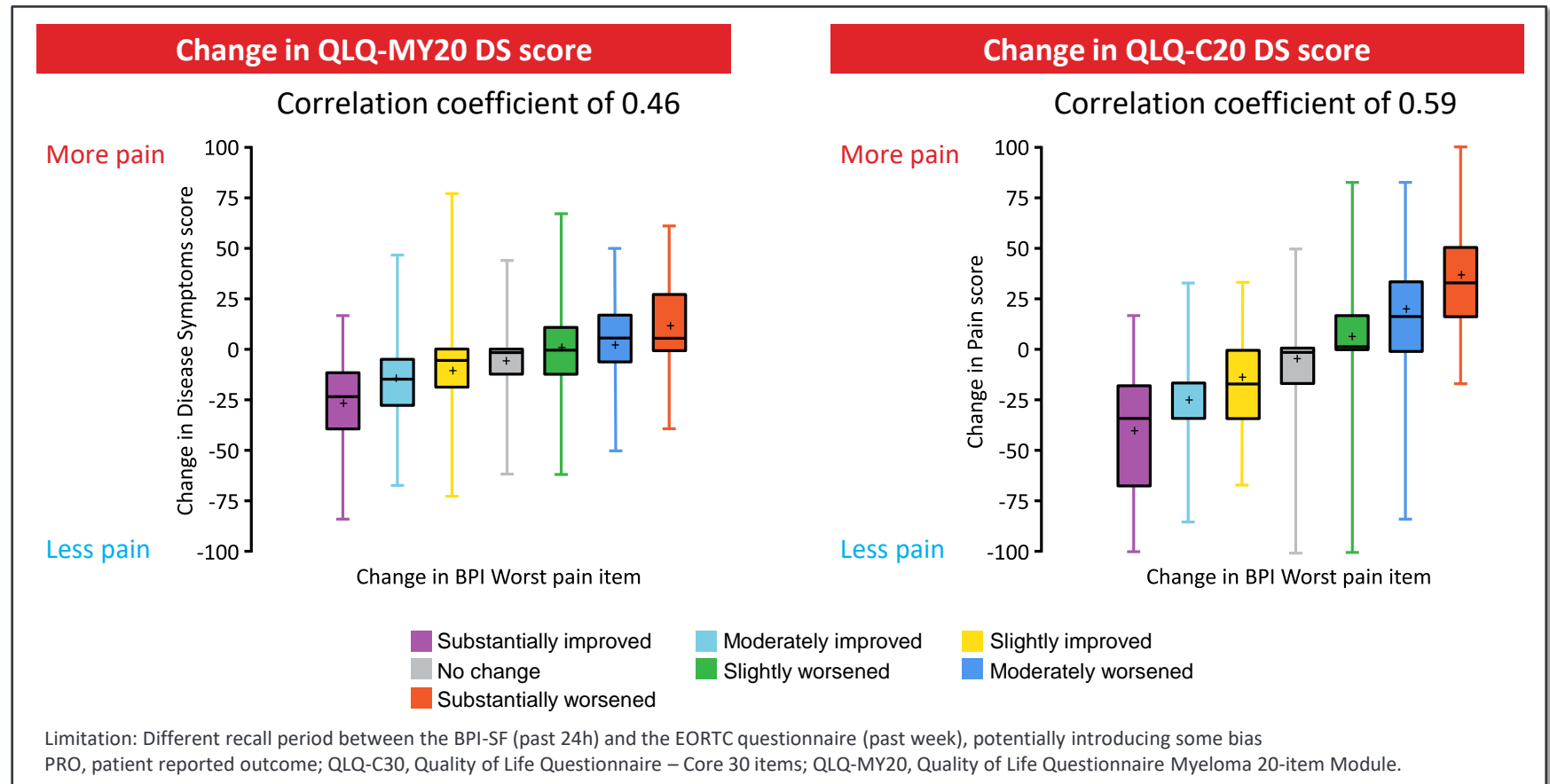
DS, disease symptoms; EORTC, European Organisation for Research and Treatment of Cancer; MM, multiple myeloma; QLQ-C30, Quality of Life Questionnaire – Core 30 items; QLQ-MY20, Quality of Life Questionnaire Myeloma 20-item Module; RMT, Rasch measurement theory.

# Supportive Analysis for the Interpretation of PRO Scores

- Supportive analysis to explore clinically meaningful within-person change (MWPC) estimates for improvement and worsening of key QLQ-C30 and QLQ-MY20 scores
- The BPI-SF worst pain item has a strong enough association with the QLQ-MY20 DS and QLQ-C30 PA score to be a good anchor: Adequate discrimination between groups defined by the change in BPI-SF worst pain item from baseline to cycle 4

## Supportive analysis

- Anchor-based methods
- Empirical cumulative function and probability density function
- Distribution-based methods
- Triangulation



**TOURMALINE-MM trials were not designed for MWPC exploration purposes, and no optimal anchor was available, therefore estimates should be considered with caution**

# Results: Exploration of MWPC for the QLQ-MY20 Disease Score

Description of change in disease symptom score across change in BPI-SF worst pain item categorization from baseline to cycle 4

	Change in BPI-SF Worst Pain Item at Cycle 4						
	Improvement			No Change	Worsening		
Variable	Category 5 or More N=117	Category 3 or 4 N=178	Category 1 or 2 N=254	N=316	Category 1 or 2 N=197	Category 3 or 4 N=73	Category 5 or More N=35
	Change in QLQ-MY20 disease symptoms score						
<b>n (missing)</b>	114 (3)	174 (4)	248 (6)	307 (9)	184 (13)	71 (2)	34 (1)
<b>Mean (SD)</b>	-25.75 (17.73)	-14.46 (17.31)	-10.08 (17.10)	-5.22 (12.75)	0.82 (19.53)	2.90 (19.25)	12.09 (20.81)
<b>Median</b>	-22.22	<b>-14.44</b>	<b>-5.56</b>	<b>0.00</b>	0.00	5.56	5.56
<b>Q1, Q3</b>	-38.89, -11.11	-27.78, <b>-5.56</b>	-18.33, <b>0.00</b>	<b>-11.11</b> , 0.00	-11.11, 11.11	-5.56, 16.67	0.00, 27.78
<b>Min, max</b>	-83.33, 16.67	-66.67, 46.67	-72.22, 77.78	-61.11, 44.44	-61.11, 66.67	-50.00, 50.00	-38.89, 61.11

## Improvement:

- Only 25% of patients with no change in the anchor had a decrease in score of -11.11 or more in QLQ-MY20 disease symptoms score
- 75% of patients with a category 1 or 2 improvement in the anchor had a decrease in their QLQ-MY20 disease symptoms score, 50% of -5.56 or more, and 25% of -18.33 or more
- 75% of patients with a category 3 or 4 improvement in the anchor had a decrease in their QLQ-MY20 disease symptoms score of -5.56 or more, and 50% of -14.44 or more

## Worsening:

- Only 25% of patients with no change in the anchor had an increase in QLQ-MY20 disease symptoms score
- 50% of patients with category 1 or 2 worsening in the anchor had an increase in QLQ-MY20 disease symptoms score, 25% of 11.11 or more
- 50% of patients with category 3 or 4 worsening in the anchor had an increase in QLQ-MY20 DS score of 5.56 or more, 25% of 16.67 or more

<sup>a</sup>Analysis conducted in the BPI population. Note: Useful values used to determine MWPC estimates have been highlighted in bold BPI-SF, Brief Pain Inventory - Short Form; DS, disease symptoms; EORTC, European Organisation for Research and Treatment of Cancer; MWPC, meaningful within-patient change; QLQ-MY20, Quality of Life Questionnaire Myeloma 20-item Module; SD, standard deviation.

# Results: Triangulation Results from MWPC Analysis

Suggested values for MWPC threshold for the QLQ-C30 physical functioning, role functioning, fatigue and pain scores, and QLQ-MY20 disease symptom score

Score	Improvement			Worsening		
	Reference Value	Minimum Value	Maximum Value	Reference Value	Minimum Value	Maximum Value
QLQ-C30 physical functioning	6.67	NE	13.33	NE	NE	NE
QLQ-C30 role functioning	NE	NE	NE	NE	NE	NE
QLQ-C30 fatigue	22.22	11.11	33.33	11.11	NE	22.22
QLQ-C30 pain	16.67	16.67	33.33	-16.67	NE	NE
QLQ-MY20 disease symptoms	-11.11	NE	-16.67	5.56	NE	11.11



Results should be interpreted with caution as the available anchor variables were not optimal

NE indicate that the improvement or worsening based on anchor variables (e.g., no change vs. 1-category change) was not clearly different; therefore, no value of MWPC was established. MWPC, meaningful within-patient change; QLQ-C30, Quality of Life Questionnaire – Core 30 items; NE, not estimated QLQ-MY20, Quality of Life Questionnaire Myeloma 20-item Module.

# Conclusions

- Based on the CTT framework, the EORTC-QLQ-C30 and EORTC-QLQ-MY20 scores showed adequate measurement properties in recent NDMM and/or RRMM clinical trials
- RMT analyses uncovered gaps in the coverage of the measured concepts that may limit the ability of these scales to detect subtle changes when used in clinical trials, especially among MM patients with mild severity of symptoms (e.g., pain) which impacts on quality of life
- MWPC estimates for the QLQ-MY20 DS score were -11.11 points (range: -5.56 to -16.67) for improvement and +5.56 (range: 5.56 to 11.11) for deterioration