

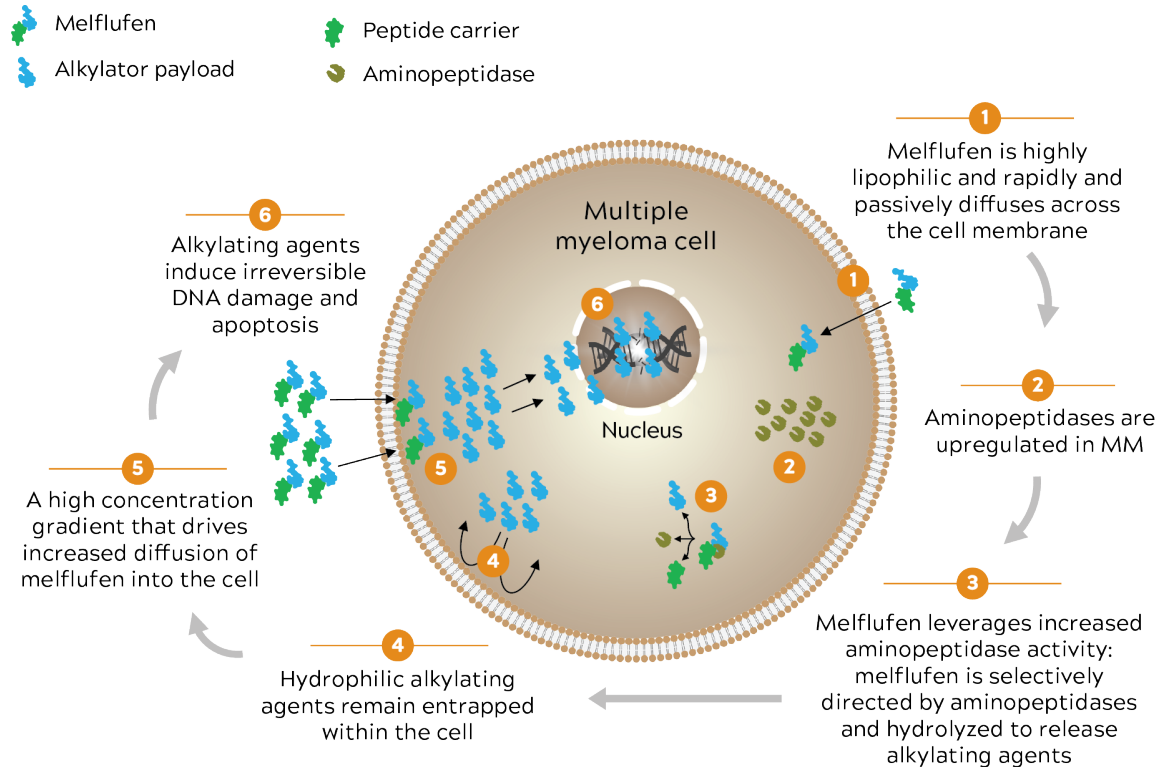
HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma – Health-Related Quality of Life (HRQoL) Analysis

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HRQoL With Melflufen in RRMM

Melphalan flufenamide (melflufen) is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**¹⁻⁵



In the pivotal, phase 2, HORIZON study, **melflufen plus dexamethasone showed clinically meaningful efficacy and a manageable safety profile** in patients with heavily pretreated and poor-risk RRMM.⁶

Patients with late-stage RRMM, often older and having comorbidities, require efficacious and tolerable therapies to maintain HRQoL⁷; a previous baseline HRQoL analysis concluded that the HORIZON population is representative of RRMM populations, with a poor overall HRQoL relative to other populations with advanced cancers.⁸

Objective: To evaluate HRQoL in patients with RRMM throughout treatment with melflufen plus dexamethasone in the HORIZON study.

HRQoL, health-related quality of life; RRMM, relapsed/refractory multiple myeloma.

1. Chauhan D, et al. *Clin Cancer Res*. 2013;19(11):3019-31. 2. Ray A, et al. *Br J Haematol*. 2016;174(3):397-409. 3. Wickström M, et al. *Oncotarget*. 2017;8(39):66641-55. 4. Wickström M, et al. *Invest New Drugs*. 2008;26(3):195-204. 5. Strese S, et al. *Biochem Pharmacol*. 2013;86(7):888-95. 6. Richardson et al. EHA 2020. Poster EP945. 7. Richardson P, et al. *Blood*. 2019;134[suppl1]:3487. 8. Richardson et al. ASH 2019. Poster #3487.

Study Design

- Eligible patients received melflufen 40 mg on day 1 of each 28-day cycle plus dexamethasone 40 mg/week^a until disease progression or unacceptable toxicity and must have had BL (predose C1) and at least 1 post-baseline HRQoL assessment
- HRQoL was added as a secondary endpoint as an amendment to the HORIZON protocol, which allowed collection of data from a subset of pts using the EORTC QLQ-C30 V.3 and the EQ-5D-3L questionnaires

HRQoL Assessments/Questionnaires

- EORTC QLC-C30 evaluates functional domains and symptoms on a scale from 0-100 (higher functional scores = better function; higher symptom scores = more symptomatology/problems)
- The EQ-5D index is evaluated on a scale from 0 (death) to 1 (perfect health) and the EQ-5D VAS is evaluated on a scale from 0 (death) to 100 (perfect health)
- Questionnaires were administered at BL (predose C1) and before dosing at intervals throughout the study (C2, C4, C6)

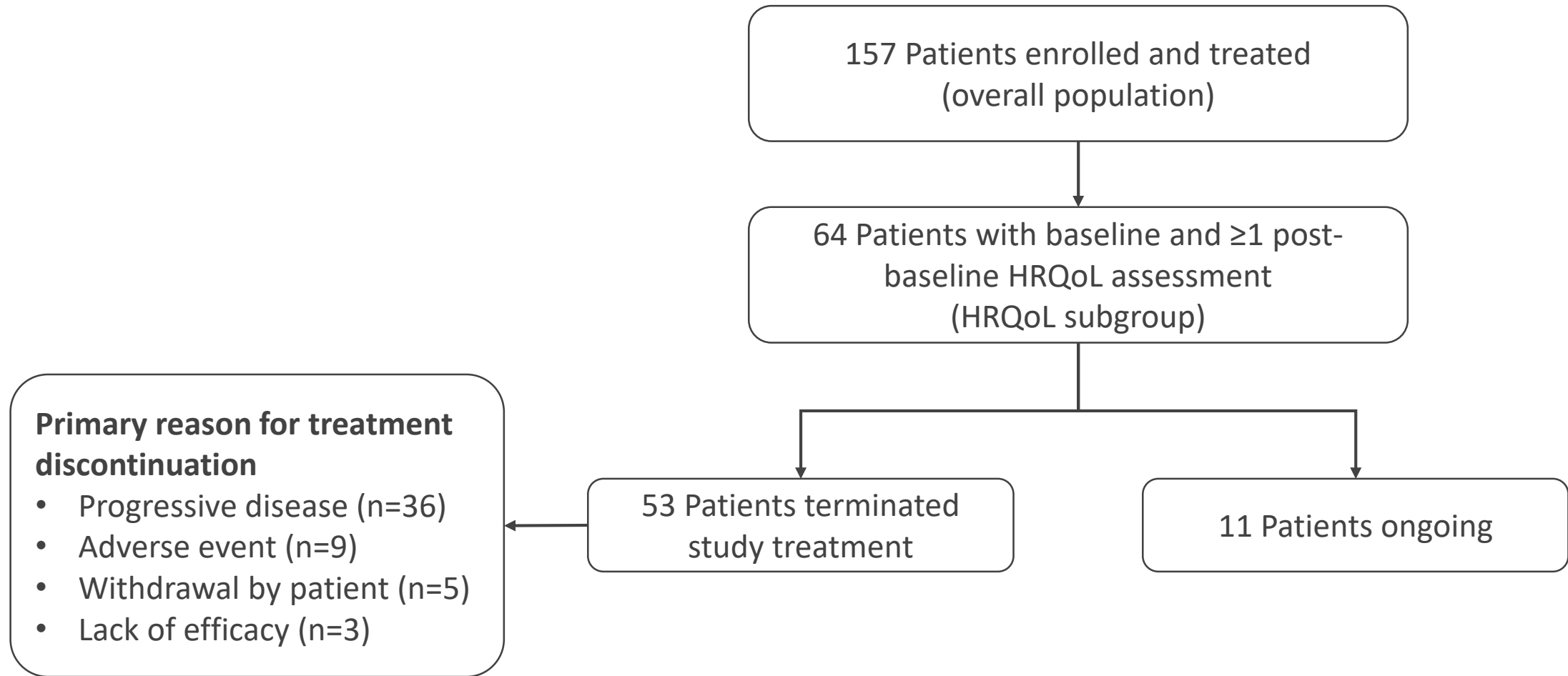
HRQoL Analysis

- Data cutoff date: 25 August 2020
- Most relevant EORTC QLQ-C30 domain scores (global health status, emotional functioning, and physical functioning) and symptom scores (fatigue and pain) and EQ-5D VAS and health utility index scores are presented
- Mean scores over time per cycle up to C6^b and number of patients with improvements within each cycle were analyzed for the overall population and for subgroups of interest (triple-class–refractory^c and extramedullary disease). A within-patient change of 5 points was considered clinically relevant¹

^aPatients aged ≥75 years received dexamethasone 20 mg. ^bDue to small sample size, analyses beyond cycle 6 were not included. ^cPatients refractory to or intolerant of ≥1 immunomodulatory agent, ≥1 proteasome inhibitor, and ≥1 anti-CD38 monoclonal antibody.

BL, baseline; C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 V.3; EQ-5D-3L, EuroQOL 5 Dimension-3 Level; HRQoL, health-related quality of life; VAS, visual analog scale.

1. Osoba D, et al. *J Clin Oncol*. 1998;16:139-44.



Characteristics	HRQoL Subgroup (n=64) ^a	Overall (N=157)
Age, median (range), years	67 (46-84)	65 (35-86)
Male sex, n (%)	33 (52)	89 (57)
Time since diagnosis at study entry, median (range), years ^b	7.0 (0.7-17.1)	6.5 (0.7-24.6)
ISS stage I / II / III, % ^c	48 / 32 / 19	40 / 31 / 25
ECOG PS 0 / 1 / 2, %	27 / 63 / 11	25 / 59 / 16
Baseline albumin, median (range), g/L ^d	39 (19-47)	38 (19-52)
<35 g/L, n (%)	11 (17)	47 (30)
≥35 g/L, n (%)	53 (83)	110 (70)
High LDH (≥1.5 × ULN) at study entry, n (%)	6 (10)	24 (15)
High-risk cytogenetics at study entry, n (%)	23 (36)	59 (38)
EMD at study entry, n (%)	19 (30)	55 (35)
No. prior lines of therapy, median (range)	5 (2-10)	5 (2-12)
Triple-class refractory, n (%) ^e	50 (78)	119 (76)
Refractory to prior alkylators, n (%)	34 (53)	92 (59)

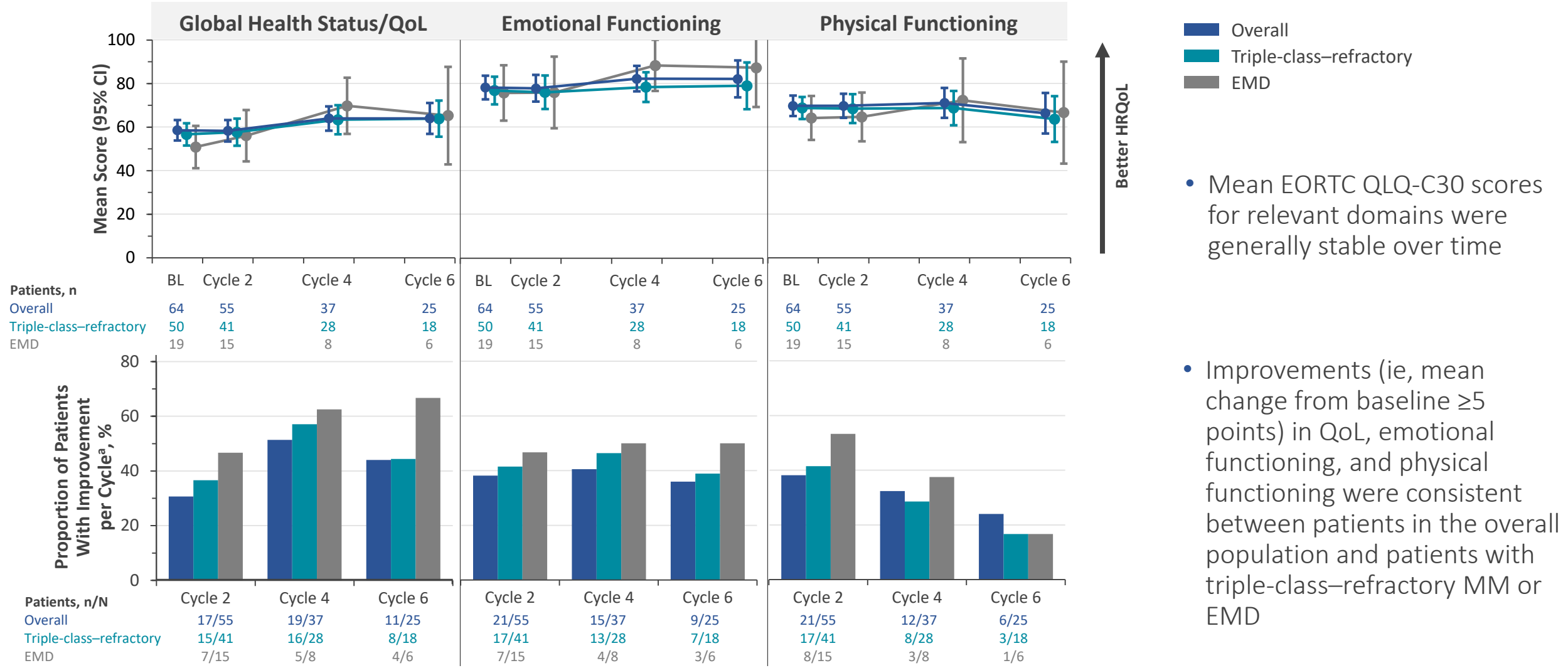
- Baseline characteristics for the HRQoL subgroup were generally consistent with the overall population and representative of a population with advanced RRMM
- Of 64 patients in the HRQoL subgroup, 19 (30%) had EMD and 50 (78%) had triple-class–refractory disease
- At Cycle 2, Cycle 4, and Cycle 6, 97.9%, 98.9%, and 99.4% of patients in the HRQoL cohort with ongoing treatment completed HRQoL assessments

Data cutoff: August 25, 2020.

^aEfficacy data were not included for this population because the data cutoff date used for the HRQoL analysis differed from that of the overall population (January 14, 2020). ^bTime since initial diagnosis is calculated relative to first dose of study drug. ^cIn the HRQoL group and the overall population, 2 patients and 6 patients had unknown/missing ISS stage, respectively. ^dBaseline labs are defined as the most recent assessment prior to administration of the first dose of study drug. ^eTriple-class refractory is defined as refractory or intolerant to ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 monoclonal antibody.

ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; LDH, lactate dehydrogenase; HR, high risk; HRQoL, health-related quality of life; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; PS, performance status; ULN, upper limit of normal.

Mean EORTC QLC-C30 Domain Scores Were Generally Stable Over Time With Melflufen Plus Dexamethasone

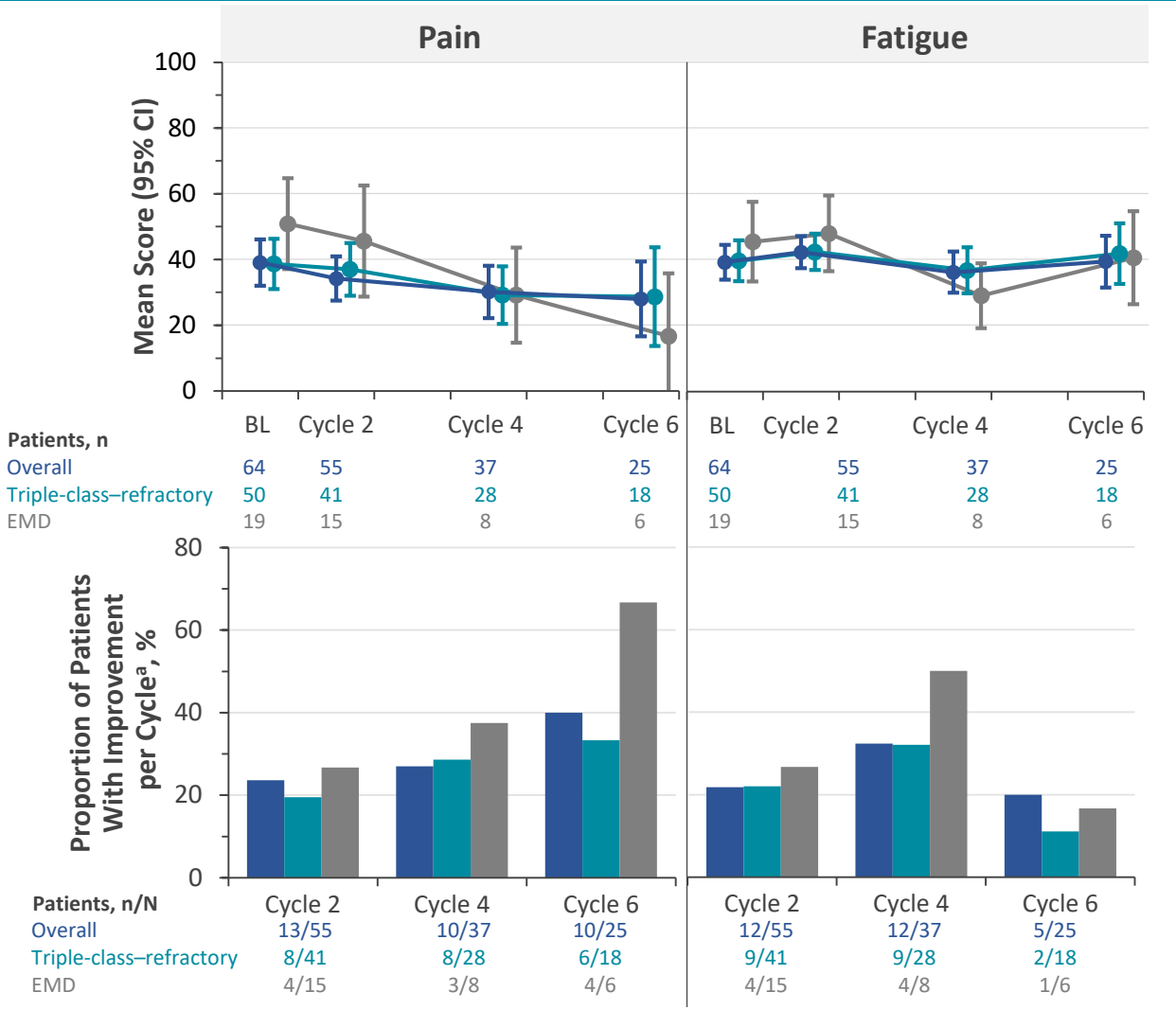


Data cutoff: August 25, 2020

^aProportion of patients with improvement (ie, within-patient change from baseline at each cycle that is ≥ 5 points) out of the total patients in each cycle.

BL, baseline; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 V.3; EQ-5D, EuroQOL 5 Dimension-3 Level; VAS, visual analog scale.

Mean EORTC QLQ-C30 Pain and Fatigue Scores Were Stable Over Time With Melflufen Plus Dexamethasone



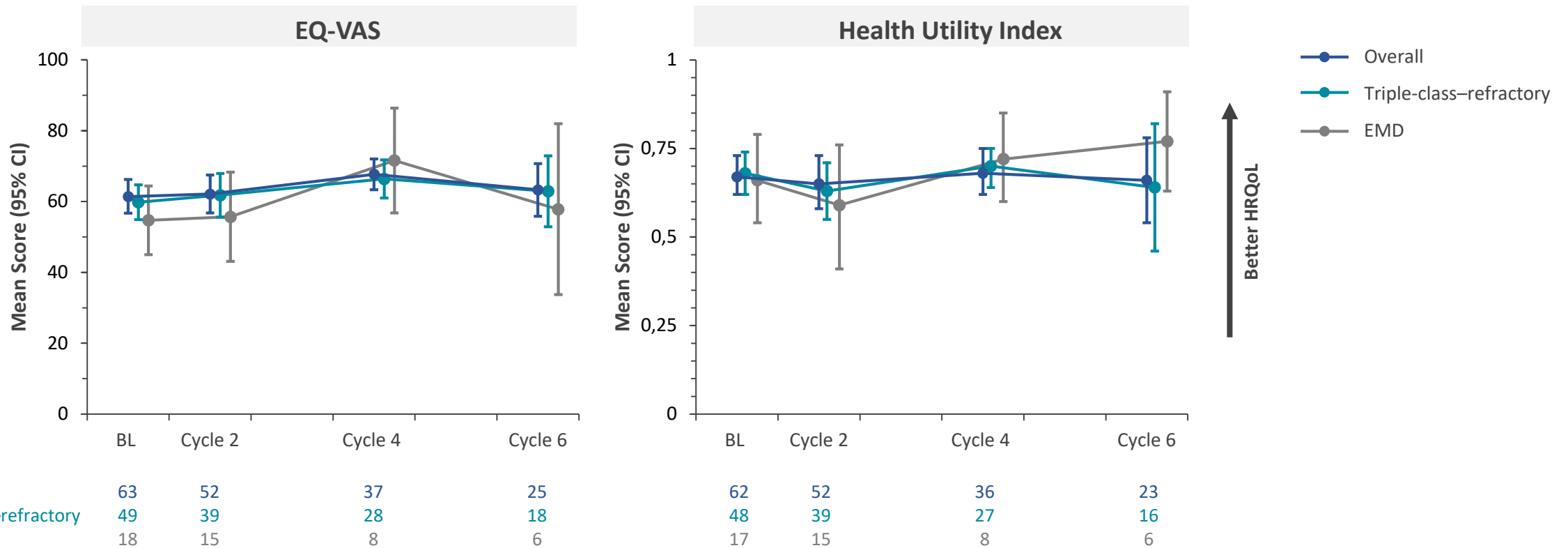
- Mean EORTC QLQ-C30 pain and fatigue symptoms scores were generally stable over time, with a slight trend in reduction in pain score
- The proportion of patients with improvements (ie, mean change from baseline ≥ 5 points) in pain and fatigue was consistent between patients in the overall population and patients with triple-class-refractory MM or EMD
- There was a trend towards an increase in the proportion of patients with improvements in pain over time

Data cutoff: August 25, 2020

^aProportion of patients with improvement (ie, within-patient change from baseline at each cycle that is ≥ 5 points) out of the total patients in each cycle.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 V.3; HRQoL, health-related quality of life; QoL, quality of life.

EQ-5D: VAS and Health Utility Index Mean Scores Over Time



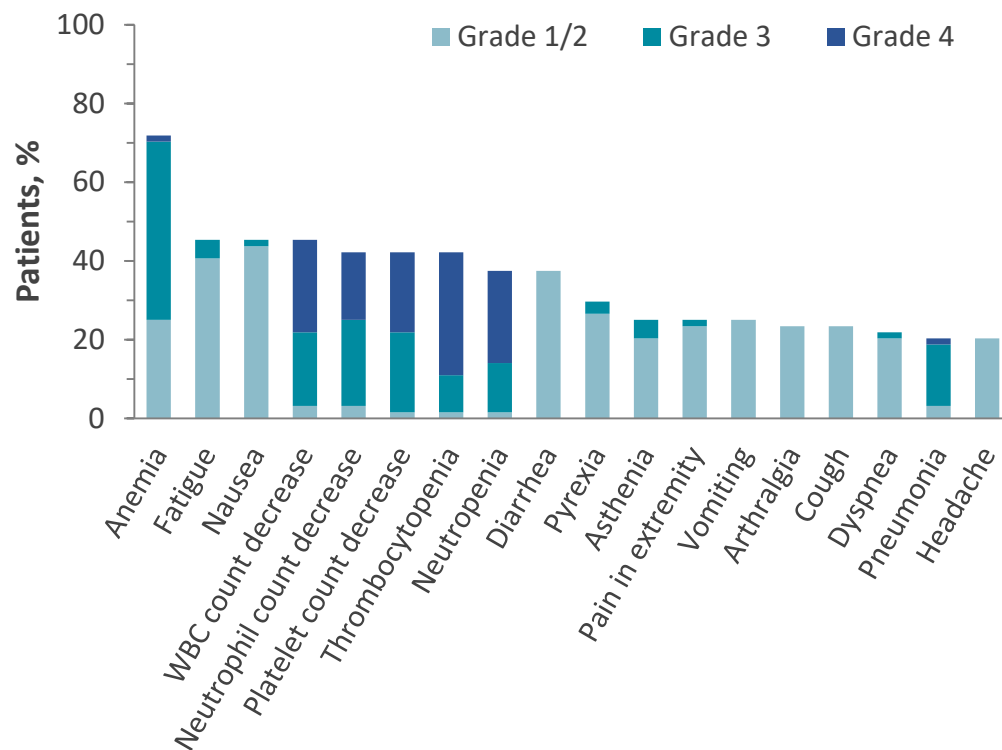
- EQ5D VAS and health utility index mean scores were generally stable over time in the overall population and in patients with triple-class-refractory MM or EMD

Data cutoff: August 25, 2020

BL, baseline; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 V.3; EQ-5D, EuroQOL 5 Dimension-3 Level; VAS, visual analog scale.

The Safety Profile of Melflufen Plus Dexamethasone In the HRQoL Subgroup Was Generally Similar to That in the Full Population

Most Common AEs (Occurring in $\geq 20\%$ of Patients) in Patients in the HRQoL Subgroup (n=64)



In the HRQoL Subgroup (n=64)

- Grade 3/4 AEs occurred in 58 patients (91%)
- SAEs occurred in 37 patients (58%)
- The most common SAEs included pneumonia (17%), acute kidney injury, Clostridium difficile infection, febrile neutropenia, general physical health deterioration, lower gastrointestinal hemorrhage, platelet count decrease, pneumonia viral, pyrexia, respiratory tract infection, thrombocytopenia, and viral URTI (3% each)
- Fatal AEs occurred in 4 patients (6%); none were considered related to melflufen

The general AE profile of the HRQoL subgroup (n=64) was similar to the full population (n=157) albeit with a somewhat higher frequency of pneumonias.

Data cutoff: August 25, 2020.

^aAEs are coded to preferred term using MedDRA, version 19.1.

AE, adverse event; HRQoL, health-related quality of life; SAE, serious adverse event; URTI, upper respiratory tract infection.

- In HORIZON, melflufen plus dexamethasone preserved HRQoL in a population with advanced RRMM, which is clinically meaningful given the poor HRQoL at baseline and that HRQoL has been shown to deteriorate in patients with more advanced disease¹
 - Clinically relevant EORTC QLQ-C30 domain scores and EQ-5D health index score and VAS were stable throughout 6 cycles of treatment with melflufen plus dexamethasone
 - Importantly, pain symptoms, which is a major contributor to impaired HRQoL at diagnosis in patients with MM,² showed a slight trend towards improvement
- The safety profile of melflufen plus dexamethasone consisted primarily of clinically manageable hematologic AEs in the overall patient population³
 - No new safety signals were observed in the HRQoL-evaluable population
- Patients in HORIZON are representative of a population with advanced RRMM with poor overall HRQoL relative to other populations with advanced cancers.⁴ Given the impact of treatment-related AEs on HRQoL, an important consideration for novel therapies is the preservation of HRQoL⁵
- These findings are encouraging as treatment-related AEs may negatively affect HRQoL in RRMM
 - Data should be interpreted with caution due to the small sample size, attrition of patients over time, and insufficient intra-patient follow up over time

AE, adverse event; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 V.3; EQ-5D, EuroQOL 5 Dimension-3 Level; HRQoL, health-related quality of life; RRMM, relapsed/refractory multiple myeloma.

1. Boland E, et al. *J Pain Symptom Manage*. 2013;46:671-680. 2. Kvam A, et al. *Health Qual Life Outcomes*. 2010;8:79. 3. Richardson PG, et al. EHA 2020. Poster EP945. 4. Richardson PG, et al. ASH 2019. Poster #3487.

5. Sonneveld P, et al. *Leukemia*. 2013;27:1959-1969.

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- **Melflufen is being discussed in other presentations at this meeting:**

- Melflufen plus dexamethasone and daratumumab or bortezomib; abstract: [417](#) (oral)
- Melflufen plus dexamethasone; abstracts: [2293](#), [2321](#), [2564](#), [3214](#), [3237](#) (posters)

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