Title: An International, Multi-Centre, Retrospective Study to Describe Treatment Pathways, Outcomes, And Resource Use in Patients with Multiple Myeloma
(INTEGRATE)

Approve Date: December 10, 2021

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NON-INTERVENTIONAL CLINICAL STUDY REPORT

An International, Multi-Centre, Retrospective Study to Describe Treatment Pathways, Outcomes, And Resource Use in Patients with Multiple Myeloma

(INTEGRATE)

1. TITLE PAGE

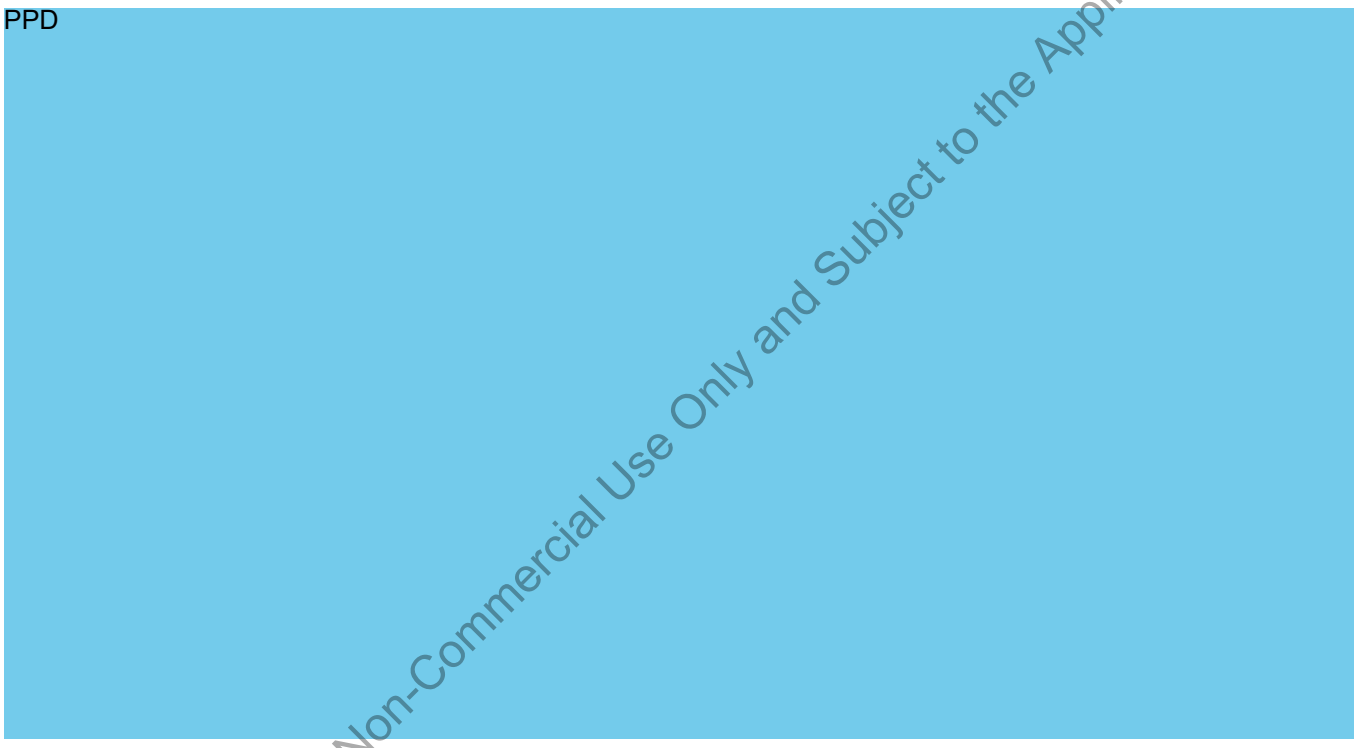
TITLE	An International, Multi-Centre, Retrospective Study to Describe Treatment Pathways, Outcomes, and Resource Use in Patients With Multiple Myeloma (INTEGRATE)
PROTOCOL/STUDY NO.	NDMM-5002
CSR VERSION	2.0 Final: 10th December 2021
SPONSOR	Takeda Pharmaceuticals International AG Thurgauerstrasse 130 8152 Glattpark-Opfikon (Zurich) Switzerland
STUDY DATES	First patient in: 21st March 2018 Last patient in: 31st December 2019
CONDUCTED BY	IQVIA Real-World Solutions 201 Broadway Cambridge, MA 02139 USA

This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), International Conference on Harmonisation E6 Good Clinical Practice (GCP): Consolidated Guideline, and the International Society of Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP).

SPONSOR SIGNATURE PAGE

Reviewed and Approved by:

PPD



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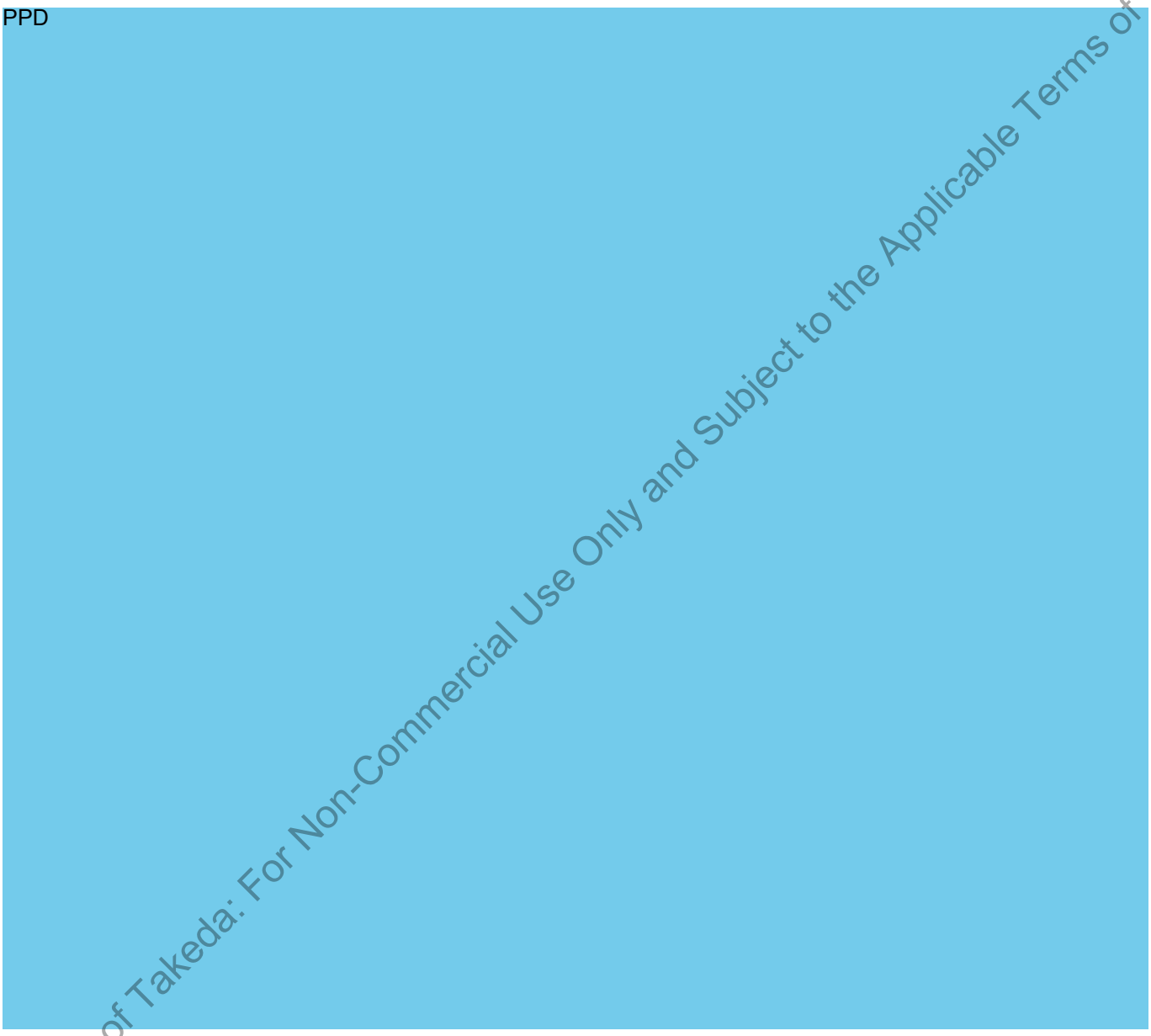

2. EXECUTIVE SUMMARY

Full Study Title: An International, Multi-Centre, Retrospective Study to Describe Treatment Pathways, Outcomes, And Resource Use in Patients with Multiple Myeloma (INTEGRATE)			
Phase:	Post-marketing/Phase IV	**Type:**	Observational
Number of Patients: 1,855 eligible		**Duration of Patient Participation**: Retrospective data collection from medical charts Eligibility period: 1st January 2010 to 31st December 2011	
Number of Study Centres: 45 Centres in 8 countries		**Milestones**: Final protocol: 27th October 2017 First patient in: 21st March 2018 Last patient in: 31st December 2019 Database lock: 29th March 2021	

Background and Rationale:

Multiple myeloma (MM) is a progressive haematological malignancy characterised by multiple bone marrow tumour foci and secretion of M-protein. According to the Global Cancer Observatory (GCO), worldwide in 2020, there were 176,404 new cases and 117,077 deaths due to MM. According to GCO 2020 data, Asia had the highest incidence of MM with 63,439 new cases recorded in year 2020. By 2040, the incidence of MM is estimated to rise by 67.5% in Asia and 96.5% in Africa. This predicted increase in incidence of MM is due to ageing populations and improvements in diagnosis.

MM is a heterogeneous disease and survival ranges from weeks to years after diagnosis. There is currently no curative treatment for MM and treatment options are dependent on patient's age and comorbidities. Patients who respond to initial treatment might maintain progression-free survival (PFS) for several years. However, inevitably, relapse will occur, and patients will

progressively become less responsive to treatment (refractory MM). Standard of care in developed countries consists of a triple drug regimen. Commonly used regimens include bortezomib, dexamethasone and a third agent (thalidomide, doxorubicin, cyclophosphamide or lenalidomide). A combination of melphalan and prednisolone, in addition to bortezomib or thalidomide may also be used. European Medicines Agency (EMA) and United States Food and Drug Administration (USFDA) have also approved key agents and regimens for newly diagnosed multiple myeloma (NDMM) and relapsed or refractory multiple myeloma (RRMM).

Emerging market (EM) countries are those developing countries, where there is rapid economic growth. There are limited real-world data from EM countries on treatment pathways, clinical outcomes, and healthcare resource use (HRU) among patients with MM, particularly those patients who relapse or are refractory to first-line therapy. Real-world evidence (RWE) on the burden of MM is needed in these countries to help make informed clinical decisions. Payers will also require local information on resource use for different treatment options to make informed decisions for their own country.

The INSIGHT-MM is a large, international, observational study of MM treatments and outcomes in 15 countries. Since the INSIGHT-MM study is still ongoing, only 2 interim analyses data have been reported. These 2 analyses from INSIGHT-MM study highlighted marked regional differences in real-world treatment patterns in NDMM/RRMM, potentially due to differences in drug availability and treatment guidelines at academic versus community centres.

Data collected in this study (INTEGRATE) will provide high quality RWE on treatment pathways, outcomes, and healthcare resource utilisation from a representative global population from EM countries to support clinical practice and payer decisions on treatment funding.

Objectives:

Primary objective

The primary objective is to describe time to next treatment (TTNT)[1] at each line of therapy[2] in patients receiving first-line treatment for NDMM (Group 1), and in patients with RRMM (Group 2).

[1] Limited retrospective availability of clinical data to measure progression-free survival (PFS).
[2] Line of therapy as determined by progression status, i.e., treatments received prior to first progression = first-line, treatments received between first and second progression = second-line, etc.

Secondary objectives

The secondary objectives are to describe the following in 2 populations of patients with MM: those receiving first-line treatment for NDMM, and those with RRMM:

1. Patient demographic and clinical characteristics.
2. Treatment patterns for MM.
3. Clinical outcomes:
   a) Relapse rate at 6, 12, 18, 24, 36, and 60 months.
   b) Overall survival (OS) rate at 6, 12, 18, 24, 36, and 60 months.
   c) Number of relapses per patient.
4. For each line of therapy[2]:
   a) Best response after start of treatment, as defined by the International Working Group Uniform Response Criteria for MM or as determined by treating physician.
   b) Time to first response.
   c) Time to best response.
   d) Duration of best response.
   e) Adverse events (AEs) experienced.
   f) MM-related HRU.
   g) MM-related healthcare costs[3].

Study Design:

INTEGRATE is an international, multi-centre, observational study involving retrospective review of the medical records of patients diagnosed with NDMM (Group 1) or patients diagnosed with RRMM (Group 2).

Forty-five sites from 8 EM countries (Argentina, Taiwan, Republic of Korea, Saudi Arabia, Republic of South Africa, Turkey, China, and Russia) were included in the study.

Study Population:

Patients who met all inclusion criteria and none of the exclusion criteria were eligible for the study.

[3] Allocation of costs (for secondary objective 4g) is optional and country dependent.

Inclusion Criteria

1. Patients with newly diagnosed symptomatic MM (for Group 1) or diagnosed with RRMM (for Group 2) between 1st January 2010 and 31st December 2011(inclusive).
2. Patients who completed at least one full line of treatment.
3. Age ≥18 years at diagnosis of MM (Group 1) or RRMM (Group 2).
4. Alive or deceased.
5. Written informed consent obtained from patients for study data collection, where necessary according to local regulations.

Exclusion criteria

1. Patients for whom the minimum study dataset (MDS)* was not available from their hospital medical records.
2. Patients who had smouldering myeloma.
3. Patients who had monoclonal gammopathy of unknown significance (MGUS).
4. Patients enrolled in a clinical trial of an investigational product during the observation period.

Patients newly diagnosed with MM between 1st January 2010 and 31st December 2011 and who were subsequently diagnosed with RRMM were included in both groups, provided that RRMM was also diagnosed between 1st January 2010 and 31st December 2011.

*MDS data were defined to ensure information on key variables were not missing from the medical records.

Data Collection and Assessments:

The data abstraction period began on 21st March 2018 with the initiation of the first site and the identification of eligible patients' medical records. It ended on 29th March 2021 at database lock. Pseudo-anonymised data were collected according to the agreed minimum dataset using a standardised web-based electronic case report form (eCRF). Key variables included those related to patient characteristics, diagnosis, treatment information, HRU, clinical outcomes, and AEs.

Statistical Methods:

For all descriptive analyses, categorical variables were summarised by the number of patients and percentages of patients in each category, with percentages calculated over the number of subjects with available (non-missing) data. Continuous variables were summarised using the

mean, standard deviation (StDev), median, first and third quartile (Q1, Q3), minimum, maximum, and the number of non-missing and missing data.

All analyses were performed separately for Group 1 and Group 2. The analyses were presented for the overall sample, at a regional level, and separately for each country studied. Some analyses were further analysed by stem cell transplantation (SCT) status.

Primary analysis

The primary effectiveness variable in this study, TTNT in patients with NDMM and RRMM, was defined as the time (in months) from the date of initiation of each line of treatment to the date of initiation of next line of treatment or death in each patient group.

TTNT duration was summarised descriptively by number of patients at risk, number of patients with the event, number of patients censored, median, Q3 and Q1 and respective 95% confidence interval (CI), using the estimates of Kaplan-Meier (KM) method. In addition, the KM curve of TTNT was presented graphically, overall and for each region and country.

Secondary analysis

Clinical outcomes for the non-SCT patients in NDMM and RRMM groups

- Number and percentage of patients by best clinical response to treatment from start of line of treatment (stringent complete response [sCR], complete remission [CR], very good partial response [VGPR], partial remission [PR], minimal response [MR], stable disease [SD], progressive disease [PD], not assessed), as determined by the International Myeloma Working Group (IMWG) Uniform Response Criteria for MM, 2010 or as determined by treating physician.
- Mean (StDev) and median (range) time to best response from first-line treatment (in months), defined as the time from initiation of frontline treatment to the first documentation of best response (sCR or CR or VGPR or PR or MR or SD).
- Median (range) duration of best response after start of frontline treatment, defined as the time from when the criteria for best response (sCR or CR or VGPR or PR or MR or SD) were met, to the first documentation of relapse or disease progression after start of frontline treatment (in months).
- Proportion of patients with documented relapse or disease progression after start of first-line treatment.
- Mean (StDev) and median (range) time to first response from start of first-line treatment (in months), defined as the time from start of first-line treatment to first documentation of response (sCR or CR or VGPR or PR or MR).

- Median OS (in months). Patients who did not die were censored on the last known date to be alive at the time of data abstraction.
- Proportion of patients alive at 6, 12, 18, 24, 36, and 60 months after start of first-line treatment, estimated from KM method.
- Relapse rate at 6, 12, 18, 24, 36, and 60 months after start of frontline treatment, using the cumulative relapse rate calculated through KM method.

OS was summarised descriptively as in the primary effectiveness analysis. The KM curves of OS and cumulative probability of relapse (1-KM estimate of survival probability) in non-stem cell transplantation (non-SCT) patients were presented graphically, overall, by region and country

Clinical outcomes for SCT patients in NDMM and RRMM groups

- Number and percentage of patients by best clinical response to treatment from start of line of treatment, at end of induction and at end of 3, 6, 12, and 18 months after SCT (sCR, CR, VGPR, PR, MR, SD, PD, not assessed), as determined by IMWG Uniform Response Criteria for MM, 2010 or as determined by treating physician.
- Mean (StDev) and median (range) time to best response from first-line treatment (in months), defined as the time from initiation of first-line treatment to the first documentation of best response (sCR or CR or VGPR or PR or MR or SD or PD or not assessed).
- Proportion of patients with documented relapse or disease progression after start of first-line treatment.
- Mean (StDev) and median (range) time to first response from start of first-line treatment (in months), defined as the time from start of first-line treatment to first documentation of response (sCR or CR or VGPR or PR or MR).
- Median (range) duration of response after start of first-line treatment, defined as the time from when the criteria for best response (sCR or CR or VGPR or PR or MR) were met, to the first documentation of relapse or disease progression after start of first-line treatment (in months).
- Number and proportion of patients with documented relapse or disease progression after first SCT.
- Number and proportion of patients in response (sCR or CR or VGPR or PR or MR) who were assessed as high risk of relapse, defined by International Staging System (ISS) stage II/III and the presence of either t(4, 14), t(14, 16) or del 17p13.
- Mean (StDev) and median (range) number of relapses per patient during the observation period (RRMM group only).
- Median OS (in months). Patients who did not die were censored on the date of last known to be alive.

- Proportion of patients alive at 6, 12, 18, 24, 36, and 60 months after start of first-line treatment, estimated from KM method.
- Relapse rate at 6, 12, 18, 24, 36, and 60 months after start of first-line treatment, using the cumulative relapse rate calculated through the KM method.
- Relapse rate at 6, 12, 18, 24, 36, and 60 months after first SCT, using the cumulative relapse rate calculated through the KM method.

OS was summarised descriptively as in the primary effectiveness analysis. The KM curves of OS and cumulative probability of relapse (1-KM estimate of relapse-free survival probability) in patients undergoing SCT were presented graphically, overall, by region and country.

Clinical outcomes in deceased patients in NDMM and RRMM groups

- Mean (StDev) and median (range) time to death from diagnosis of MM (in months).
- Mean (StDev) and median (range) time to death from completion of first-line therapy (in months).
- Mean (StDev) and median (range) time to death from first relapse (in months, RRMM group only).
- Mean (StDev) and median (range) time to death from first SCT, autologous SCT and allogeneic-SCT (allo-SCT) (in months, RRMM group only).
- Mean (StDev) and median (range) time to death from relapse after first SCT, autologous SCT and allo-SCT (in months, RRMM group only).
- Distribution of cause of death (MM-related, AE, treatment-related and other).

Adverse events

The number and percentage of patients having at least one AE was summarised overall and by System Organ Class (SOC) and Preferred Term (PT). Separate summaries were given for all AEs, treatment-related AEs (TRAEs) (associated with SCT, each treatment regimen received by non-SCT patients, and each post-SCT treatment regimen), and serious adverse events (SAEs) by AE outcome and by treatment regimen. The number of AEs, number and percentage of patients with AEs, total person-years of exposure, and incidence rate (IR) were reported.

Healthcare resource use

The following resource use data was described for NDMM and RRMM groups:

- Number and proportion of patients reporting at least one hospitalisation.
- Annualised number of hospitalisations.
- Mean (StDev) and median (range) number of hospitalisations per patient.

- For hospitalisations, mean (StDev) and median (range) length of stay (defined as the difference between discharge and admission date + 1), overall and by unit/ward (general, high dependency/intermediate, Intensive Care Unit [ICU], Bone Marrow Transplant [BMT] Unit).
- Number and proportion of patients with any emergency room (ER) visit.
- Annualised number of ER visits.
- Mean (StDev) and median (range) number of ER visit.
- Number and proportion of patients with any outpatient visit.
- Annualised number of outpatient visits.
- Mean (StDev) and median (range) number of outpatient visits.
- Number and proportion of patients with any home health care visit.
- Annualised number of home health care visits.
- Mean (StDev) and median (range) number of home health care visit days.
- Mean (StDev) number and median (range) of assisted living facility, nursing home, hospice and rehabilitation facility visits and length of stay by type of facility.
- Mean (StDev) and median (range) number of each type of scan/procedure including:
    - Cytogenetic tests
    - Skeletal surveys, serum/urine M-protein assays, light chain assays, fluorescence in situ hybridisation (FISH), and other diagnostic tests
- Annualised number of procedures.
- Mean (StDev) and median (range) dose and duration (in days) of concomitant medications e.g., analgesics.

Results:

PATIENT DISPOSITION

- Of the 2,068 enrolled patients, 1,855 were eligible for the study and 213 were excluded due to eligibility criteria not being met. The main reasons for ineligibility were non-availability of MDS from hospital medical records, patients not being diagnosed with symptomatic NDMM or RRMM between 1st January 2010 and 31st December 2011 (inclusion criterion 1), and patients not completing at least one full line of treatment (inclusion criterion 2).

NDMM Group (Group 1)

- A total of 1,511 patients were eligible for analysis: 565 (37.4%) from East Asia (329 [21.8%] from Republic of Korea, 145 [9.6%] from China and 91 [6.0%] from Taiwan), 500 (33.1%) from the Middle East & Republic of South Africa (MESA) region (348 [23.0%] from Turkey, 104 [6.9%] from Republic of South Africa and 48 [3.2%] from

Saudi Arabia, and 446 (29.5%) from other countries (387 [25.6%] from Russia and 59 [3.9%] from Argentina).
- A total of 934 (61.8%) patients were alive at the time of last documented follow-up. The most common reason for death in NDMM group was MM-related (60.5%, n=349).

RRMM Group (Group 2)

- A total of 621 patients were eligible for analysis: 196 (31.6%) from East Asia (118 [19.0%] from Republic of Korea, 54 [8.7%] from Taiwan, and 24 [3.9%] from China), 178 (28.7%) from the MESA region (109 [17.6%] from Turkey, 56 [9.0%] from Republic of South Africa and 13 [2.1%] from Saudi Arabia), and 247 (39.8%) from other countries (239 [38.5%] from Russia and 8 [1.3%] from Argentina).
- A total of 273 (44.0%) patients were alive at the time of last documented follow-up. The most common reason for death was MM-related (66.4%, n=231).

A total of 277 patients were included both in Group 1 and in Group 2 for analysis.

NDMM GROUP

NDMM patients

Patient demographics of NDMM patients

- A total of 765 (50.6%) patients were male.
- The most common ethnicities were White (50.2%, n=758) and Asian (37.9%, n=572).

Clinical characteristics at MM diagnosis of NDMM patients

- The mean ± StDev age at MM diagnosis and at first-line treatment of the 1,511 NDMM patients was 59.6 ± 10.9 years (range 24.4 – 97.3) and 59.7 ± 10.9 years (range 24.5 – 97.3), respectively. The median (Q1 – Q3) age at MM diagnosis was 59.5 (52.0 – 67.2) years. The top 3 types of myeloma were Immunoglobulin G (IgG) kappa (32.0%, n=484), IgG lambda (15.8%, n=239), and light chain alone (kappa or lambda) (15.6%, n=235). In East Asia, a higher proportion of patients (24.2%, n=137) had light chain alone myeloma compared to patients in the MESA region (12.6%, n=63).
- The most common stage for patients in ISS was Stage III (35.9% (n=377).
- The Eastern Cooperative Oncology Group (ECOG) performance status was available for 998 (66.1%) NDMM patients. Most patients were at grade 0 (10.8%, n=163), grade 1 (28.8%, n=435) or grade 2 (22.1%, n=334).

- The mean height, body weight, body mass index (BMI), and body surface area (BSA) at MM diagnosis were 164.2 ± 9.6 cm (range 130 – 195), 68.1 ± 14.9 kg (range 35.0 – 130.0), 25.2 ± 4.42 kg/m^2 (range 15.0 – 46.6), and 1.8 ± 0.22 m^2 (range 1.2 – 2.5), respectively.
- A total of 314 (20.8%) NDMM patients had plasmacytoma. Bone lesions were reported in 81.5% (n=1,231) of patients. The bone lesions were mostly assessed via skeletal surveys (57.8%, n=711). Most patients had 1 – 3 (43.3%, n=533) or >3 (36.7%, n=452) areas with bone lesions. Almost all NDMM patients (99.8%, n=1,508) met the calcium (elevated), renal failure, anaemia, bone lesions (CRAB) criteria, and the most commonly met CRAB criterion was bone lesion (81.6%, n=1,231). The proportion of patients with elevated calcium was 6.7% (n=101).
- FISH assessment was normal or not done for 1,284 (85.0%) patients. A total of 214 (63.3%) out of 338 NDMM patients with FISH data had a confirmed gene mutation. The top 3 gene mutations (identified using FISH analysis) were del(13), t(4;14), and Immunoglobulin H (IgH) rearrangement in 48.6% (n=104), 22.0% (n=47), and 21.0% (n=45) of patients, respectively.

Medical history of NDMM patients

- A total of 698 (46.2%) patients reported at least one co-morbid condition in their medical records. The top 5 comorbidities were hypertension (27.2%, n=411), cardiovascular (CV) disease (20.0%, n=302), diabetes (13.0%, n=196), renal disease (non-MM related) (6.9%, n=105), and chronic pulmonary disease (6.1%, n=92).

Eligibility for SCT of NDMM patients

- A total of 479 (31.7%) patients had SCT performed at MM diagnosis and 987 (65.3%) did not have SCT performed at MM diagnosis. Of the 987 patients who did not have SCT performed at MM diagnosis, 866 (87.7%) were not considered eligible for SCT and 121 (n=12.3%) were considered eligible for SCT. Among the 866 patients, the reason for ineligibility for SCT was unknown for a high number of patients (55.8%, n=483) and 240 (27.7%) patients were ineligible due to advanced age. Of the 121 (12.3%) NDMM patients who were considered eligible for SCT but did not have SCT performed, 15 (12.4%) patients did not undertake transplant due to chemo-resistant disease and 17 (14.0%) patients refused to undergo transplant.
- Of the 479 (31.7%) patients who had SCT performed at MM diagnosis, the majority of the patients (95.2%, n=456) received autologous SCT.
- A total of 185 (26.1% of all patients who relapsed or had a refractory diagnosis) patients were considered eligible for SCT at relapse or refractory diagnosis. Of the 185 patients

who were considered eligible for SCT at relapse or refractory diagnosis, 115 (62.2%) had SCT performed at relapse or refractory diagnosis. Of the 115 patients who had SCT performed at relapse or refractory diagnosis, the majority of patients (91.3%, n=105) received autologous SCT.

- Of the 185 patients who were considered eligible for SCT at relapse or refractory diagnosis, 70 (37.8%) did not have SCT performed at relapse or refractory diagnosis. Among these 70 patients, the reason for transplant not being performed was unknown for 52.9% (n=37) of patients and 14.3% (n=10) of patients refused to undergo transplant.
- A total of 525 (34.7%) patients were considered ineligible for SCT at relapse or refractory diagnosis. The most common reason for ineligibility was advanced age of the patients (45.1%, n=237).

Non-SCT NDMM patients

Patient demographics of non-SCT NDMM patients

- Of the 987 non-SCT NDMM patients, 866 (87.7%) patients were ineligible for SCT and 121 (12.3%) patients were SCT-eligible but did not undergo SCT.
- Of the total 987 non-SCT NDMM patients, 478 (48.4%) were male. The most common ethnicities were White (52.5%, n=518) and Asian (40.1%, n=396).

Clinical characteristics at MM diagnosis of non-SCT NDMM patients

- The mean ± StDev age at MM diagnosis and at first-line treatment for 987 non-SCT NDMM patients was 62.4 ± 11.1 years (range 26.8 – 97.3) and 62.5 ± 11.1 years (range 26.9 – 97.3), respectively. The median (Q1– Q3) age at MM diagnosis and at first-line treatment was 63.1 (54.7 – 70.5) years and 63.1 (54.7 – 70.8) years, respectively. The top 3 types of myeloma were IgG kappa (33.6%, n=332), IgG lambda (16.1%, n=159), and light chain alone (kappa or lambda) (15.3%, n=151). The ISS was used more (n=462, 46.8%) than Durie-Salmon staging system (n=349, 35.4%). The most common stage for patients in ISS was Stage III (40.1%, n=252). A total of 195 (19.8%) patients had plasmacytoma. Bone lesions were reported in 82.3% (n=812) of patients. All but 2 of the 987 patients met CRAB criteria as per medical records. There was 1 patient for which bone pain was present but as the patient was initially seen at another hospital at initial diagnosis, PIs only had the report that the skeletal survey did not show any bone lesions. They did not have access to the original X-ray, nor MRI or PET scans. Clinically, the patient had anaemia though not severe enough for CRAB criteria, a very high monoclonal peak and severe uncontrollable lower back pain. She was treated for myeloma and the bone pain responded. The second patient in the NDMM group was CRAB negative, however, there was a note in the medical records stating that the patient

had systemic amyloidosis (heart, bone marrow and intestine). A total of 62 (6.3%) patients had elevated calcium.

- The mean age at MM diagnosis for 866 non-SCT NDMM patients who were ineligible for SCT was 63.3 ± 10.8 years (range 26.8 – 97.3). The median (Q1– Q3) age at diagnosis was 64.0 (56.1 – 71.3) years. IgG kappa (34.6%, n=300) was the most frequently observed myeloma. A large percentage of patients were in Stage III in both the ISS and Durie-Salmon staging systems; 41.9% (n=217) were classified as ISS Stage III and 72.0% (n=342) were classified as Durie-Salmon Stage III. A total of 163 (18.8%) had plasmacytoma. All 866 patients met CRAB criteria. A total of 49 (5.7%) patients had elevated calcium. A large proportion of patients had bone lesions (82.9%, n=718).
- The mean age at MM diagnosis for 121 non-SCT NDMM patients who were eligible for SCT but did not undergo SCT was 55.6 ± 10.9 years (range 29.4 – 81.5), which is noticeably younger than non-SCT NDMM patients ineligible for SCT. The median (Q1– Q3) age at MM diagnosis was 54.9 (48.9 – 63.2) years. Light chain alone (kappa or lambda) was the most frequently observed myeloma. A large percentage of patients were in Stage III for both the staging systems, overall; 31.8% (n=35) were classified as ISS Stage III and 67.5% (n=27) were classified as Durie-Salmon Stage III. A total of 32 (26.4%) patients had plasmacytoma. All 121 patients met CRAB criteria. A total of 13 (10.7%) patients had elevated calcium. Bone lesions were present in 77.7% (n=94) of patients.

NDMM patients undergoing SCT

Patient demographics of NDMM patients undergoing SCT

- Of the 479 NDMM patients undergoing SCT, 261 (54.5%) patients were male.
- The most common ethnicities were White (43.2%, n=207) and Asian (35.3%, n=169).

Clinical characteristics at MM diagnosis of NDMM patients undergoing SCT

- The mean age at MM diagnosis and at first-line treatment for the 479 NDMM patients undergoing SCT was 53.8 ± 7.9 years (range 24.4 – 73.8) and 53.9 ± 7.9 years (range 24.5 – 73.8), respectively. The median (Q1 – Q3) age at MM diagnosis and at first-line treatment was 54.7 (48.4 – 59.6) years and 54.8 (48.4 – 59.7) years, respectively. The top 3 types of myeloma were IgG kappa (29.6%, n=142), IgG lambda (16.1%, n=77), and light chain alone (kappa or lambda) (17.1%, n=82). ISS system (53.2%, n=255) was used more in patients. The most common stage for patients in ISS was Stage III (30.9%, n=119). The ECOG status (calculated including the patients with unavailable ECOG) was 0-2 for a majority of patients (n=164, 61.6%). A total of 116 (24.2%) patients had

plasmacytoma. Bone lesions were reported in 80.8% (n=387) of patients. A total of 476 (99.4%) patients met CRAB criteria. A total of 38 (8.0%) patients had elevated calcium.

Comparing patient demographics and clinical characteristics of non-SCT NDMM patients and NDMM patients undergoing SCT

- Overall, of the 1,511 NDMM patients, 987 patients did not undergo SCT (non-SCT NDMM patients) and 479 NDMM patients had SCT performed. The mean age at MM diagnosis and mean age at first-line treatment for non-SCT NDMM patients were higher than the NDMM patients who had SCT performed (62.4 ± 11.1 years versus 53.8 ± 7.9 years at diagnosis and 62.5 ± 11.1 years versus 53.9 ± 7.9 years at first-line treatment). The top 3 types of myeloma (IgG kappa, IgG lambda, and light chain alone [kappa or lambda]) were the same irrespective of SCT status. Both non-SCT NDMM patients and NDMM patients who had SCT performed were mostly in Stage III and had an ECOG grade 0-2.

Clinical characteristics of NDMM patients undergoing more than one SCT

- A total of 81 NDMM patients received more than one SCT (i.e., patients undergoing any SCT). The mean age at MM diagnosis and at first-line treatment for 81 NDMM patients undergoing more than one SCT was 51.0 ± 9.5 years (range 28.9 – 69.2 and 51.0 ± 9.5 years (range 29.0 – 69.2), respectively. The median (Q1 – Q3) age at MM diagnosis and at first-line treatment was 52.0 (44.4 – 56.7) years and 52.1 (44.4 – 56.8) years, respectively. The top 3 types of myeloma were IgG kappa (29.6%, n=24), IgG lambda (13.6.%, n=11), light chain alone (kappa or lambda) (13.6%, n=11), and IgA kappa (9.9%, n=8). The most common stage for patients at diagnosis in ISS was Stage I (29.3%, n=17). A total of 21 (25.9%) patients had plasmacytoma. Bone lesions were reported in 87.7% (n=71) of patients. All 81 patients met CRAB criteria. A total of 6 (7.4%) patients had elevated calcium.

Primary objective - Time to next treatment at each line of treatment in NDMM patients

- When considering TTNT from the initiation of first-line treatment, amongst the 1,510 NDMM patients at risk, 952 (63.0%) patients had an event (i.e., initiated a next line of therapy or death) and 558 (37.0%) patients were censored. The median (Q1– Q3) TTNT (from initiation of first-line treatment for MM) was 39.5 (15.1 – 96.9) months overall. In East Asia and the MESA region, the median (Q1 – Q3) TTNTs were 31.8 (13.5 – 73.6) months and 45.2 (16.6 – Not Reached [NR]) months, respectively.
- When considering TTNT from initiation of second-line treatment, amongst the 647 NDMM patients at risk, 402 (62.1%) patients had an event and 245 (37.9%) patients

were censored. The median (Q1 – Q3) TTNT (from initiation of second-line treatment for MM) was 33.9 (11.5 – 74.5) months. In East Asia and the MESA region, the median (Q1 – Q3) TTNT were 20.1 (7.4 – 41.1) months and 27.8 (9.3 – 82.5) months, respectively.

- When considering TTNT from initiation of third-line treatment, amongst the 230 NDMM patients at risk, 131 (57.0%) patients had an event and 99 (43.0%) patients were censored. The median (Q1 – Q3) TTNT (from initiation of third-line treatment for MM) was 20.9 (7.9 – 46.3) months. In East Asia and the MESA region, the median (Q1 – Q3) TTNT were 13.0 (6.4 – 27.1) months and 18.4 (6.2 – 61.1) months, respectively.
- When considering TTNT from initiation of fourth-line treatment, amongst the 80 NDMM patients at risk, 54 (67.5%) patients had an event and 26 (32.5%) patients were censored. The median (Q1 – Q3) TTNT (from initiation of fourth-line treatment for MM) was 11.2 (4.9 – 19.2) months. In East Asia and the MESA region, the median (Q1 – Q3) TTNT were 8.1 (3.7 – 17.1) months and 11.2 (6.4 – 18.8) months, respectively.
- When considering TTNT from initiation of fifth-line treatment, amongst the 21 NDMM patients at risk, 17 (81.0%) patients had an event and 4 (19.0%) patients were censored. The median (Q1 – Q3) TTNT (from initiation of fifth-line treatment for MM) was 7.1 (3.8 – 22.1) months. In East Asia and the MESA region, the median (Q1 – Q3) TTNT were 7.1 (3.8 – 9.3) months and 5.7 (2.8 – 22.1) months, respectively.
- Comparing TTNT across lines of treatment, the further along a patient is on treatment, the shorter is the TTNT.

Secondary Objectives – Treatment patterns for MM in NDMM patients

Treatment in NDMM patients

- The mean duration of first-line treatment for 1,511 NDMM patients was 10.1 ± 12.7 months (range 0.03 – 116.4). The most common first-line treatment for MM in NDMM patients was bortezomib, cyclophosphamide, and dexamethasone (VCD) with 277 (18.3%) patients receiving this treatment. The average duration of treatment was 5.4 ± 2.8 months (range 0.03 – 23.1).
- A total of 647 (42.8%) NDMM patients had a second-line treatment. The mean duration of second-line treatment for 646 NDMM patients (data missing for 1 patient) was 9.7 ± 10.9 months (range 0.03 – 81.3). The most common second-line treatment was bortezomib and dexamethasone (VD), received by 132 (20.4%) NDMM patients. The treatment duration average was 5.2 ± 4.7 months (range 0.03 – 33.5).
- The mean duration of third-line treatment for 230 (15.2%) NDMM patients was 8.7 ± 9.1 months (range 0.03 – 70.2). The most common third-line treatment was lenalidomide

and dexamethasone (RD). A total of 61 (26.5%) patients received RD for an average of 9.1 ± 8.7 months (range 0.03 – 42.6).

- Fourth-line treatment was received by 80 (5.3%) NDMM patients. The mean duration of fourth-line treatment was 7.9 ± 10.0 months (range 0.1 – 58.3). The only regimen received by more than 10 patients in fourth-line treatment was RD. A total of 11 (13.8%) patients received RD with an average duration of 8.9 ± 11.5 months (range 0.5 – 40.7).
- The mean duration of fifth-line treatment for 21 (1.4%) NDMM patients was 4.9 ± 4.7 months (range 0.03 – 21.6). None of the regimens were received by more than 3 patients.

Treatment in non-SCT NDMM patients

- The mean duration of first-line treatment for all 987 non-SCT NDMM patients was 9.9 ± 11.7 months (range 0.03 – 116.4). The most common first-line treatment for non-SCT NDMM was VD with 170 (17.2%) patients receiving this treatment. The average duration of treatment was 5.9 ± 7.9 months (range 0.1 – 91.0).
- The mean duration of second-line treatment for 430 (43.6%) non-SCT NDMM patients was 8.8 ± 9.8 months (range 0.03 – 81.3). The most common second-line treatment for non-SCT NDMM patients was VD with 75 (17.4%) patients receiving this treatment. The average duration of treatment was 4.6 ± 3.9 months (range 0.4 – 22.7).
- The mean duration of third-line treatment for 145 (14.7%) non-SCT NDMM patients was 8.2 ± 9.1 months (range 0.03 – 70.2). The only regimens received by more than 10 patients in third-line were RD (n=33) and Rd (n=21). A total of 33 (22.8%) non-SCT NDMM patients received treatment with RD. The average duration of treatment was 10.5 ± 9.7 months (range 0.7 – 42.6).
- The mean duration of fourth-line treatment for 50 (5.1%) non-SCT NDMM patients was 8.9 ± 11.6 months (range 0.4 – 58.3). None of the regimens were received by more than 7 patients.
- The mean duration of fifth-line treatment for 11 (1.1%) non-SCT NDMM patients was 5.3 ± 6.2 months (range 0.03 – 21.6). None of the regimens were received by more than 1 patient.

Treatment in non-SCT NDMM patients ineligible for SCT

- The mean duration of first-line treatment for 866 non-SCT NDMM patients who were ineligible for SCT was 9.9 ± 11.1 months (range 0.2 – 116.4). The most common first-line treatment was VCD with 148 (17.1%) patients receiving this treatment. The average duration of treatment was 6.0 ± 2.3 months (range 0.3 – 16.2).
- The mean duration of second-line treatment for 365 (42.1%) non-SCT NDMM patients who were ineligible for SCT was 8.6 ± 8.6 months (range 0.03 – 53.0). The most common second-line treatment for non-SCT NDMM patients who were ineligible for

SCT was VD with 58 (15.9%) patients receiving this treatment. The average duration of treatment was 4.7 ± 4.1 months (range 0.4 – 22.7).

- The mean duration of third-line treatment for 117 (13.5%) non-SCT NDMM patients who were ineligible for SCT was 9.1 ± 9.7 months (range 0.3 – 70.2). The only regimens received by more than 10 non-SCT NDMM patients who were ineligible for SCT in third-line were RD (n=16) and Rd (n=20). A total of 20 (17.1%) patients had third-line treatment with Rd for an average of 11.1 ± 9.2 months (range 2.4 – 35.9).
- The mean duration of fourth-line treatment for 37 (4.3%) non-SCT NDMM who were ineligible for SCT patients was 9.3 ± 11.3 months (range 0.4 – 58.3). None of the regimens were received by more than 6 patients.
- The mean duration of fifth-line treatment for 7 (0.8%) non-SCT NDMM patients who were ineligible for SCT was 7.1 ± 7.0 months (range 0.72 – 21.6).

Treatment in non-SCT NDMM patients eligible for SCT but did not undergo SCT

- The mean duration of first-line treatment for 121 NDMM patients who were eligible for SCT but did not undergo SCT was 10.0 ± 15.4 months (range 0.03 – 89.5). The most common first-line treatment was VD with 31 (25.6%) patients receiving this treatment. The average duration of treatment was 4.5 ± 4.3 months (range 1.0 – 21.6).
- The mean duration of second-line treatment for 65 (53.7%) NDMM patients who were eligible for SCT but did not undergo SCT was 9.5 ± 14.9 months (range 0.03 – 81.3). The only regimen received by more than 10 patients in second-line treatment was VD (n=17) and VCD (n=12). A total of 17 (26.2%) patients had second-line treatment with VD for an average of 4.2 ± 2.9 months (range 0.7 – 9.3).
- The mean duration of third-line treatment for 28 (23.1%) NDMM patients who were eligible for SCT but did not undergo SCT was 4.6 ± 4.0 months (range 0.03 – 14.7).
- The mean duration of fourth-line treatment for 13 (10.7%) NDMM patients who were eligible for SCT but did not undergo SCT was 7.8 ± 12.5 months (range 0.6 – 48.1).
- The mean duration of fifth-line treatment for 4 (3.3%) NDMM patients who were eligible for SCT but did not undergo SCT was 2.2 ± 3.1 months (range 0.03 – 6.5).

Treatment in NDMM patients undergoing SCT

- A total of 479 NDMM patients underwent SCT.
- The most common source of stem cells in patients was peripheral blood at first (75.4%, n=361) and second (72.5%, n=58) SCT.
- At first SCT:
    - A total of 454 (94.8%) patients had induction regimens administered before SCT. The most commonly administered induction regimen for patients was

bortezomib, doxorubicin, and dexamethasone (PAD) with 77 (16.1%) patients receiving this regimen.
    - Consolidation and maintenance regimens after SCT were administered in few patients although this could be explained by phase data not being recorded in medical files.
- Overall, the number of patients with sCR and CR after first SCT were 40 (8.4%) and 222 (46.3%), respectively. A total of 85 (17.7%), 32 (6.7%), and 6 (1.3%) patients had VGPR, PR, and MR, respectively. A total of 3 (0.6%) and 16 (3.3%) patients had SD and PD, respectively.
- At second SCT:
    - A total of 80 (16.7%) NDMM patients had second SCT. A total of 38 (47.5%) patients had induction regimens administered before SCT. The most commonly administered induction regimen for patients was VCD with 17 (21.3%) patients receiving this induction regimen. None of these patients were in East Asia.
- Overall, the number of patients with sCR and CR after second SCT was 2 (2.5%) and 30 (37.5%), respectively. A total of 15 (18.8%), 6 (7.5%), and 2 (2.5%) patients had VGPR, PR, and MR, respectively. None of the patients had SD and 2 (2.5%) patients had PD.

Clinical outcomes in NDMM patients

Relapse rate in NDMM patients

Non-SCT NDMM patients

- For non-SCT NDMM patients, relapse-free rates at 1-year after start of first-line treatment was 88.4% (95% CI: 86.1% – 90.3%), at 2-years after start of first-line treatment was 75.5% (95% CI: 72.4% – 78.3%), and at 5-years after start of first-line treatment was 49.3% (95% CI: 45.4% – 53.1%).

- Minimal differences were seen between ineligible for SCT and non-SCT patients. Patients eligible but not undergoing SCT had a better outcome in comparison to non-SCT patients overall.

NDMM patients undergoing SCT

- For NDMM patients undergoing SCT, relapse-free rate at 1-year after start of first-line treatment was 94.2 % (95% CI: 91.7% – 96.0%), at 2-years after start of first-line treatment was 80.5% (95% CI: 76.5% – 83.8%) and at 5-years after start of first-line treatment was 58.2% (95% CI: 53.2% – 62.9%).

- For NDMM patients undergoing SCT, relapse-free rate at 1-year after first SCT was 85.2% (95% CI: 81.6% – 88.2%), at 2-years after first SCT was 74.3% (95% CI: 69.9% – 78.2%) and at 5-years after first SCT was 54.9% (95% CI: 49.8% – 59.8%).

OS rate in NDMM patients

Non-SCT NDMM patients

- OS was calculated on 986 non-SCT NDMM patients at risk of which 394 (40.0%) had an event (i.e., death). The median (Q1 – Q3) OS for patients was 85.9 (38.7 – NR) months. Q3 was not reached because less than 50% of patients had an event.
- OS rates at 2-years after start of first-line treatment was 83.5 % (95% CI: 81.0% – 85.8%), and at 5-years after start of first-line treatment was 64.6% (95% CI: 61.2% – 67.9%).

NDMM patients undergoing SCT

- OS was calculated on 479 NDMM patients undergoing SCT at risk of which 168 (35.1%) had an event. Overall, the median (Q1 – Q3) OS for patients was 114.1 (55.7 – NR) months.
- OS rate at 2-years after start of first-line treatment was 89.7 % (95% CI: 86.6% – 92.1%) and at 5-years after start of first-line treatment was 73.5 % (95% CI: 69.1% – 77.4%).

Number of relapses per patient in NDMM patients

Non-SCT NDMM patients

- A total of 434 (44.0%) non-SCT NDMM patients had a documented relapse or disease progression after first-line treatment: 295 (29.9%) patients had relapse only, 54 (5.5%) had disease progression only, and 85 (8.6%) patients had both relapse and disease progression.

NDMM patients undergoing SCT

- A total of 207 (43.2%) NDMM patients undergoing SCT had a documented relapse or disease progression after first-line treatment: 171 (35.7%) patients had relapse only, 1 (0.2%) had disease progression only, and 35 (7.3%) patients had both relapse and disease progression.

- A total of 204 (42.6%) NDMM patients undergoing SCT had documented relapse or disease progression after first SCT. ISS Stage II/III and presence of either t(4,14), t(14,16) or del 17p13 gene mutation were high risk factors for relapse.
- A total of 219 (45.7%) patients had ISS Stage II/III.
- A total of 14 (3.3%) patients with response (sCR or CR or VGPR or PR or MR) were assessed as high risk of relapse.

Best response after start of treatment by line of therapy in NDMM patients

Non-SCT NDMM patients

- Amongst the 987 non-SCT NDMM patients who received first-line treatment, 727 (73.7%) had documented clinical response (sCR or CR or VGPR or PR or MR) from this treatment. The median (Q1 – Q3) time to response from first-line treatment was 7.2 (4.9-15.0) months. The median (Q1 – Q3) time difference between first response and first documented relapse or disease progression, after start of first-line treatment was 10.8 (1.3 – 26.9) months.
- At first-line treatment, the number of non-SCT NDMM patients with a clinical best response of sCR and CR were 10 (1.0%) and 195 (19.8%), respectively. A total of 193 (19.6%), 245 (24.8%), 27 (2.7%) patients had VGPR, PR, and MR, respectively. The number of non-SCT NDMM patients with SD and PD were 136 (13.8%) and 67 (6.8%), respectively.
- At second-line treatment, none of the patients had sCR and the number of patients with CR was 87 (20.2%). A total of 103 (24.0%), 78 (18.1%), and 12 (2.8%) patients had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 36 (8.4%) and 41 (9.5%), respectively.
- At third-line treatment, none of the patients had sCR and the number of patients with CR was 47 (32.4%). A total of 15 (10.3%), 22 (15.2%), and 2 (1.4%) patients had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 16 (11.0%) and 18 (12.4%), respectively.

NDMM patients undergoing SCT

- Of the 479 NDMM patients undergoing SCT, 423 (88.3%) had documented clinical response (sCR or CR or VGPR or PR or MR) from first-line treatment. The median (Q1 – Q3) time to response from first-line treatment was 4.9 (3.2 – 10.1) months. The median (Q1 – Q3) time difference between first response and first documented relapse or disease progression, after start of first-line treatment was 24.7 (10.2 – 46.3) months.
- At first-line treatment, the number of NDMM patients undergoing SCT with a clinical best response of sCR and CR were 15 (3.1%) and 146 (30.5%) respectively. A total of

109 (22.8%), 138 (28.8%), and 4 (0.8%) patients had VGPR, PR, and MR, respectively. The number of non-SCT NDMM patients with SD and PD were 22 (4.6%) and 3 (0.6%), respectively.

- At second-line treatment, the number of patients with a clinical best response of sCR and CR were 5 (2.5%) and 52 (25.9%) and. A total of 40 (19.9%), 42 (20.9%), and 9 (4.5%) patients had VGPR, PR, and MR, respectively. The number of patients with SD and PD was 12 (6.0%), each.
- At third-line treatment, the number of patients with a clinical best response of sCR and CR and was 3 (3.8%) and 13 (16.3%), respectively. A total of 11 (13.8%), 20 (25.0%), and 5 (6.3%) patients had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 6 (7.5%) and 9 (11.3%), respectively.

Time to first or best response by line of therapy in NDMM patients

Non-SCT NDMM patients

- Amongst the 987 non-SCT NDMM patients who received first-line treatment, 727 (73.7%) had documented clinical response (sCR or CR or VGPR or PR or MR) from this treatment. The median (Q1 – Q3) time to response from first-line treatment was 7.2 (4.9 – 15.0) months. The median (Q1 – Q3) time difference between first response and first documented relapse or disease progression, after start of first-line treatment was 10.8 (1.3 – 26.9) months.

NDMM patients undergoing SCT

- Of the 479 NDMM patients undergoing SCT, 423 (88.3%) had documented clinical response (sCR or CR or VGPR or PR or MR) from first-line treatment. The median (Q1 – Q3) time to response from first-line treatment was 4.9 (3.2 – 10.1) months. The median (Q1 – Q3) time difference between first response and first documented relapse or disease progression, after start of first-line treatment was 24.7 (10.2 – 46.3) months.

Clinical outcomes in deceased NDMM patients

- The mean (StDev) time from MM diagnosis to death for NDMM patients (n=577) was 41.3 ± 27.9 months (range 0.3 – 117.8). The mean time from completion of first-line therapy to death for patients was 31.0 ± 27.3 months (range 0.03 – 113.3). For 349 (60.5%) patients the cause of death was MM-related.

Summary of AEs in NDMM patients

- A total of 1,623 AEs was reported for 579 (38.3%) of the 1,511 NDMM patients. A percentage of 36.9% (599 AEs) of the AEs reported were related to treatment regimen.
- A total of 478 SAEs were reported for 267 (17.7%) of the 1,511 NDMM patients. A total of 61 (4.0%) NDMM patients had 88 SAEs related to treatment regimen.
- A total of 210 life-threatening SAEs were reported for 171 (11.3%) NDMM patients, 155 SAEs resulted in prolongation of hospitalisation for 88 (5.8%) NDMM patients, and 401 SAEs required hospitalisation for 207 (13.7%) NDMM patients.

AEs in NDMM patients

- A total of 1,623 AEs were reported for 579 of the 1,511 NDMM patients with an IR of 53.4 events per 100 PY. The most frequently reported AEs were pneumonia (24.4%, n=141), peripheral neuropathy (11.6%, n=67), pyrexia (8.1%, n=47), anaemia (7.9%, n=46), back pain (7.4%, n=43), diarrhoea (6.6%, n=38), peripheral sensory neuropathy (5.5%, n=32), febrile neutropenia (5.4%, n=31), nausea (5.2%, n=30), and cardiac arrest (4.0%, n=23).

AEs associated with post SCT treatment regimens in NDMM patients

- A total of 148 AEs were reported for all 61 (100.0%) NDMM patients with post-SCT treatment with an IR of 13.3 events per 100 PY. The most frequently reported AEs were peripheral neuropathy (29.5%, n=18), peripheral sensory neuropathy (13.1%, n=8), pneumonia (11.5%, n=7), asthenia (11.5%, n=7), thrombocytopenia (9.8%, n=6) and neutropenia (8.2%, n=5).

TRAEs in NDMM patients

- A total of 599 TRAEs were reported for 274 NDMM patients with an IR of 19.7 events per 100 PY. The most frequently reported TRAEs, by PT, were peripheral neuropathy (20.8%, n=57), pneumonia (11.7%, n=32), peripheral sensory neuropathy (10.2%, n=28), diarrhoea (8.4%, n=23), and asthenia (7.3%, n=20).
- During the 228.5 PY of VCD treatment (longest given regimen for NDMM patients), 26 NDMM patients had 38 AEs with an IR of 16.6 events per 100 PY. The most frequently reported TRAEs were polyneuropathy (2.6%, n=7), diarrhoea (1.8%, n=5), peripheral neuropathy (1.8%, n=5), neutropenia (1.5%, n=4), and peripheral sensory neuropathy (1.5%, n=4).

TRAEs in non-SCT NDMM patients

- For all regimens (PY=1,869.1), 355 TRAEs were reported for all 176 (100.0%) non-SCT NDMM patients with an IR of 19.0 events per 100 PY. The most frequently reported TRAEs were peripheral neuropathy (11.9%, n=21), pneumonia (11.9%, n=21), peripheral sensory neuropathy (10.8%, n=19), polyneuropathy (6.8%, n=12), and diarrhoea (8.5%, n=15), anaemia (5.7%, n=10), asthenia (5.7%, n=10), and decreased appetite (5.7%, n=10).
- During the 137.3 PY of VD treatment (longest given regimen to non-SCT NDMM patients), 43 (24.4%) patients had 64 TRAEs with an IR of 46.6 events per 100 PY. None of the TRAEs listed by PT were reported in more than 10 patients.

SAEs in NDMM patients

- A total of 478 SAEs were reported for 267 NDMM patients with an IR of 15.7 events per 100 PY. The most frequently reported SAEs were pneumonia (31.1%, n=83), cardiac arrest (8.6%, n=23), septic shock (6.7%, n=18), febrile neutropenia (6.4%, n=17), pyrexia (6.4%, n=17), and cardiac failure (4.1%, n=11).
- During the 226.1 PY of VD treatment, 12 patients had 17 SAEs for an IR of 7.5 events per 100 PY.

SAEs in non-SCT NDMM patients

- A total of 323 SAEs were reported for 175 non-SCT NDMM patients with an IR of 17.3 events per 100 PY. The most frequently reported SAEs were pneumonia (33.7%, n=59), septic shock (9.1%, n=16), cardiac failure (6.3%, n=11), urinary tract infection (5.1%, n=9), febrile neutropenia (5.1%, n=9), and pyrexia (4.6%, n=8).

SAEs associated with post SCT treatment regimens in NDMM patients

- A total of 18 SAEs were reported in 13 NDMM patients with an IR of 1.6 events per 100 PY. The most frequently reported SAE was pneumonia (46.2%, n=6).

SAEs occurring at the same time as regimen in NDMM patients

- A total of 263 SAEs concurrent with treatment regimens were reported for 145 NDMM patients with an IR of 8.7 events per 100 PY. The most frequently reported SAEs that occurred during any treatment regimen were pneumonia (33.1%, n=48), febrile neutropenia (10.3%, n=15), pyrexia (7.6%, n=11), septic shock (7.6%, n=11), and urinary tract infection (5.5%, n=8).

- During the 228.5 PY of VCD treatment, 4 (2.8%) NDMM patients had 6 SAEs concurrent with VCD treatment with an IR of 2.6 events per 100 PY. The most frequently reported SAE was neutropenia (1.4%, n=2), which was fatal.

MM-related healthcare resource use associated with each line of treatment in NDMM patients

MM-related healthcare resource use by line of treatment in NDMM patients

- A total of 505 (33.4%) NDMM patients had a record of MM-related inpatient hospitalisation during first-line treatment. The median (Q1 – Q3) number of hospitalisations per patient was 2.0 (1.0 – 6.0). Of the 2,594 MM-related admissions, 1,933 (74.5%) were due to MM-related treatment during first-line treatment. The overall median (Q1 – Q3) length of stay was 7.0 (0.0 – 14.0) days. Of the 2,594 MM-related admissions, 2,542 were in the general ward where NDMM patients stayed (median [Q1 – Q3]) for 7.0 (0.0 – 14.0) days. A total of 5 admissions were recorded to High Dependency Unit, 14 admissions were recorded to BMT Unit, and 1 to ICU.
- MM-related ER visits were reported for 9 (0.6%) NDMM patients during first-line treatment. Each patient had 1 ER visit. A total of 581 (99.5%) outpatient visits were reported for NDMM patients during first-line treatment. The median (Q1 – Q3) number of outpatient visits per patient was 4.0 (1.0 – 10.0).
- A total of 144 (22.3%) NDMM patients had a record of MM-related inpatient hospitalisation during second-line treatment. The median (Q1 – Q3) number of hospitalisations per patient was 1.0 (1.0 – 5.0).
- Of the 687 MM-related admissions, 481 (70.0%) were due to MM-related treatment during second-line treatment. The overall median (Q1 – Q3) length of stay was less than one day. Of the 687 MM-related admissions, 675 were in the general ward. The median (Q1 – Q3) length of stay in general ward was less than one day. Only 1 admission was recorded to the High Dependency Unit, 5 admissions were recorded to BMT Unit and, 1 admission to ICU.
- MM-related ER visits were reported for 5 (0.8%) NDMM patients during second-line treatment. Each patient had 1 ER visit. A total of 174 (26.9%) outpatient visits were reported for all NDMM patients during second-line treatment. The median (Q1 – Q3) number of outpatient visits per patient was 3.0 (1.0 – 9.0).
- A total of 35 (15.2%) NDMM patients had a record of MM-related inpatient hospitalisation during third-line treatment. The median (Q1 – Q3) number of hospitalisations per patient was 2.0 (1.0 – 5.0).
- Of the 166 MM-related admissions, 88 (53.0%) were due to treatment for MM during third-line treatment. Of the 166 MM-related admissions, 163 were related to the general

ward. The median length of stay in general ward was 4.0 (0.0 – 11.0) days. Only 1 admission was recorded to the High Dependency Unit, to BMT Unit and to ICU, each.
- No ER visits were reported for NDMM patients during third-line treatment. A total of 80 (34.8%) NDMM patients had outpatient visits during third-line treatment. The median (Q1 – Q3) number of outpatient visits per patient was 41.0 (2.0 – 9.5).

MM-related healthcare resource use: procedure in NDMM patients

- CT scans were performed for 478 of 1,511 NDMM patients. The mean (StDev) number of CT scans performed per patient was 1.9 ± 1.7 (range 1.0 – 14.0).
- PET scans were performed for 223 of 1,511 NDMM patients. The mean number of PET scans performed per patient was 1.4 ± 0.9 (range 1.0 – 6.0).
- Bone marrow biopsies were performed for 37 of 1,511 NDMM patients. The mean number of biopsies performed per patient was 1.3 ± 0.6 (range 1.0 – 4.0).
- Skeletal surveys were performed for 948 of 1,511 NDMM patients. The mean number of skeletal surveys performed per patient was 1.7 ± 2.7 (range 1.0 – 37.0).
- Karyotypes was performed for 352 of 1,511 NDMM patients. The mean number of karyotypes performed per patient was 1.2 ± 0.5 (range 1.0 – 4.0).
- FISH procedure was performed for 342 of 1,511 NDMM patients. The mean number of FISH procedure performed per patient was 1.1 ± 0.3 (range 1.0 – 3.0).
- Of the 1,511 NDMM patients 108 (7.1%) received G-CSF. The mean duration of GSF treatment (n=107) was 0.7 ± 0.7 months (range 0.0 – 5.0).
- Of the 1,511 NDMM patients, 425 patients had blood transfusions performed. The mean number of blood transfusions performed per patient was 4.5 ± 11.7 months (range 1.0 – 169.0).
- The mean number of treatment regimens per patient (n=1,511) was 2.3 ± 1.6 (range 1.0 – 16.0).

RRMM GROUP

RRMM patients

Patient demographics for RRMM patients

- A total of 621 RRMM patients, 311 (50.1%) patients were male.
- The most common ethnicities were White and Asian, with 354 (57.0%), and 200 (32.2%) patients, respectively.

Clinical characteristics at MM diagnosis for RRMM patients

- The mean ± StDev age at MM diagnosis and at first-line treatment of the 621 RRMM patients was 57.9 ± 10.9 years (range 17.7 – 86.4) and 57.9 ± 10.8 years (range 17.9 – 86.5), respectively. The median (Q1 – Q3) age at MM diagnosis and at first-line treatment was 58.1 (50.2 – 65.8) years and 58.2 (50.2 – 66.0) years, respectively.
- The top 3 types of myeloma were IgG kappa (33.5%, n=208), IgG lambda (14.0%, n=87), and light chain alone (kappa or lambda) (15.8%, n=98). A further 31 (5.0%) patients had a myeloma of the IgG (light chain unknown) type making IgG the type of myeloma in over 50% of patients.
- The most common stage for patients in Durie-Salmon staging system was Stage III (54.5%, n=206). The ECOG performance status was available for 443 (71.4%) patients. Most patients were at grade 0 (11.3%, n=70), grade 1 (32.4%, n=201), or grade 2 (24.8%, n=154).
- The mean height, body weight, BMI, and BSA at MM diagnosis were 165.8 ± 10.1 cm (range 130.0 – 189.0), 71.9 ± 16.2 kg (range 36.0 – 132.0), 26.0 ± 4.5 kg/m^2 (range 15.2 – 41.8), and 1.8 ± 0.3 m^2 (range 1.2 – 2.6), respectively.
- A total of 140 (22.5%) RRMM patients had plasmacytoma.
- Bone lesions were reported in 81.8% (n=508) of patients. The bone lesions were mostly assessed via skeletal surveys (67.3%, n=342). Most of the patients had 1 – 3 (37.6%, n=191) or >3 (44.1%, n=224) areas with bone lesions.
- The majority of patients (91.9%, n=571) met CRAB criteria, and the CRAB criterium which was more often met was bone lesion (88.3%, n=504). A total of 43 (7.5%) patients had elevated calcium.
- A total of 77 (72.6%) out of 106 RRMM patients with FISH data had a confirmed gene mutation while FISH assessment was normal or not done for 542 (87.5%) patients. The top 3 gene mutations (as detected using FISH analysis) were del(13), t(4;14), and del(17p)/p53 in 48.1% (n=37), 23.4% (n=18), and 22.1% (n=17) of patients, respectively.

Clinical characteristics at MM relapse for RRMM patients

- Of the 621 RRMM patients, a total of 132 (21.3%) patients had refractory only disease, 419 (67.5%) patients had relapse only disease, and 70 (11.3%) patients had both refractory and relapsed disease.
- At first relapse or refractory diagnosis, the mean ± StDev age for 621 RRMM patients was 59.5 ± 10.8 years (range 18.8 – 87.0). A large percentage of RRMM patients were in Stage III for both the staging systems: 19.2% (n=50) were classified as ISS Stage III and 53.4% (n=171) were classified as Durie-Salmon Stage III. The majority of patients

had ECOG performance status with either grade 1 (30.1%, n=187) or grade 2 (26.1%, n=162). A proportion of 60.9% (n=378) of patients met the CRAB criteria at first relapse or refractory diagnosis. A total of 9 (2.4%) patients had elevated calcium. A total of 236 (38.0%) patients died after first relapse or refractory disease diagnosis.

- Of the patients that were not lost to follow-up and alive, a total of 176 (28.3%) RRMM patients had a second relapse after the first relapse or refractory disease diagnosis. At second relapse, the mean age for 176 patients was 61.5 ± 11.1 years (range 33.5 – 83.1). A high percentage of patients (57.4, n=54) were in Stage III of Durie-Salmon staging system. The majority of the patients had ECOG performance status with either grade 1 (17.0%, n=30) or grade 2 (30.1%, n=53). A total of 68 (38.6%) patients died after the second relapse and 68 (38.6%) had another relapse (third relapse).
- At third relapse, the mean age for the 68 RRMM patients that were not lost to follow-up and still alive was 62.9 ± 10.4 years (range 38.0 – 79.7). Most patients were in Stage III; 24.0% (n=6) were classified as ISS Stage III and 54.1% (n=20) were classified as Durie-Salmon Stage III. A high percentage of patients at the third relapse had ECOG performance status with grade 2 (33.8%, n=23). A total of 26 (38.2%) RRMM patients died after third relapse and 25 (36.8%) had another relapse (fourth relapse).

Medical history of RRMM patients

- A total of 306 (49.3%) of the 621 RRMM patients reported at least one co-morbid condition in their medical records.
- The top 5 comorbidities were hypertension (28.5%, n=177), CV disease (23.7%, n=147), diabetes (16.1%, n=100), chronic pulmonary disease (8.5%, n=53), and renal disease (non-MM related) (7.7%, n=48) and peptic ulcer disease (7.7%, n=48).

Eligibility for SCT for RRMM patients

- Of the 621 RRMM patients, 126 (20.3%) patients had SCT performed and 474 (76.3%) did not undergo SCT at MM diagnosis.
- Of the 474 patients who did not undergo SCT at MM diagnosis, 402 (84.8%) were not considered eligible for SCT. Among these 402 patients, 97 (24.1%) patients were ineligible for SCT due to advanced age. Of the 474 RRMM patients who did not undergo SCT at MM diagnosis, 72 (15.2%) were eligible for SCT. Of the 72 patients eligible for SCT, transplant was not performed for 12 (16.7%) patients due to chemo-resistant disease. Of the 126 patients who had SCT performed at MM diagnosis, the majority of the patients (91.3%, n=115) received autologous SCT.
- Of the 144 patients who were considered eligible for SCT at relapse or refractory diagnosis, 98 (68.1%) had SCT performed at relapse or refractory diagnosis. Of the 98 patients who had SCT performed at relapse or refractory diagnosis, the majority of

patients (88.8%, n=87) received autologous SCT. Of the 144 patients who were considered eligible for SCT at relapse or refractory diagnosis, 46 (31.9%) did not have SCT performed at relapse or refractory diagnosis.

- Of the 621 RRMM patients, a total of 477 (76.8%) patients were considered ineligible for SCT at relapse or refractory diagnosis. The most common reason for ineligibility was advanced age of the patients (23.7%, n=113).

Non-SCT RRMM patients

Patient demographics for non-SCT RRMM patients

- Of the 522 non-SCT RRMM patients, 449 (86.0%) patients were ineligible for SCT and 73 (14.0%) patients were SCT-eligible but did not undergo SCT. Of the 522 non-SCT NDMM patients, 252 (48.3%) patients were male.
- The most common ethnicities were White (59.0%, n=308) and Asian (31.0%, n=162).

Clinical characteristics at MM diagnosis for non-SCT RRMM patients

- The mean ± StDev age at MM diagnosis for 522 non-SCT RRMM patients was 59.2 ± 10.5 years (range 17.7 – 86.4). The median (Q1 – Q3) age at MM diagnosis was 59.9 (51.9 – 66.6) years. The mean age for these patients at first-line treatment was 59.3 ± 10.5 years (range 17.9 – 86.5). The median (Q1 – Q3) age at first-line treatment was 60.0 (52.0 – 66.6) years. The top 3 types of myeloma were IgG kappa (35.1%, n=183), IgG lambda (14.2%, n=74), and light chain alone (kappa or lambda) (14.4%, n=75). The most common stage for patients in Durie-Salmon staging system was Stage III (53.7%, n=173). A total of 113 (21.6%) patients had plasmacytoma. Bone lesions were reported in 82.6% (n=431) of patients. A total of 481 (92.1%) patients met CRAB criteria. A total of 40 (8.3%) patients had elevated calcium.
- Of the 522 non-SCT RRMM patients, 449 patients were ineligible for SCT. The mean age at MM diagnosis for these 449 patients was 60.1 ± 10.40 (range 29.1 – 86.4). The median (Q1 – Q3) age at MM diagnosis was 60.9 (53.2 – 67.3) years. IgG kappa (35.4%, n=159) was the most frequently observed type of myeloma. A high percentage of patients were in Stage III in both the staging systems; 37.4% (n=80) were classified as ISS Stage III and 50.4% (n=140) were classified as Durie-Salmon Stage III. A total of 94 (20.9%) patients had plasmacytoma. Bone lesions were present in 84.0% (n=377) of patients. A total of 415 (92.4%) patients met CRAB criteria. A total of 32 (7.7%) patients had elevated calcium.
- Of the 522 non-SCT RRMM patients, a total of 73 patients were eligible for SCT but did not undergo SCT. The mean age at MM diagnosis for these 73 patients was 53.8 ±

9.2 years (range 17.9 – 78.6), which is noticeably younger than all non-SCT RRMM patients. The median (Q1 – Q3) age at MM diagnosis was 52.0 (49.0 – 58.9) years. IgG kappa (32.9%, n=24) was the most frequently observed type of myeloma. A high percentage of patients were in Stage III in both the staging systems; 46.7% (n=21) were classified as ISS Stage III and 75.0% (n=33) were classified as Durie-Salmon Stage III. A total of 19 (26.0%) patients had plasmacytoma. Bone lesions were present in 74.0% (n=54) of patients. A total of 66 (90.4%) patients met CRAB criteria. A total of 8 (12.1%) patients had elevated calcium.

RRMM patients undergoing SCT

Patient demographics for RRMM patients undergoing SCT

- Of the 99 NDMM patients undergoing SCT, 59 (59.6%) patients were male.
- The most common ethnicities were White (46.5%, n=46) and Asian (38.4%, n=38).

Clinical characteristics at MM diagnosis for RRMM patients undergoing SCT

- The mean age at MM diagnosis for the 99 RRMM patients undergoing SCT was 50.5 ± 9.9 years (range 22.3 – 78.5). The median (Q1 – Q3) age at MM diagnosis was 50.3 (45.0 – 57.3) years. The mean age for these patients at first-line treatment was 50.6 ± 9.9 years (range 22.5 – 78.5). The median (Q1 – Q3) age at first-line treatment was 50.3 (45.2 – 57.6) years. The top 3 types of myeloma were IgG kappa (25.3%, n=25), light chain alone (kappa or lambda) (23.2%, n=23), and IgA kappa (14.1%, n=14). The most common stage for patients in ISS was Stage III (31.9%, n=22). A total of 27 (27.3%) patients had plasmacytoma. Bone lesions were reported in 77.8% (n=77) of patients. A total of 90 (90.9%) patients met CRAB criteria. A total of 3 (3.3%) patients had elevated calcium.

Comparing patient demographics and clinical characteristics of non-SCT RRMM patients with RRMM patients undergoing SCT

- The mean age at MM diagnosis and mean age at first-line treatment for non-SCT RRMM patients was higher than the RRMM patients who had SCT performed (59.2 ± 10.5 years (range 17.7 – 86.4) versus at MM diagnosis, 59.3 ± 10.5 years (range 17.9 – 86.5) versus 50.5 ± 9.9 years (range 22.3 – 78.5) at first-line treatment). The most common stage was Stage III in Durie-Salmon staging system (53.7%, n=173) for non-SCT RRMM patients

whereas for RRMM patients who had SCT performed most common stage was Stage III in ISS system (31.9%, n=22).

Clinical characteristics of RRMM patients undergoing more than one SCT

- A total of 35 RRMM patients received more than one SCT (i.e., patients undergoing any SCT). The mean age at MM diagnosis for 35 RRMM patients undergoing more than one SCT was 45.5 ± 10.4 years (range 22.3 – 62.7). The median (Q1 – Q3) age at MM diagnosis was 46.2 (37.5 – 53.8) years. The mean age for these patients at first-line treatment was 45.6 ± 10.5 years (range 22.5 – 62.7). The median (Q1 – Q3) age at first-line treatment was 46.3 (37.6 – 53.9) years. The top 3 types of myeloma were IgG kappa (20.0%, n=7), IgA kappa (11.4.%, n=4), IgA lambda (11.4.%, n=4), and light chain alone (kappa or lambda) (22.9%, n=8). The ISS system (48.6%, n=17) was used more than Durie-Salmon staging system (34.3%, n=12), and the majority of patients were in Stage III of the ISS (30.4%, n=7). A total of 11 (31.4%) patients had plasmacytoma. Bone lesions were reported in 85.7% (n=30) of patients. A total of 32 (91.4%) patients met CRAB criteria. Only 1 (3.1%) patient had elevated calcium.

Comparing patient demographics and clinical characteristics of RRMM patient undergoing more than one SCT with RRMM patients undergoing at least 1 SCT

- Patients undergoing multiple SCTs were noticeably younger at diagnosis than patients undergoing at least 1 SCT (45.5 ± 10.4 years versus 50.5 ± 9.9 years). Bone lesions were more common in patients undergoing multiple SCTs (85.7% versus 77.8%) in comparison to patients undergoing any number of SCTs.

Primary Objective – Time to next treatment in RRMM patients

- When considering TTNT from the initiation of first-line, amongst the 621 RRMM patients at risk, 599 (96.5%) had an event (i.e., initiated a next line of therapy or death) and 22 (3.5%) patients were censored. The median (Q1 – Q3) TNTT (from initiation of first-line treatment for MM) was 16.8 (7.5 – 33.3) months. In East Asia and the MESA region, the median (Q1 – Q3) TNTT were 15.9 (7.8 – 25.7) months and 15.3 (8.0 – 32.5) months, respectively.
- When considering TTNT from the initiation of second-line, amongst the 555 RRMM patients at risk, 375 (67.6%) had an event and 180 (32.4%) patients were censored. The median (Q1 – Q3) TNTT was 35.5 (12.1 – 80.0) months. In East Asia and the MESA region, the median (Q1 – Q3) TNTT were 18.0 (6.2 – 38.1) months and 19.9 (7.7 – 49.5) months, respectively.

- When considering TTNT from the initiation of third line, amongst the 171 RRMM patients at risk, 129 (75.4%) had an event and 42 (24.6%) patients were censored. The median (Q1 – Q3) TNTT was 14.5 (6.0 – 46.3) months. In East Asia and the MESA region, the median (Q1 – Q3) TNTT were 10.9 (5.6 – 19.3) months and 13.8 (4.7 – 53.9) months, respectively.
- When considering TTNT from the initiation of fourth – line, amongst the 74 RRMM patients at risk, 55 (74.3%) had an event and 19 (25.7) patients were censored. The median (Q1 – Q3) TNTT was 11.1 (5.1 – 25.1) months. In East Asia and the MESA region, the median (Q1 – Q3) TNTT were 6.2 (3.5 – 17.1) months and 13.6 (8.0 – 33.8) months, respectively. Patients in the MESA region had a longer TNTT than patients in East Asia.
- When considering TTNT from the initiation of fifth – line, amongst the 29 RRMM patients at risk, 25 (86.2%) had an event and 4 (13.8%) patients were censored. The median (Q1 – Q3) TNTT was 5.7 (3.6 – 20.3) months. In East Asia and the MESA region, the median (Q1 – Q3) TNTT were 3.7 (2.8 – 4.7) months and 8.5 (3.7 – 20.3) months, respectively.

Secondary objectives in RRMM patients

Treatment in RRMM patients

- All RRMM patients (100.0%, n=621) were given treatment at first-line. At second-line and third-line, 63 (10.1%) patients, and 9 (1.4%) patients received treatment, respectively.
- The most frequently received regimens at first-line by RRMM patients were bortezomib, cyclophosphamide, and dexamethasone (VCD) (20.5%, n=127), bortezomib and dexamethasone (VD) (13.2%, n=82), vincristine, doxorubicin, and dexamethasone (VAD) (11.4%, n=71), PAD (9.2%, n=57), and thalidomide and dexamethasone (TD) (6.9%, n=43). The most frequently used regimens at second-line by RRMM patients were VD (19.0%, n=12), bortezomib, melphalan, and prednisone (VMP) (11.1%, n=7), and VCD (9.5%, n=6).
- A total of 621 RRMM patients recorded 715 previous first-line treatments which means that a proportion of patients had a within-line switch from one regimen to another. Nonetheless, the majority of patients had only 1.0 treatment line: the mean number of previous treatment lines before RRMM diagnosis was 1.1 ± 0.4 (range 1.0 – 6.0; Q1 – Q3 1.0 – 1.0). The mean time from the end of first-line treatment to first relapse or diagnosis of refractory disease for these 621 RRMM patients was 18.8 ± 17.5 months (range 0.5 – 95.7).

- For RRMM patients who relapsed during the first-line treatment (n=122), the mean time from the end of first-line treatment to first relapse or diagnosis of refractory disease was 6.1 ± 6.0 months (range 0.7 – 35.2).
- For RRMM patients who relapsed after the first-line treatment, the mean time from the end of first-line treatment to first relapse or diagnosis of refractory disease was 21.9 ± 18.0 months (range 0.53 – 95.7).
- The mean duration of first-line treatment for 621 RRMM patients was 8.1 ± 8.1 months (range 0.03 – 78.4). The most common first-line treatment for MM in RRMM patients was VCD with 129 (20.8%) RRMM receiving this treatment. The average duration of treatment was of 5.4 ± 2.5 months (range 0.3 – 17.3).
- The mean duration of second-line treatment for 557 (89.7%) RRMM patients was 8.5 ± 9.1 months (range 0.03 – 76.9). The most common second-line treatment for MM in RRMM patients was VCD with 81 (14.5%) patients receiving this treatment. The average duration of treatment was 7.3 ± 7.0 months (range 0.1 – 51.2).
- The mean duration of third-line treatment for 171 (27.5%) RRMM patients was 9.2 ± 11.4 months (range 0.03 – 90.1). The most common third-line treatment for MM in RRMM patients was VCD with 18 (10.5%) patients receiving this treatment. The average duration of treatment was 7.2 ± 5.1 months (range 1.4 – 20.4).
- Fourth-line treatment was received by 74 (11.9%) RRMM patients. The mean duration of this line of treatment was 8.0 ± 8.3 months (range 0.03 – 45.2). The only regimen received by more than 10 patients in fourth-line was RD. A total of 14 (18.9%) RRMM patients received RD for an average duration of 9.1 ± 10.3 months (range 0.49 – 40.7).
- The mean duration of fifth-line treatment for 29 (4.7%) RRMM patients was 6.8 ± 7.9 months (range 0.03 – 35.9).

Treatment in non-SCT RRMM patients

- All 522 non-SCT RRMM patients received first-line treatment. The most common first-line treatment was VCD with 116 (22.2%) patients receiving this treatment. The average duration of treatment was 5.5 ± 2.5 months (range 0.3 – 17.3).
- A total of 467 (89.5%) non-SCT RRMM patients received second-line treatment. The most common second-line treatment for patients was VD with 74 (15.8%) patients receiving this treatment. The average duration of treatment was 4.5 ± 4.3 months (range 0.03 – 30.1).
- The third-line treatment was received by 129 (24.7%) non-SCT RRMM patients. The only regimens received by more than 10 patients in third-line were bortezomib, lenalidomide and dexamethasone (RVD) and VCD. A total of 14 (10.9%) patients received treatment with RVD. The average duration of treatment was 7.2 ± 3.6 months (range 1.0 – 14.8).

- The mean (StDev) time from relapse/refractory disease diagnosis (after first-line treatment) to first treatment post-relapse for 474 patients was 39.9 ± 174.6 days (range 1.0 – 2,693.0)
- The mean time from start of first-line treatment to initiation of the subsequent treatment for 467 patients was 669.0 ± 547.8 days (range 1.0 – 2927.0).
- Of the 522 non-SCT RRMM patients, 449 were ineligible for SCT. The most common first-line treatment was VCD with 106 (23.6%) patients receiving this treatment. The average duration of treatment was 5.5 ± 2.6 months (range 0.3 – 17.3).
- The second-line treatment was received by 402 (89.5%) non-SCT RRMM patients who were ineligible for SCT. The most common second-line treatment for non-SCT RRMM patients who were ineligible for SCT was VCD with 58 (14.4%) patients receiving this treatment. The average duration of treatment was 8.1 ± 7.9 months (range 0.3 – 51.2).
- The third-line treatment was received by 111 (24.7%) non-SCT RRMM patients who were ineligible for SCT. The regimens received by more than 10 non-SCT RRMM patients who were ineligible for SCT in third-line were RVD (n=14) and VCD (n=11). A total of 14 (12.6%) patients had third-line treatment with RVD for an average of 7.2 ± 3.6 months (range 1.02 – 14.8). The most frequent reasons for treatment change were completion of RVD treatment (42.9%, n=6).
- The mean (StDev) time from relapse/refractory disease diagnosis (after first-line treatment) to first treatment post-relapse for 406 patients was 40.0 ± 181.8 days (range 1.0 – 2,693.0).
- The mean time from start of first-line treatment to initiation of the subsequent treatment for 402 patients was 663.8 ± 566.07 days (range 1.0 – 2,927.0).
- Of the 522 non-SCT RRMM patients, 79 were eligible for SCT but did not undergo SCT. All of these 79 patients received first-line treatment. A total of 65 (89.0%) patients who were eligible for SCT but did not undergo SCT received second-line treatment. A total of 18 (24.7%) patients who were eligible for SCT but did not undergo SCT received third-line treatment.
- For both non-SCT RRMM patients (22.2%, n=116) and non-SCT RRMM patients who were ineligible for SCT (23.6%, n=106), the most common first-line treatment was VCD. The most common second-line treatment for non-SCT RRMM patients was VD (15.8%, n=74). whereas for non-SCT RRMM patients who were ineligible for SCT it was VCD (14.4%, n=58). For both non-SCT RRMM (10.9%, n=14) patients and non-SCT RRMM who were ineligible for SCT (12.6%, n=14), the most common third-line treatment was RVD.

Treatment in RRMM patients undergoing SCT

- A total of 99 RRMM patients were undergoing SCT.
- The mean time from relapse/refractory disease diagnosis (after end of first-line treatment) to first SCT in 74 RRMM patients undergoing SCT was 9.3 ± 13.0 months (range 0.03 – 76.9).
- The most common source of stem cells in patients was peripheral blood at first SCT (77.8%, n=77) and second (82.9%, n=29) SCT.
- At first SCT:
    - A total of 94 (94.9%) patients had induction regimens administered before SCT. The most commonly administered induction regimen for patients was VD with 28 (24.3%) patients receiving this induction regimen. The average duration of VD induction regimen before SCT was 3.7 ± 3.1 months (range 1.1 – 17.2).
    - Few patients had consolidation or maintenance regimens recorded in their medical file although this is most likely because phase is not routinely collected.
- The number of patients with sCR and CR after first SCT was 9 (9.1%) and 34 (34.3%) and respectively. A total of 19 (19.2%), 12 (12.1%), and 2 (2.0%) patients undergoing SCT had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 4 (4.0%), each.
- At second SCT:
    - A total of 35 (35.4%) patients underwent second SCT. The mean time from relapse/refractory disease diagnosis (after end of first-line treatment) to second SCT in 29 patients was 16.6 ± 22.8 months (range 0.03 – 87.3).
    - A total of 15 (42.9%) patients had induction regimens administered before SCT. The most commonly administered induction regimen for patients was VCD with 5 (14.3%) patients receiving this induction regimen. The average duration of this regimen was 4.8 ± 3.4 months (range 2.0 – 10.0).
- The number of patients with sCR and CR after second SCT was 2 (5.7%) and 13 (37.1%), respectively. A total of 7 (20.0%), 3 (8.6%), and 1 (2.9%) patient had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 1 (2.9%) and 2 (5.7%), respectively.

Treatment in RRMM patients who relapsed after SCT

- A total of 62 RRMM patients who relapsed after SCT received first-line treatment. At first line, the most common regimen for RRMM patients who relapsed after SCT was VAD with 15 (24.2%) patients receiving this treatment regimen. The average duration of VAD treatment regimen was 5.4 ± 4.1 months (range 0.1 – 18.0).

- A total of 59 RRMM patients who relapsed after SCT received second-line treatment. None of the second-line treatment regimens were received by more than 10 patients.
- A total 38 RRMM patients who relapsed after SCT received third-line treatment. None of the third-line treatment regimens were received by more than 10 patients.
- The mean time from SCT to first treatment after RRMM diagnosis in 29 patients was 20.9 ± 17.3 months (range 2.9 – 76.1).
- The mean time from completion of first treatment after RRMM diagnosis (post-SCT) to initiation of subsequent treatment in 43 patients was 361.6 ± 535.3 days (range 2.0 – 2,093.0).
- Out of 62 patients, 31 (50.0%) were undergoing subsequent SCTs. The mean number of SCTs per patient was 2.1 ± 0.3 (range 2.0 – 3.0). The mean time from first SCT to second SCT was 25.5 ± 24.1 months (range 3.1 – 82.4).

Relapse rate in non-SCT RRMM patients

- For non-SCT RRMM patients, the relapse-free rate at 1-year after start of first-line treatment was 77.7% (95% CI: 73.8% – 81.1%), at 2-years after start of first-line treatment was 51.1% (95% CI: 46.6% – 55.5%), and at 5-years after start of first-line treatment was 18.0% (95% CI: 14.5% – 21.7%).

OS rate in non-SCT RRMM patients

- OS was calculated on 521 non-SCT RRMM patients at risk of which 306 (58.7%) had an event (i.e., death). Overall, the median (Q1 – Q3) OS for patients was 77.1 (40.4 – 135.0) months.
- For non-SCT RRMM patients, OS rate at 2-years after start of first-line treatment was 84.3 % (95% CI: 80.8% – 87.2%) and at 5-years after start of first-line treatment was 62.4% (95% CI: 57.9% – 66.6%).

Number of relapses per patient in non-SCT RRMM patients

- A total of 457 (87.5%) non-SCT RRMM patients had a documented relapse or disease progression after first-line treatment: 318 (60.9%) patients had relapse only, 45 (8.6%) had disease progression only, and 94 (18.0%) patients had both relapse and disease progression.

Best response after start of treatment by line of treatment in non-SCT RRMM patients

- At first-line treatment, the number of non-SCT RRMM patients with a clinical best response of sCR and CR were 4 (0.8%) and 113 (21.6%) respectively. A total of 92 (17.6%), 131 (25.1%), and 20 (3.8%) patients had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 74 (14.2%) and 56 (10.7%), respectively.
- At second-line treatment, the number of patients with a clinical best response of sCR and CR was 1 (0.2%) and 66 (14.1%). A total of 106 (22.7%), 117 (25.1%), and 11 (2.4%) patients had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 47 (10.1%) and 49 (10.5%), respectively.
- At third-line treatment, none of the patients had sCR and the number of patients with a clinical best response of CR was 16 (12.4%). A total of 14 (10.9%), 21 (16.3%), and 1 (0.8%) patient had VGPR, PR, and MR, respectively. The number of patients with SD and PD were 30 (23.3%) and 21 (16.3%), respectively.

Time to first or best response by line of treatment in non-SCT RRMM patients

- Amongst the 522 non-SCT RRMM patients who received first-line treatment, 425 (81.4%) had documented clinical response (sCR or CR or VGPR or PR or MR) from first-line treatment. The median (Q1 – Q3) time to response from first-line treatment was 7.9 (4.9-18.4) months. The median (Q1 – Q3) time difference between first response and first documented relapse or disease progression, after start of first-line treatment was 11.9 (2.8 – 26.8) months.

Clinical outcomes in deceased RRMM patients

- The mean (StDev) time from MM diagnosis to death for RRMM patients (n=348) was 54.0 ± 35.1 months (range 1.2 – 261.4). The mean time from completion of first-line therapy to death for patients was 45.4 ± 35.0 months (range 0.03 – 234.3). For 231 (66.4%) patients the cause of death was MM-related.

Summary of AEs experienced by line of treatment in RRMM patients

- A total of 702 AEs was reported for 241 (38.8%) of the 621 RRMM patients and 198 (28.2%) of these AEs were related to a treatment regimen. A total of 292 SAEs were reported for 122 (19.6%) RRMM patients and 22 (3.5%) RRMM patients had 28 SAEs related to treatment regimen.

- A total of 113 life-threatening SAEs were reported for 87 (14.0%) patients and 105 SAEs resulted in prolongation of hospitalisation for 52 (8.4%) patients. A total of 260 SAEs required hospitalisation for 104 (16.7%) patients.

AEs associated with post SCT treatment regimens in RRMM patients

- A total of 17 AEs were reported for all 7 (100.0%) RRMM patients with post-SCT treatment with an IR of 5.1 events per 100 PY. The most frequently reported AEs were peripheral neuropathy (71.4%, n=5) and back pain (28.6%, n=2).

TRAEs in RRMM patients

- A total of 198 TRAEs were reported for 110 RRMM patients with an IR of 10.5 events per 100 PY. The most frequently reported TRAEs were peripheral neuropathy (21.8%, n=24), polyneuropathy (19.1%, n=21), pneumonia (16.4%, n=18), diarrhoea (9.1%, n=10), peripheral sensory neuropathy (5.5%, n=6), vomiting (5.5%, n=6), back pain (4.5%, n=5), fatigue (4.5%, n=5), febrile neutropenia (4.5%, n=5), thrombocytopenia (4.5%, n=5) and neutropenia (3.6%, n=4).
- During the 172.6 PY of VCD treatment, 21 (19.1%) RRMM patients had 25 TRAEs with an IR of 14.5 events per 100 PY. The most frequently reported TRAE was polyneuropathy (13.6%, n=15).

TRAEs in non-SCT RRMM patients

- For all regimens (PY=1,550.6), 175 TRAEs were reported for 101 non-SCT RRMM patients with an IR of 11.3 events per 100 PY. The most frequently reported TRAEs were polyneuropathy (20.8%, n= 21), peripheral neuropathy (18.8%, n=19), and pneumonia (17.8%, n=18).
- During the 136.0 PY of VCD treatment, 21 patients had 25 TRAEs for an IR of 18.4 events per 100 PY.

SAEs in RRMM patients

- A total of 292 SAEs were reported in 122 (100.0%) RRMM patients with an IR of 15.5 events per 100 PY. The most frequently reported SAEs were pneumonia (41.8%, n=51), febrile neutropenia (14.8%, n=18), cardiac failure (9.0%, n=11), pyrexia (6.6%, n=8), urinary tract infection (6.6%, n=8), respiratory failure (5.7%, n=7) and sepsis (5.7%, n=7).
- A total of 28 SAEs were reported in 22 RRMM patients with an IR of 1.5 events per 100 PY. The most frequently reported AEs were pneumonia (31.8%, n=7) and febrile

neutropenia (18.2%, n=4). During the 172.6 PY of VCD treatment, only 1 patient had 1 SAEs (bacterial arthritis) for an IR of 0.6 events per 100 PY.

SAEs in non-SCT RRMM patients

- A total of 252 SAEs were reported for 108 non-SCT RRMM patients with an IR of 16.3 events per 100 PY. The most frequently reported SAEs were pneumonia (39.8%, n=43), febrile neutropenia (13.9%, n=15), cardiac failure (10.2%, n=11), pyrexia (7.4%, n=8), urinary tract infection (7.4%, n=8), and sepsis (6.5%, n=7).

The MM-related healthcare resource use associated with each line of treatment in RRMM patients

- A total of 137 (22.1%) RRMM patients had a record of MM-related inpatient hospitalisation during first-line treatment. The median (Q1 – Q3) number of hospitalisations per patient was 2.0 (1.0 – 3.0).
- Of the 420 MM-related admissions, 332 (79.0%) were due to treatment for MM during first-line treatment. The overall median (Q1 – Q3) length of stay was 10.0 (3.0 – 19.0). Of the 420 MM-related admissions, 413 were in the general ward where RRMM patients stayed a median (Q1 – Q3) of 9.0 (3.0 – 19.0) days. Only 1 admission was recorded to a BMT Unit.
- The MM-related ER visits were reported for 2 (0.8%) RRMM patients during first-line treatment. All 168 (100%) RRMM patients during first-line treatment had outpatient visits. The median (Q1 – Q3) number of outpatient visits per patient was 4.0 (2.0 – 11.0).
- A total of 120 (21.5%) RRMM patients had a record of MM-related inpatient hospitalisation during second-line treatment. The median (Q1 – Q3) number of hospitalisations per patient was 1.0 (range 1.0 – 3.0).
- Of the 445 MM-related admissions, 330 (74.2%) were due to treatment for MM during second-line treatment. The overall median (Q1 – Q3) length of stay was less than one day. The median (Q1 – Q3) length of stay in general ward was less than one day. A total of 2 admissions were recorded to High Dependency Unit, 2 admissions were recorded for to BMT Unit and 1 to ICU.
- MM-related ER visits were reported for 2 (0.4%) RRMM patients during second-line treatment. Each patient had 1 ER visit. All 146 (100%) RRMM patients during second-line treatment had outpatient visits. The median (Q1 – Q3) number of outpatient visits per patient was 5.0 (1.0 – 14.0).
- A total of 41 (24.0%) RRMM patients had a record of MM-related inpatient hospitalisation during third-line treatment. The median (Q1 – Q3) number of hospitalisations per patient was 1.0 (1.0 – 4.0).

- Of the 149 MM-related admissions, 105 (70.5%) were due to treatment for MM during third-line treatment. The overall median length of stay was 6.0 (0.0 – 14.0) days. Of the 149 MM-related admissions, 147 were in the general ward where RRMM patients stayed a median (Q1 – Q3) of 6.0 (0.0 – 14.0) days.
- No ER visits were reported for RRMM patients during third-line treatment. A total of 70 (40.9%) RRMM patients had outpatient visits during third-line treatment. The median (Q1 – Q3) number of outpatient visits per patient was 5.0 (2.0 – 12.0).

MM-related healthcare resource use: procedure in RRMM patients

- CT scans were performed for 158 of 621 RRMM patients. The mean (StDev) number of CT scans performed per patient was 1.8 ± 1.2 (range 1.0 – 7.0).
- PET scans were performed for 63 of 621 RRMM patients. The mean number of PET scans performed per patient was 1.3 ± 1.2 (range 1.0 – 9.0).
- Biopsies were performed for 29 of 621 RRMM patients. The mean number of biopsies performed per patient was 1.7 ± 0.6 (range 1.0 – 3.0).
- Skeletal surveys were performed for 419 of 621 RRMM patients. The mean number of skeletal surveys performed per patient was 2.1 ± 3.6 (range 1.0 – 36.0).
- Karyotypes were performed for 127 of 621 RRMM patients. The mean number of karyotypes performed per patient was 1.2 ± 0.4 (range 1.0 – 3.0).
- FISH procedure was recorded for 106 of 621 RRMM patients. The mean number of FISH procedure performed per patient was 1.0 ± 0.2 (range 1.0 – 2.0).
- Of the 621 RRMM patients, 62 (10.0%) received G-CSF. The mean duration of GSF treatment (n=62) was 0.8 ± 0.9 months (range 0.0 – 5.0).
- Of the 621 RRMM patients, 205 patients had blood transfusions. The mean number of blood transfusions per patient was 6.1 ± 12.0 (range 1.0 – 79.0).
- The mean number of treatment regimens per patient (n=621) was 3.0 ± 1.7 (range 1.0 – 12.0).

Discussion:

High-quality, population-based studies in real-world examining the care, quality of life and survival of MM patients in its full complexity are rare, often limited in size and mostly concern developed regions such as North American, Western European, and Japan (1-5). Specifically, for patients in EM countries, there is a clear paucity of adequate real-world data on treatment pathways, clinical outcomes, and HRU among patients with MM (6-8), particularly for those patients who relapse or are refractory to frontline therapy.

The rational of INTEGRATE was to collect information in EM countries on the clinical characteristics of MM and real-world outcomes following treatment, and the factors that could influence treatment decisions across multiple lines of therapy to support clinical practice and payer decisions on treatment funding.

Baseline patient characteristics

Study population

Participating countries were chosen to represent a diverse sample of EM countries, and the aim was that in each participating country, a range and distribution of care settings typical of that country (e.g., hospitals, cancer institutes and academic medical centres) be selected.

Patient demographics

In the INTEGRATE study, the male:female ratio was balanced in the overall NDMM (50.6% males) and RRMM (50.1% males) groups. However, the distribution of sexes was uneven at each country level (for example, Russia had only 36.8% males). When stratified by SCT, status, the proportions of males were slightly higher in the SCT subgroups (NDMM: SCT – 59.6% and non SCT – 48.4%; RRMM: SCT – 59.6% and non SCT – 48.3%).

The proportion of males reported in the INTEGRATE study is in line with epidemiological expectations (9) and that reported in other real-world studies (2-4), as males are at a higher risk of developing myeloma. However, the proportion of males reported in those real-world studies was significantly higher (56-61%) than the current study (2-4). The higher proportion of males in the SCT subgroup is in line with other real-world studies, where a higher proportion of males were reported among ASCT patients (1).

The median (Q1 – Q3) age at MM diagnosis for the NDMM group was 59.5 years (52.0 – 67.2) and for RRMM patients was 58.1 years (50.2 – 65.8). Overall, patients in the INTEGRATE study were relatively younger than patients in other real world studies reported from Europe and EM countries (1, 3, 4) and in comparison to patients in other real-world studies in EM countries (8, 10, 11). The median age of patients with NDMM was 61 years (IQR 53-69) in the Haemato-Oncology Latin America (HOLA) Observational study (8), and 59 years in a Chinese retrospective study (10). The median age in the Asian Myeloma Network study was 62 years (range 19-106), which is higher than in the INTEGRATE. This difference could be because the year of diagnosis was noticeably earlier being between 1986 and 2011 (11).

In INTEGRATE, non-SCT NDMM subgroup at MM diagnosis was older at 62.4 ± 11.1 years in comparison to all NDMM patients. Non-SCT RRMM patients were also older than all RRMM

patients at 59.2 ± 10.5 years. RRMM patients undergoing SCT were younger with a median age at MM diagnosis of 50.5 ± 9.9 years. This was also observed in other studies (7) and is expected as the European Society of Medical Oncology (ESMO) guidelines have consistently recommended ASCT (and novel chemotherapy) for patients aged <65 years or fit patients <70 years in good clinical condition (12-18).

The relatively younger age of INTEGRATE patients should be considered when interpreting clinical outcomes (19, 20).

Comorbidities

The proportions of NDMM and RRMM patients with comorbidities were close to the ones of other real-world studies based in EM countries (8) but slightly lower than for studies based in Europe (21).

Clinical characteristics

Clinical Practice Guidelines published by the National Comprehensive Cancer Network (NCCN) detail the medical history, physical examination, and laboratory studies that should be carried out at initial MM diagnosis (22-24). The initial diagnostic workup includes calcium/albumin, beta-2-microglobulin, FLC assay, SPEP, UPEP, skeletal survey, FISH, etc. and further investigations that could be carried in some circumstances (MRI, CT scan, PET/CT scan, tissue biopsy etc.) to help better characterise the clinical presentation of MM. These parameters were collected as part of INTEGRATE to describe the baseline characteristics of NDMM and RRMM patients but also to put into perspective reported depth of response to therapy. Apart from variables related to CRAB, which were part of the MDS, there were issues with missing data with many of these parameters because standard of care medical records routinely have lost or incomplete data (25).

Of interest, the proportion of reported gene mutations at diagnosis for NDMM patients varied greatly across countries, ranging from 34.6% of patients having a FISH analysis with a gene mutation in China to 94.1% of patients having a FISH analysis in Saudi Arabia (Argentina had 12.5% [n=1] of patients with a FISH analysis with a gene mutation and Taiwan had 100.0% [n=1] of patients having a FISH analysis with a gene mutation but they also only had few patients with data).

ISS Stage III was the most common stage at MM diagnosis for INTEGRATE patients and for several other real-world studies, albeit with a larger proportion of patients in Stage III (3, 4, 8). Lin et al (2014) described how Chinese MM patients had much more advanced-stage disease at

diagnosis compared with Western MM patients and this was also seen in INTEGRATE when comparing patients from China to other participating countries (26).

Clinical characteristics for NDMM and RRMM patients by SCT status did not noticeably vary.

The recorded clinical characteristics of INTEGRATE patients show that they have considerable MM-related organ damage at diagnosis, so initiatives facilitating earlier diagnosis may be considered in EM countries.

Stem cell transplantation

ASCT is standard of care in most countries in patients who are fit (i.e., of good performance status, and generally younger than 70 years) (27).

In the NDMM group, the reason for ineligibility for SCT was advanced age for 27.7% of patients. This was the main known reason across all countries. This was supported by the higher median age of non-SCT NDMM patients in comparison to NDMM patients undergoing SCT. Of the 12.3% of NDMM patients who were considered eligible for SCT but did not have SCT performed, 12.4% of patients did not undertake transplant due to chemo-resistant disease and 14.0% patients refused to undergo transplant. Advanced age was also the primary reason for RRMM patients (overall and at country-level) not being eligible for SCT (24.1%), and this was corroborated by the higher median age of non-SCT NDMM patients observed in INTEGRATE. The primary reason for RRMM patients not undergoing SCT despite being eligible was chemo-resistant to disease (16.7%). A proportion of 68.1% of RRMM patients were considered eligible for SCT at relapse or refractory diagnosis, although 31.9% of these patients did not undergo SCT.

In INTEGRATE, 31.7% of NDMM patients and 20.3% of RRMM patients had SCT performed at first MM diagnosis, although these proportions varied widely at country-level (from 9.0% in Russia to 66.7% in Saudi Arabia for NDMM patients; from 8.3% in China to 38.5% in Saudi Arabia for RRMM patients).

The proportion of patients undergoing SCT in INTEGRATE is in line with results from the Europe, Middle East and Africa Multiple Myeloma Observational Study (EMMOS) (7) and HOLA (8), although approximately 10% higher than in a large multi-centre study in Central and Eastern European countries (6). Coriu et al (2018) acknowledged that although SCT is considered a highly effective and cost-efficient procedure, 45% of eligible patients did not receive it because of logistical challenges (6).

Primary objective: TTNT

The central objective of INTEGRATE was to describe time TTNT at each line of therapy in patients receiving frontline treatment for NDMM and RRMM patients.

When considering TTNT from the initiation of first-line treatment, amongst the 1,510 NDMM patients at risk, 952 (63.0%) patients had an event (i.e., initiated a next line of therapy or death) and 558 (37.0%) patients were censored. The median (Q1 – Q3) TTNT (from initiation of first-line treatment for MM) was 39.5 (15.1 – 96.9) months overall. TTNT from initiation of first-line treatment ranged widely across countries, almost tripling from the shortest TTNT to the longest: the median TTNT was 25.2 (7.0 – 46.2) months in Taiwan, 27.6 (11.5 – 45.3) months in the Republic of South Africa, 30.8 (12.0 – 68.3) months in the Republic of Korea, 37.5 (9.0 – 71.5) months in Argentina, 44.1 (18.4 – NR) in Russia, 46.3 (25.0 – 81.7) months in China; 57.0 (18.5 – NR) months in Turkey, and 71.0 (23.3 – NR) months in Saudi Arabia. Taiwan (n=91) and Saudi Arabia (n=48) had wider variation in results but this could also be because they were the countries with the smallest number of patients for this analysis in INTEGRATE.

The TTNT for NDMM patients decreased progressively in subsequent lines of treatment. When considering TTNT from initiation of second-line treatment, the median (Q1 – Q3) TTNT was 33.9 (11.5 – 74.5) months. The median TTNT from initiation of third-, fourth- and fifth-line treatments were 20.9 (7.9 – 46.3) months, 11.2 (4.9 – 19.2) months, and 7.1 (3.8 – 22.1) months, respectively. Comparing TTNT across lines of treatment, the further along a patient was on treatment, the shorter was the TTNT. Beyond the possibility that patients became more and more treatment resistant with each treatment line, TTNT estimates in later lines could have been skewed by the smaller number of patients included in the analysis. Of note, there were some discrepancies in country-level TTNT results in comparison to overall data. Results from Russia showed a noticeably longer TTNT in second-line treatment in comparison to first-line (65.6 months versus 44.4 months); patients in Saudi Arabia and Turkey had a shorter TTNT for second line in comparison to third line (22.4 months versus 23.5 months, and 37.6 months versus 40.4 months respectively). Discrepancies between the overall result and country-level results could be explained by missing treatment regimens in certain patients, or the small number of patients in the analysis.

When considering TTNT from the initiation of first-line, amongst the 621 RRMM patients at risk, 599 (96.5%) had an event and 22 (3.5%) patients were censored. The median (Q1 – Q3) TNTT was 16.8 (7.5 – 33.3) months overall. At country-level, the TTNT from initiation of first-line treatment varied minimally. From shortest to longest, the median TTNT was 13.2 (8.0 – 31.5) months in the Republic of South Africa, 14.1 (5.3 – 22.5) months in Taiwan, 14.6 (8.7 – 22.5) months in China, 15.4 (7.2 – 33.0) months in Turkey, 15.8 (11.8 – 31.3) months in Saudi Arabia, 17.4 (10.4 – 29.0) months in the Republic of Korea, and 20.2 (7.4 – 41.2) months in

Russia. The median TTNT from the initiation of first – line in Argentina was 5.4 (3.7 – 9.1) months but included only 8 patients in the analysis and thus should only be considered as an indication of what could be a true TTNT in a larger sample.

The median (Q1 – Q3) TNTT from the initiation of second line was double that of the first-line TTNT with 35.5 (12.1 – 80.0) months. Potential explanations for this notable increase in second-line TTNT in RRMM patients could be because of the timing of INTEGRATE, with patients being less likely to have received bortezomib (which improves TTNT in comparison to more traditional chemotherapy treatments (28)) in first-line in comparison to second- and third-line treatment due to its launch date on the market. Bortezomib was included in the ESMO guidelines from 2009 onwards (12-18). It could also be linked to the characteristics of the RRMM patient group, which by definition would have relapsed or been diagnosed as refractory after the first-line treatment. The median TTNT from initiation of third-, fourth and fifth-line treatments in RRMM patients were 14.5 (6.0 – 46.3) months, 11.1 (5.1 – 25.1) months and 5.7 (3.6 – 20.3) months, respectively.

In comparison in a large US EMR-based real-world study focusing on RRMM patients receiving their first-line treatment between 2011-2017, the median TTNT was 5.7 months from first-line treatment. It was 9.2 months from second-line treatment, and thereafter reduced with each treatment being 6.9 from third-line treatment, 5.7 months from fourth-line treatment, and 3.7 months from fifth-line treatment (2). When analysing only chart records, Bruno and colleagues (2020) reported that the median TTNT ranged from a maximum of 14.3 months (from first to second-line treatments) to a minimum of 3.9 months (from fourth- to fifth-line treatments) (2). The median times from second- to third-line, third- to fourth-line, and fifth- to sixth-line treatments were 10.0 months, 6.9 months, and 4.1 months, respectively. In comparison to INTEGRATE's RRMM group, the TTNT across lines of treatment were closer to the ones from the chart review, which may illustrate the impact of the methodology (EMR-based versus chart review) of the study on the results. The notable increase in TTNT from second-line treatment was also replicated in the US-based study (2).

In the multi-centre registry study in Finland, TTNT for first line for patients taking what the authors referred as conventional treatment (i.e., not novel treatments) was 7.8 (95% CI: 6 – 18.8) months, for patients receiving novel treatments (lenalidomide, thalidomide, bortezomib and/or pomalidomide), this was 12.6 (95% CI: 10.2 – 15.8) months, and for patients receiving novel treatments and undergoing transplant, this was 33.9 (95% CI: 27.8 – NR) months (1). In comparison to INTEGRATE, where TTNT data were not subdivided by regimen or SCT status, the estimates match most closely those of patients who received novel treatment and underwent SCT in the Remes et al study (1).

It is difficult to determine which aspect of the analysis had a bigger impact on the dissimilar INTEGRATE TTNT results in comparison to other real-world studies. Undoubtedly, the choice of and access to regimen will have an impact and this is discussed in more detail below. Additionally, 'healthier' baseline characteristics could positively impact TTNT. As already described in the patient demographics and patient clinical characteristics section of the discussion, INTEGRATE patients were indeed younger than in other studies, recorded fewer comorbidities and were relatively less likely to be in ISS Stage III than studies in Europe and the US. Although there is strong evidence that SCT prolongs TTNT at least in the first few lines of treatment (6, 7), TTNT result inconsistencies cannot be explained by the difference in SCT utilisation amongst patients as these were similar across studies compared here.

Lastly, it must be considered that TTNT is not without limitations and does not always accurately reflect treatment effectiveness since the reasons for starting a new therapy are not systematically related to disease progression and may vary between different centres. It could be that patients with shorter TTNT have more aggressive or fast progressing disease, or it would be that patients have just simply switched to a novel treatment to follow a change in clinical practice.

Secondary objectives

Treatment patterns

The mean duration of first-line treatment for NDMM patients was 10.1 ± 12.7 months. The most common first-line treatment was VCD with 18.3% of patients receiving this treatment. Less than half of (42.8%) of NDMM patients had a second-line treatment. This treatment lasted on average 9.7 ± 10.9 months and the most common second-line treatment was VD, received by 20.4% of patients. Third-, fourth- and fifth-line treatment were received by 15.2%, 5.3% and 1.4% of NDMM patients, respectively. The median treatment duration decreased from 8.7 ± 9.1 months, to 7.9 ± 10.0 months and 4.9 ± 4.7 months across the 3 lines of treatment. The most common treatment was RD in all 3 lines.

Non-SCT NDMM patients had relatively shorter treatment lines in comparison to all NDMM patients and in contrast to all NDMM patients, VD was the most common treatment in first-line (17.2%) for non-SCT NDMM patients instead of VCD, but the most common treatments in subsequent treatment lines were similar independent of SCT status. No notable differences in treatment duration and treatment choice could be seen when comparing non-SCT NDMM patients according to their eligibility for SCT. Although, exemptions are possible, possible reasons for treatment change include completing planned treatment or disease progression. Those that stopped due to completion of planned treatment were most likely to have responded

(and thus would have a short duration). However, those that stopped due to disease progression did not respond (and would have a longer duration).

The majority of NDMM patients undergoing SCT had induction regimens administered before their first SCT, and the most commonly used regimen was PAD (16.1% patients). About 16.7% patients had a second SCT, of whom 47.5% had an induction regimen and the most common induction regimen was VCD (21.3%).

Little data was collected on consolidation and maintenance regimens after SCT, regardless of whether it was the first or second SCT, although this is more likely because of phase data not being recorded in medical files rather than these regimens not been administered.

All 621 RRMM patients recorded 715 previous first-line treatments which means that a proportion of patients had a within-line switch from one regimen to another. At second-, third-, fourth- and fifth-line, 89.7%, 27.5% 11.9% and 4.7% of patients received chemotherapy, respectively. The mean duration of first-line treatment was 8.1 ± 8.1 months. The mean duration of second-line treatment was 8.5 ± 9.1 months, and for third-line treatment, it was 9.2 ± 11.4 months. VCD was the most common across the first 3 lines of treatment with 20.8%, 14.5% and 10.5% of patients receiving this regimen in first-, second- and third-line treatment, respectively. The mean duration of fourth-line treatment was 8.0 ± 8.3 months, and of fifth-line treatment was 6.8 ± 7.9 months.

For RRMM patients who relapsed during the first-line treatment, the mean time from the end of first-line treatment to first relapse or diagnosis of refractory disease was 6.1 ± 6.0 months.

Non-SCT RRMM patients had relatively shorter treatment duration across lines of treatment when compared to all RRMM patients. The most common regimens in each line of treatment differed slightly. The most common first-line treatment was VCD (22.2%) as in all RRMM patients, however, in the second-line more patients received VD (15.8%) in comparison to VCD for all RRMM patients.

No noteworthy differences were seen when comparing treatment duration and regimen use for non-SCT RRMM patients according to their SCT eligibility status.

Following relapse or refractory diagnosis after first-line treatment in non-SCT patients, the mean time to the first treatment post-relapse was approximately 1.3 ± 5.8 months.

The majority of RRMM patients (94.9%) undergoing a first SCT had an induction regimen and was most commonly VD with 24.3% of patients receiving this induction regimen. The average duration of VD induction regimen before SCT was 3.7 ± 3.1 months (range 1.1 – 17.2). A

proportion of 35.4% of RRMM patients underwent second SCT. Less than half (42.9%) of these patients had an induction regimen, and most received VCD (14.3%) with an average duration of this regimen of 4.8 ± 3.4 months.

The most common first-line regimen for RRMM patients who relapsed after SCT was VAD (24.2%). It was received for a median duration of 5.4 ± 4.1 months.

The proportion of NDMM and RRMM patients receiving a second-, third-, fourth- and fifth-line treatment is in line with what has been observed in other studies albeit with slightly lesser patients reaching the next lines of treatments (2, 3, 6, 29).

There are a number of reasons why an increasingly small proportion of patients reach later lines of treatment. Beyond frailty and loss to follow-up, another hypothesis is that in non-reimbursed markets, out of pocket treatments translate to cheaper drugs being used first, and as patients progress, the cost for more expensive treatment becomes prohibitive.

In line with other observational studies, there was a wide selection of treatment patterns in clinical practice, with specific regimens rarely being used by over 22% of patients, and many categorised in the 'Other' regimens. However, with bortezomib-based regimens being almost always the most used regimen in the first and second lines, INTEGRATE reflects a common treatment selection pattern in clinical trials and real-world clinical practice alike (1, 4, 6, 7, 28, 30). In INTEGRATE, and other real-world studies, lenalidomide-based regimens were preferred as third-, fourth- and fifth-line treatment (2, 3, 6).

In NDMM patients, the most common reason for treatment change after first-line was the completion of the treatment. For RRMM patients, the common reasons for treatment after first-line was the completion of the treatment and because of disease progression.

Interestingly, there were several examples of NDMM patients receiving regimens for over 2 years suggesting that those regimens can be tolerated for long durations and that there was no disease progression, which is a reason for treatment discontinuation. For example, PAD was received up to 23.6 months; bortezomib was received up to 46.2 months (which is unexpected); MP was received up to 49.7 months; KR was received up to 60.8 months; Rd was received up to 62.2 months; lenalidomide was received up to 67.3 month (probably maintenance); TP was received up to 77.0 months; RD was received up to 78.0 months; VD was received up to 91.0 months; and TD was received up to 95.4 months.

Relapse rate

The majority of patients with multiple myeloma experience numerous relapses of their disease.

For non-SCT NDMM patients, the relapse-free rates at 1-year after start of first-line treatment was 88.4 % (95% CI: 86.1% – 90.3%). Minimal differences were seen between ineligible for SCT and non-SCT patients. Patients eligible but not undergoing SCT had a better outcome in comparison to non-SCT patients overall.

For NDMM patients undergoing SCT, relapse-free rate at 1-year after start of first-line treatment was 94.2 % (95% CI: 91.7% – 96.0%). The positive impact of SCTs on relapse rates is mostly seen in the early years of the disease.

For non-SCT RRMM patients, the relapse-free rate at 1-year after start of first-line treatment was 77.7% (95% CI: 73.8 % – 81.1%). It is expected to have significantly less patients with second and third relapses because patients die or are lost to follow-up over time. This may make the results less statistically robust.

Overall survival

The median (Q1 – Q3) OS for non – SCT NDMM patients was 85.9 (38.7 – NR) months. In comparison, the median (Q1 – Q3) OS for NDMM patients undergoing SCT was 114.1 (55.7 – NR) months. In non – SCT RRMM patients, the median (Q1 – Q3) OS for patients was 77.1 (40.4 – 135.0) months. In RRMM patients undergoing SCT, the median (Q1 – Q3) OS for patients was 108.8 (49.6 – NR) months. Both the positive impact of SCT in NDMM patients, and the worse prognosis for RRMM patients can be seen in these results. In general, INTEGRATE NDMM and RRMM patients had a better OS (from first-line treatment) than patients in the HOLA where the median OS following first-line initiation was 79.3 months (95% CI: 77 – NR) in ASCT patients, and 52.8 months (95% CI: 46.3 – 68.6) in non-ASCT patients (8). Other real-world studies had lower estimates for OS in comparison to INTEGRATE (2, 26). RRMM patients receiving bortezomib in China had a median overall OS of 475 days (approximately 15.8 months) (26). All treatments combined, the median real-world OS from first-line treatment was 48.2 (95% CI: 39.7 – 57.7) months in RRMM US-based patients (2). These differences could be due to the younger age and 'healthier' clinical characteristics of INTEGRATE patients, selection bias due to INTEGRATE's MDS, or a difference of care.

Best response

At first-line treatment, the proportion of non-SCT NDMM patients with a clinical best response of sCR and CR was 1.0% and 19.8%, respectively. A proportion of 19.6%, 24.8%, 2.7% of

patients had VGPR, PR, and MR, respectively. The proportion of non-SCT NDMM patients with SD and PD was 13.8% and 6.8%, respectively. At second-line, these proportions were marginally the same, although marginally worse at third-line.

At first-line treatment, the proportion of NDMM patients undergoing SCT with a clinical best response of sCR and CR was 3.1% and 30.5%, respectively. A proportion 22.8%, 28.8%, and 0.8% of patients had VGPR, PR, and MR, respectively. The proportion of non-SCT NDMM patients with SD and PD was 4.6% and 0.6%, respectively. In line with other findings in INTEGRATE, these response rates were noticeably better than in non-SCT NDMM patients. There was still a slight decline in best responses, with second- and third-line rates worse than at first-line.

Response in INTEGRATE was determined by the treatment physician, and as data was collected respectively, it is not known whether laboratory tests were formally carried out and whether response evaluation followed a pre-defined standard.

It seems that INTEGRATE had better overall response rates than these 2 other real-world studies in EM countries (6, 8). Apart from INTEGRATE having generally 'healthier' patients, this could be due to more patients in INTEGRATE receiving bortezomib-based treatments in early lines. Findings from EMMOS showed that in their SCT group, the best overall response rate (ORR) at any time during frontline therapy was over 85% for patients receiving bortezomib and/or thalidomide/lenalidomide, including over or equal to 50% rates of VGPR or better (7). The ORR for patients receiving other therapies was 71% and the VGPR or better rate was 29%. In comparison, in the INTEGRATE NDMM group undergoing SCT, for all regimens combined, the ORR was 86.0% (sCR, CR, VGPR, PR and MR) and the proportion with VGPR or better was 56.4%. In the non-SCT population, the ORR was 80%, with 40% of the patients achieving a VGPR or better. For patients treated with a thalidomide/lenalidomide-based regimen without bortezomib, the ORR and VGPR or better rate was 64% and 24%, respectively. In those patients receiving other combinations, the ORR was 51%, with only 10% achieving a VGPR or better. In comparison, in INTEGRATE, in the non-SCT NDMM group for all regimens combined, the ORR was 67.9% VGPR or better represented 40.4% of responses.

Results in INTEGRATE showed that SCT was associated with best response rates, and this was also reported in other real-world studies (3, 8).

Duration and time to response

Considering only first-line treatment received by more than 10 NDMM patients as an example, patients receiving regimens without bortezomib, lenalidomide, nor thalidomide tended to have a shorter mean treatment duration than patients receiving regimens with bortezomib,

lenalidomide, or thalidomide. The mean treatment durations for high-dose cyclophosphamide, melphalan (Alkeran), VAD and MP were 0.6 ± 1.3 months, 3.6 ± 3.9 months, 3.7 ± 2.7 months and 9.5 ± 11.3 months, respectively. On the other hand, for regimens including bortezomib, lenalidomide or thalidomide, the regimens and mean treatment durations in months were MPR (2.8 ± 2.9), bortezomib, doxorubicin and dexamethasone (4.1 ± 3.4), CTD (4.8 ± 4.8), VTD (5.3 ± 5.4), VCD (5.4 ± 2.8), VD (5.4 ± 6.6), bortezomib (6.8 ± 8.3), TD (7.1 ± 11.9), VMP (8.9 ± 7.3), MPT (9.5 ± 11.3), RVD (10.1 ± 12.7), RD (15.7 ± 19.0), TP (16.0 ± 19.3), and lenalidomide (22.2 ± 16.1). The observed duration of treatments in first-line in INTEGRATE for both NDMM and RRMM patients was in line with those reported in other studies (2, 4, 6).

Adverse events

Adverse events in INTEGRATE were assessed by severity, by line of treatment and whether they were related to treatments (either recorded as related or co-occurring). There are challenges associated with collecting AE data retrospectively, and it is expected that such information will be incomplete or missing. For example, nausea is a common and expected AE that many sites would not formally record in medical records. Therefore, differences observed across countries may be a reflection of recording practices rather than actual treatment practices. Nonetheless, SAEs are expected to be more accurately collected than non-serious AEs since they often require hospitalisation.

Although the types of the most common AEs and TRAEs reported in INTEGRATE match those in other studies, the proportion of patients affected is noticeably lower than what is usually reported in the literature on MM (2, 26). According to a recent review, the most common comorbidities and toxicities at first line were peripheral neuropathy (all grades, 45% of patients), anaemia (23%), neutropenia (22%) and thrombocytopenia (15%) (3).

Healthcare utilisation

Resource use in INTEGRATE was addressed in terms of hospital care (i.e., inpatient hospitalisations, emergency visits, and outpatient visits), home health care visits, procedures (such as CT, PET, biopsies, skeletal surveys, karyotypes, FISH etc.) and treatments (i.e., G-CSF or other high-cost medications).

It is expected that patients will not undergo all listed imaging techniques during their diagnosis and treatment, and that the choice of procedures gives an indication of the standard of care available in their treatment centre. For example, it is noteworthy that none of the 352 patients in Russia had any PET scans reported. They were indeed performed for 223 of 1,511 NDMM patients (14.7%), and for 63 of 621 RRMM patients (10.1%). However, Russia was the country with the highest proportion of patients using skeletal surveys (354 out of 387 patients, 91.5%).

Overall, they were performed for 948 of 1,511 NDMM patients (62.7%), with a mean number of skeletal surveys performed per patient of 1.7 ± 2.7, and for 419 of 621 RRMM patients (67.5%), with a mean number of surveys performed per patient of 2.1 ± 3.6. The country with the smallest proportion of patients with skeletal surveys, Turkey, on the other hand, had a higher proportion of patients using CT scans (158 out of 348 patients, 45.45%) in comparison to the overall NDMM group (478 of 1,511 patients, 31.6%). For comparison, in a Central and Eastern European study (6), the imaging system usually used for staging was X-rays in 79%, CT in 32%, MRIs in 24%, bone scintigraphy in 5%, and PET in 3% of their participating centres.

FISH results were recorded for 342 of 1,511 NDMM patients (22.6%), and 106 of 621 RRMM patients (17.1%). Interestingly, patients in the Republic of Korea (57.1%) and in the Republic of South Africa (37.7%) had noticeably more FISH analyses recorded at first-line in comparison to other countries: Taiwan (1.3%), Turkey (3.5%), Russia (4.2%), Argentina (4.2%) China (14.3%), and Saudi Arabia (14.3%). The mean number of UPEPs per patient was 1.6 ± 2.1 in all NDMM patients, and 1.9 ±1.8 in all RRMM patients, and varied greatly across countries. As these specific tests cannot be replaced by other diagnostic tests as seen above for imaging, the differences at country-level could be due to standard of care variations (even though those tests are recommended by the NCCN) and costs. These tests may not have been considered a priority if choices were to be made. Other reasons include these tests not being readily available in certain sites or better record keeping in Taiwan.

Study limitations

Given the retrospective, observational nature of INTEGRATE, all the results should be interpreted whilst considering that the physician's assessments recorded in medical charts were based on their usual practice and not necessarily on conventionally defined criteria (as is the case in randomized clinical trials). Missing information cannot exclude absence of events, treatments, etc. Low patient numbers in further treatment lines due to deficiencies in the follow-up data limit the generalisability of the findings for these later lines of treatment. Caution should be used in the interpretation of findings by regimen use only, as it does not take into account the intentions underlying the treatment choices. Other limitations include not assessing progression-free survival and not assessing resource use for AEs or SCTs. These factors do not diminish the usefulness of the data but merely clarify the parameters of applicability.

Conclusion:

This study has provided a large body of information that enables researchers to better understand how diagnostic practices and treatments are utilised across countries in the emerging market region for both NDMM and RRMM patients. Treatment pathways are described in relation to clinical outcomes, adverse events and healthcare resource use. The reliability of INTEGRATE

is supported by the baseline demographic data and clinical characteristics of the study cohort, which were as expected for a MM population. These retrospective real-world data highlight the large diversity of treatments used to manage MM in normal practice. Undergoing SCT was further established as having a positive impact on several clinical outcomes. The findings of this study provide a rich source of information, creating a real-world evidence-base, including TTNT data observed in NDMM and RRMM patients by line of treatment across 8 EM countries, that will inform how best to meet the future needs of this patient group.

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