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Outcomes in patients with triple-class–exposed relapsed/refractory multiple myeloma treated with real-life standard-of-care therapies in LocoMMotion and MoMMent final data

Katja Weisel[1], María-Victoria Mateos[2], Max Bittrich[3], Maria Esther Gonzalez Garcia[4], Valerio De Stefano[5], Britta Besemer[6], Laure Vincent[7], Suriya Kirkpatrick[8], Lionel Karlin[9], Hartmut Goldschmidt[10], Concetta Conticello[11], Wilfried Roeloffzen[12], Niels WCJ van de Donk[13], Michel Delforge[14], Eilidh Duncan[15], Silene ten Seldam[15], Margaret Doyle[16], Kathleen S Gray[17], Katharine S Gries[18], Claire Albrecht[19], Lorenzo Acciarri[20], Jozefien Buyze[21], Nicholas Francella[21], Krystof Subrt[22], Philippe Moreau[23]

[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [3]University Hospital of Würzburg, Würzburg, Bavaria, Germany; [4]University Hospital Cabueñes, Gijón, Spain; [5]Catholic University, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy; [6]University of Tübingen, Tübingen, Germany; [7]Centre Hospitalier Universitaire de Montpellier, Montpellier, France; [8]University of the West of England, Bristol, UK; [9]Centre Hospitalier Lyon Sud, Pierre-Bénite, France; [10]Internal Medicine V, GMMG-Study Group at University Clinic Heidelberg, Heidelberg, Germany; [11]Azienda Policlinico-OVE, University of Catania, Catania, Italy; [12]University Medical Center Groningen, Groningen, The Netherlands; [13]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [14]University of Leuven, Leuven, Belgium; [15]Myeloma Patients Europe, Brussels, Belgium; [16]Johnson & Johnson, Dublin, Ireland; [17]Johnson & Johnson, Bridgewater, NJ, USA; [18]Johnson & Johnson, Raritan, NJ, USA; [19]Johnson & Johnson, Issy-les-Moulineaux, France; [20]Valos, Genova, Italy; [21]Johnson & Johnson, Beerse, Belgium; [22]Johnson & Johnson, Prague, Czech Republic; [23]Hematology Clinic, University Hospital Hôtel-Dieu, Nantes, France

Key Takeaway

A significant unmet need remains for novel therapies beyond the standard classes (PIs, IMiDs, and anti-CD38 antibodies) that improve outcomes and HRQoL in patients with TCE RRMM, especially for those who are TCR

Conclusions

Poor outcomes were observed in patients with TCE RRMM treated with real-life SOC treatments from 2019 to 2024, with <15% of patients able to achieve ≥VGPR

- Response rates were even lower in patients who were TCR
- Although CAR-T cell therapies were available beginning in 2021 and bispecific antibodies in 2022, uptake of these novel agents was limited during the study period

A lower depth of response was associated with poorer outcomes, including shorter median DOR, PFS, and OS and worse HRQoL

Patients who were TCR had a lower ORR and a shorter median DOR, PFS, and OS compared with those who were not TCR

These results highlight the urgent need to integrate novel therapies in earlier LOT in patients with RRMM before they become TCR

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Poster

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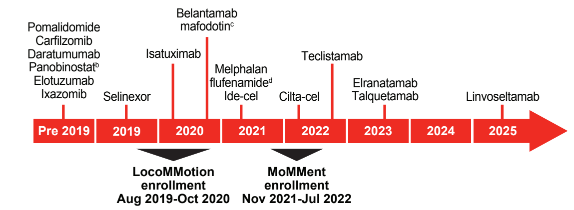
Introduction

- The therapeutic landscape for patients with relapsed/refractory multiple myeloma (RRMM) has continued to evolve in recent years with the approval of new drug classes, such as chimeric antigen receptor (CAR)–T cell therapies and bispecific antibodies (**Figure 1**)
- Continuous assessment of real-world standard-of-care (SOC) treatments in RRMM is needed to further guide clinical development
- LocoMMotion (ClinicalTrials.gov Identifier: NCT04035226)[1] and MoMMent (ClinicalTrials.gov Identifier: NCT05160584) were prospective, noninterventional, multinational studies that evaluated the effectiveness of real-world SOC in patients with triple-class–exposed (TCE) RRMM; MoMMent enrolled patients at a later time period than LocoMMotion and was designed to allow pooling of data between the 2 studies
- The first pooled analysis of LocoMMotion (end of study: October 27, 2022) and MoMMent (data cut-off: March 13, 2023) reported an overall response rate (ORR) of 31.8% and a median progression-free survival (PFS) and overall survival (OS) of 4.6 and 14.5 months, respectively,[2] demonstrating poor treatment outcomes and a high unmet need for novel effective therapies in TCE RRMM
  - The initial pooled results have been used to inform indirect treatment comparisons of recently approved agents and real-world SOC[3,4]
- We report effectiveness and patient-reported outcomes (PROs) in patients with TCE RRMM treated with SOC in a final pooled analysis of the LocoMMotion and MoMMent studies

Figure 1: Evolving treatment landscape in RRMM[a]



[a]Representative of initial regulatory approval across the United States and the European Union. These represent the available approved treatments but are not necessarily reflective of the treatments observed in this study.
[b]Panobinostat was withdrawn from the United States in 2022.
[c]Belantamab mafodotin was withdrawn from the United States in 2023 and the European Union in 2024. In 2025, belantamab mafodotin was approved in combination with bortezomib plus dexamethasone in the United Kingdom.
[d]Melphalan flufenamide was withdrawn from the United States in 2024.
Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; RRMM, relapsed/refractory multiple myeloma.

Methods

Study design and patients

- The LocoMMotion and MoMMent study designs have been previously reported[1,2]
- Patients were enrolled from Belgium, France, Germany, Italy, The Netherlands, Poland, Russia, Spain, the United Kingdom, and the United States
- Key eligibility criteria included the following:
  - ≥3 prior lines of therapy (LOT), including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody; LocoMMotion allowed <3 prior LOT if patients were double refractory to a PI and an IMiD
    - Prior exposure to B-cell maturation antigen (BCMA)–targeted therapy was permitted but not required for this analysis
  - Measurable disease
  - Disease progression since last LOT
  - Eastern Cooperative Oncology Group performance status of 0 or 1

Endpoints and assessments

- The primary outcome was ORR per International Myeloma Working Group (IMWG) criteria assessed by an independent response review committee (RRC)
- Secondary endpoints included very good partial response or better (≥VGPR) rate, complete response or better rate, duration of response (DOR), time to response, PFS, time to next treatment, OS, and PROs
- PROs were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-Item (EORTC QLQ-C30) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire to measure key health-related quality of life (HRQoL) domains
  - EORTC QLQ-C30 assessments included pain, fatigue, global health status (GHS), and physical functioning
  - The EQ-5D-5L was used to generate visual analog scale (VAS) scores
  - PROs were measured using a 0 to 100 scale; higher scores indicated worse symptoms (pain and fatigue) and better GHS, physical functioning, and VAS score

Statistical analyses

- Outcomes were reported for the response-evaluable analysis set (ie, all treated patients with ≥1 response evaluation by the RRC), except for OS and PROs, which were analyzed based on the all-treated analysis set
- Outcomes were stratified by responder status and triple-class–refractory (TCR) status
- ORR was reported with corresponding 95% Clopper-Pearson exact confidence intervals (CIs)
- Time-to-event data for the effectiveness outcomes were summarized by Kaplan-Meier methods
- Responder status was defined during the postbaseline period and not at baseline, meaning that best response was achieved during the conduct of the study and not at baseline, resulting in immortal time bias. Therefore, sensitivity analyses were performed for PFS and OS using a Cox proportional hazards model fitted with responder status as a time-varying covariate to estimate hazard ratios (HRs) and 95% CIs
- Within-group change in PRO endpoints was assessed by change from baseline using mixed models for repeated measures
  - Sensitivity analyses with responder status as a time-varying variable were also performed for PRO endpoints
- Meaningful improvement (decrease from baseline of ≥10 points for symptom scales, increase of ≥10 points for physical functioning and GHS, and increase of ≥7 points for VAS score) in PRO scores compared with baseline health status was evaluated using established meaningful change thresholds
- Data were analyzed as observed, and missing data were not imputed

Results

Patients and SOC treatments

- Data were pooled from LocoMMotion (end of study: October 27, 2022; median follow-up: 26.4 months [range: 0.1, 35.0]; N=248) and MoMMent (end of study Cohort 1: August 26, 2024; median follow-up: 27.1 months [range: 0.4, 32.7]; N=54)
- The pooled analysis included 302 patients with a median follow-up of 26.7 months (range: 0.1, 35.0)
- Patients received a median of 4 prior LOT (range: 2, 13); 222 (73.5%) were TCR and 54 (17.9%) were penta-drug refractory (**Table 1**)

Table 1: Baseline demographic and disease characteristics

Characteristic	Pooled (N=302)
Median age, years (range)	69.0 (41, 89)
Sex, male, n (%)	163 (54.0)
Race, n (%)	
White	229 (75.8)
Black/African American	6 (2.0)
Other	1 (0.3)
Not reported	63 (20.9)
Unknown	3 (1.0)
ECOG PS, n (%)[a]	
0	69 (22.9)
1	228 (75.7)
2	3 (1.0)
3	1 (0.3)
Median time since MM diagnosis, years (range)	6.3 (0.3, 22.8)
Median number of prior LOT (range)	4 (2, 13)
Number of prior LOT, n (%)	
2	17 (5.6)
3	69 (22.8)
4	81 (26.8)
≥5	135 (44.7)
Prior therapy exposure, n (%)	
Triple-class[b]	302 (100)
Penta-drug[c]	140 (46.4)
BCMA-targeted therapy	19 (6.3)
Refractory status, n (%)	
Triple-class[b]	222 (73.5)
Penta-drug[c]	54 (17.9)

[a]n=301.
[b]≥1 each of PI + IMiD + anti-CD38 antibody.
[c]≥2 PIs + ≥2 IMiDs + ≥1 anti-CD38 antibody.
BCMA, B-cell maturation antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; LOT, lines of therapy; MM, multiple myeloma; PI, proteasome inhibitor.

- Overall, patients were treated with 101 unique antimyeloma treatment regimens, reflecting SOC heterogeneity
  - The most frequently reported regimens (≥10% of patients) were pomalidomide-cyclophosphamide-dexamethasone (14.6%), carfilzomib-dexamethasone (13.2%), and pomalidomide-dexamethasone (10.9%; **Table 2**)
  - Four patients in MoMMent received CAR-T cell therapy (idecabtagene vicleucel), and no patients received bispecific antibodies as they were not approved at the time of enrollment for LocoMMotion or MoMMent

Table 2: SOC treatment regimens[a]

Regimens reported in ≥3% of patients, n (%)	Pooled (N=302)
Pomalidomide-cyclophosphamide-dexamethasone	44 (14.6)
Carfilzomib-dexamethasone	40 (13.2)
Pomalidomide-dexamethasone	33 (10.9)
Belantamab mafodotin	15 (5.0)
Ixazomib-lenalidomide-dexamethasone	14 (4.6)
Bortezomib-panobinostat-dexamethasone	13 (4.3)
Carfilzomib-cyclophosphamide-dexamethasone	9 (3.0)
Elotuzumab-pomalidomide-dexamethasone	9 (3.0)

[a]Excluding subsequent therapy.
SOC, standard-of-care.

Effectiveness outcomes

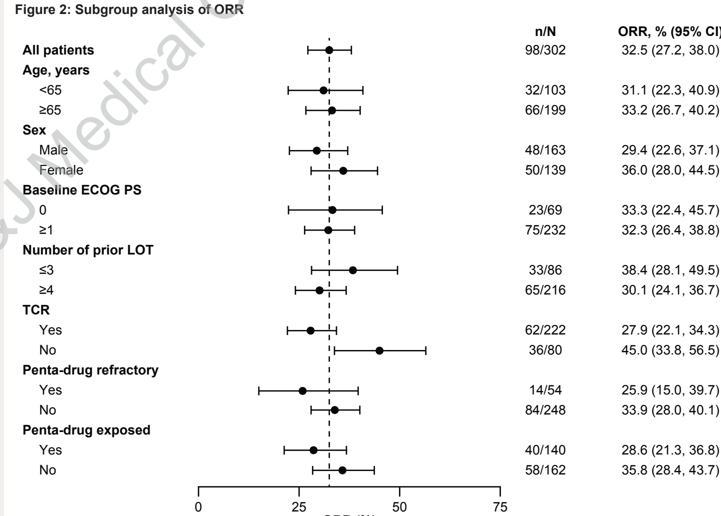
- The ORR by RRC for the overall pooled analysis was 32.5% (95% CI: 27.2, 38.0; **Table 3**)
  - ORRs were consistent across patient subgroups, except for a lower ORR in patients who were TCR compared with those who were not TCR (27.9% [95% CI: 22.1, 34.3] vs 45.0% [95% CI: 33.8, 56.5], respectively; **Figure 2**)
- The median time to response in all 302 patients was 5.7 months (95% CI: 4.4, 8.1)
- The median DOR, PFS, and OS was 8.3 months (95% CI: 5.8, 11.1), 4.6 months (95% CI: 4.1, 5.7), and 14.8 months (95% CI: 11.8, 18.1), respectively (**Table 3**)
- Patients with VGPR had better outcomes compared with patients with <VGPR (**Table 3**, **Figure 3**)
- Patients who were TCR had poorer outcomes compared with patients who were not TCR (**Table 3**)
- Results were consistent in sensitivity analyses based on responder status (≥VGPR vs <VGPR) over time for PFS (HR: 0.473 [95% CI: 0.292, 0.766]) and OS (HR: 0.254 [95% CI: 0.129, 0.499])

Table 3: Summary of effectiveness outcomes in the overall pooled population and stratified by responder and TCR status

		Responder status		TCR status	
Outcome	**Pooled (N=302)**	**≥VGPR (n=40)**	**<VGPR (n=262)**	**TCR (n=222)**	**Not TCR (n=80)**
ORR, % (95% CI)	32.5 (27.2, 38.0)	–	–	27.9 (22.1, 34.3)	45.0 (33.8, 56.5)
≥VGPR	13.2 (9.6, 17.6)	–	–	11.7 (7.8, 16.7)	17.5 (9.9, 27.6)
≥CR[a]	0.7 (0.1, 2.4)	–	–	0.9 (0.1, 3.2)	0 (NE, NE)
Median DOR, months (95% CI)	8.3 (5.8, 11.1)[b]	14.4 (9.5, 26.3)	5.1 (4.5, 8.3)[c]	7.2 (4.5, 9.5)[d]	11.1 (7.7, 18.6)[e]
Median PFS, months (95% CI)	4.6 (4.1, 5.7)	15.3 (12.0, NE)	4.0 (3.4, 4.6)	4.1 (3.5, 4.6)	8.5 (6.0, 12.0)
Median TTNT, months (95% CI)	5.3 (4.6, 6.0)	17.9 (12.3, 26.4)	4.5 (4.1, 5.3)	–	–
Median OS, months (95% CI)	14.8 (11.8, 18.1)	NE (NE, NE)	11.6 (9.3, 14.8)	12.4 (9.7, 15.3)	24.6 (17.0, NE)

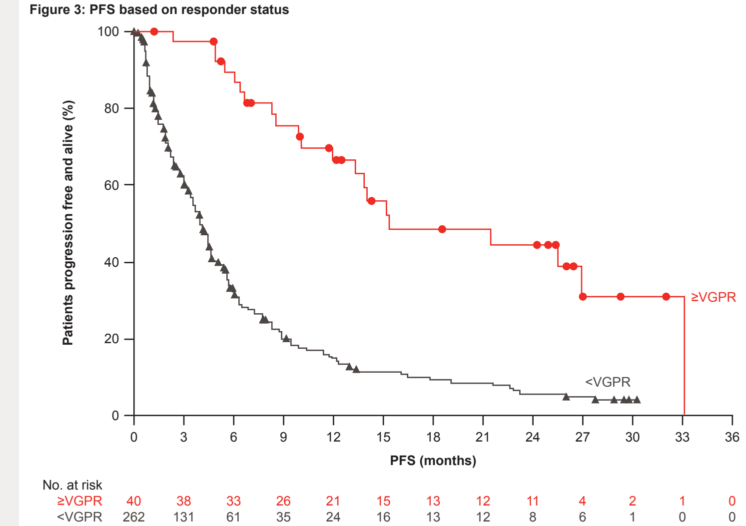
[a]Bone marrow and immunofixation data were collected where available, but these are not part of SOC evaluation; therefore, CR could not be confirmed in all patients. [b]n=98. [c]n=58. [d]n=62. [e]n=36.
CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard-of-care; TCR, triple-class refractory; TTNT, time to next treatment; VGPR, very good partial response.

Figure 2: Subgroup analysis of ORR



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LOT, lines of therapy; ORR, overall response rate; TCR, triple-class refractory.

Figure 3: PFS based on responder status



PFS, progression-free survival; VGPR, very good partial response.

PROs

- Meaningful improvement in EORTC QLQ-C30 and EQ-5D-5L scales at ≥1 time point during SOC treatment was observed in 120/251 (47.8%) patients for pain, 149/251 (59.4%) for fatigue, 121/248 (48.8%) for GHS, 107/251 (42.6%) for physical functioning, and 131/249 (52.6%) for VAS score
- Least squares mean changes from baseline in EORTC QLQ-C30 and EQ-5D-5L VAS scores generally indicated no meaningful improvements in PROs during the overall SOC treatment period (**Table 4**)
- Patients who achieved ≥VGPR showed greater improvement from baseline across scales compared with those with a partial response or no response (with and without disease progression; **Table 4**)
- Sensitivity analyses were consistent with the observed results when comparing responders (≥VGPR) and non-responders

Table 4: Change from baseline in PROs during SOC treatment in the overall pooled population and stratified by response and TCR status

LS mean change from baseline (95% CI)	Pooled (n=226)	≥VGPR (n=33)	PR (n=54)	NR, excluding PD (n=105)	PD (n=34)	TCR (n=163)	Not TCR (n=63)
EORTC QLQ-C30							
Pain[a]	−1.0 (−4.5, 2.5)	−8.8 (−15.0, −2.7)	−2.9 (−8.7, 2.8)	−1.4 (−7.7, 4.9)	9.2 (−1.6, 20.0)	−2.1 (−6.4, 2.3)	−3.5 (−8.7, 1.6)
Fatigue[a]	−1.1 (−4.0, 1.9)	−6.8 (−11.8, −1.9)	0.1 (−5.0, 5.2)	3.4 (−2.2, 9.0)	0.3 (−7.2, 7.8)	−2.4 (−6.2, 1.4)	0.7 (−3.6, 4.9)
GHS[b]	2.7 (−0.1, 5.4)[c]	8.5 (3.9, 13.2)	4.3 (−0.2, 8.8)[d]	−6.3 (−11.8, −0.8)[e]	−5.7 (−12.4, 1.1)	6.8 (3.4, 10.2)[f]	−1.1 (−5.1, 2.9)[g]
Physical functioning[b]	−1.0 (−3.5, 1.6)	2.4 (−2.6, 7.5)	1.4 (−2.9, 5.7)	−3.7 (−8.3, 0.9)	−12.1 (−20.0, −4.2)	−1.8 (−5.1, 1.4)	0.3 (−3.3, 3.9)
EQ-5D-5L							
VAS score[b]	3.0 (0.8, 5.2)[h]	7.0 (1.7, 12.3)[i]	3.0 (−0.6, 6.5)	−2.1 (−6.1, 1.9)	−8.7 (−14.8, −2.6)[j]	4.4 (1.5, 7.3)[k]	2.5 (−0.3, 5.2)[g]

[a]Higher score indicates worse outcome. [b]Higher score indicates better outcome. [c]n=223. [d]n=53. [e]n=103. [f]n=161. [g]n=62. [h]n=224. [i]n=32. [j]n=33. [k]n=162.
CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-Item; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GHS, global health status; LS, least squares; NR, no response; PD, disease progression; PR, partial response; PRO, patient-reported outcome; SOC, standard-of-care; TCR, triple-class refractory; VAS, visual analog scale; VGPR, very good partial response.

Limitations

- LocoMMotion and MoMMent were both single-arm studies with no comparator groups
- Due to the observational nature of both studies, data for some parameters, including laboratory assessments required per IMWG criteria, were missing
- The subgroup analyses by response should be interpreted with caution as the subgroups were not randomized, some groups had a low number of patients, and there were different numbers of patients at various time points
- Responder status was also defined during the postbaseline period, causing immortal time bias since best response was achieved during the conduct of the study and not at baseline
  - However, the sensitivity analyses for PFS and OS based on responder status over time support the main results stratified by responder status

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Multiple Myeloma