How to address real-world challenges in RR Multiple Myeloma

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HUSalamanca

RR: Relapsed/Refractory; MM: Multiple Myeloma
Conflict of Interest

• Honoraria from lectures and participation in advisory boards: janssen, Celgene, amgen, takeda, GSK, EDO, Pharmamar, Adaptive
MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma.
Treatment intentions derived from evidence from RCTs may not reflect what is possible in real-life practice

- Clinical trials suggest that patients benefit from treatment at later stages, however, in reality, few patients reach fourth and fifth lines of treatment
- Understanding the reasons for discontinuation of treatment can provide an insight into patient outcomes and treatment decisions

RCT, randomised clinical trials.
Main objectives for the treatment of RRMM patients

- Induces deep, long-lasting responses
- Well-tolerated
- Minimal impact on patient lifestyle and healthcare resources

RRMM: relapsed/refractory multiple myeloma.
Factors influencing the decision in order to make the right choice for RRMM patients

Type of relapse

Efficacy and toxicity of the previous therapies

Further options

RRMM: relapsed/refractory multiple myeloma.
Relapse/Refractory MM patients
ESMO guidelines 2017

First relapse after IMiD-based induction
- Doublets: Kd / Vd
- Triplets based on Bortezomib: DaraVD or PanoVD or EloVD or VCD

First relapse after Bortezomib-based induction
- Triplets based on Rd: DaraRd or KRd or IxaRd or EloRd

At second or subsequent relapse
- Pomalidomide-Dex (as a backbone)
  + Cyclo or Ixa or Bort or Dara or Elo
- Daratumumab (single agent or combination)
- Clinical trial

Main challenges
- The selection of the rescue therapy is mainly influenced by the first line of therapy
- The first line of therapy is rapidly evolving towards new standards of care
- Treatment recommendations vary internationally

IMiD: Immunomodulatory drug; Kd: Carfilzomib and dexamethasone; Vd: Bortezomib and dexamethasone; DaraVD: Daratumumab, bortezomib and dexamethasone; PanoVd: Panobinostat, bortezomib and dexamethasone; EloVD: Elotuzumab, bortezomib and dexamethasone; Rd: Lenalidomide and dexamethasone; DaraRd: Daratumumab, lenalidomide and dexamethasone; KRd: Carfilzomib, lenalidomide and dexamethasone; IxaRd: Ixazomib, lenalidomide and dexamethasone; EloRd: Elotuzumab, lenalidomide and dexamethasone

Which patients do they fit today in the ESMO guidelines 2017?

1st line

- Bortezomib-based combinations
- Exposed or not to lenalidomide but no progressing under lenalidomide therapy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>POLLUX DaraRd vs Rd</th>
<th>ASPIRE KRd vs Rd</th>
<th>ELOQUENT-2 ERd vs Rd</th>
<th>TOURMALINE-MM1 IRd vs Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.44 (0.35–0.55) 44.5 m vs 17.5 m</td>
<td>0.670 (0.558–0.803) 26.3 m vs 17.6 m</td>
<td>0.71 (0.59–0.86) 19.4 m vs 14.9 m</td>
<td>0.74 (0.59–0.94) 20.6 m vs. 14.7 m</td>
</tr>
<tr>
<td>ORR, %</td>
<td>93</td>
<td>87</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>≥ CR, %</td>
<td>57 (MRDneg 30%)</td>
<td>32</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>DOR, months</td>
<td>NE</td>
<td>28.6</td>
<td>21.2</td>
<td>20.5</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.63 (0.42–0.95) 48 m vs 40 m</td>
<td>0.79 (0.63–0.99) 43.7 m vs 39.6 m</td>
<td>0.78 (0.63–0.96)</td>
<td>NE</td>
</tr>
</tbody>
</table>

Rd: Lenalidomide and dexamethasone; DaraRd: Daratumumab, lenalidomide and dexamethasone; KRd: Carfilzomib, lenalidomide and dexamethasone; IxaRd: Ixazomib, lenalidomide and dexamethasone; EloRd: Elotuzumab, lenalidomide and dexamethasone. PFS: Progression free survival; HR: Hazard ratio; ORR: Overall response rate; CR: Complete response; DOR: Duration of treatment; OS: Overall Survival; CI: Confidence interval; MRDneg: Minimal residual disease; NE: Non-estimated.

Carfilzomib + lenalidomide and dexamethasone vs lenalidomide and dexamethasone in RRMM: ASPIRE

KRd vs Rd: ORR 87% vs 66.7%; ≥CR 32% vs 9%

PFS

OS

KRd in first relapse resulted in median PFS of 29 months

Rd: Lenalidomide and dexamethasone; KRd: Carfilzomib, lenalidomide and dexamethasone; CR: Complete response; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence interval; PFS: Progression free survival

Siegel D et al. JCO 2017

Stewart K et al. NEJM 2015
Daratumumab + lenalidomide and dexamethasone vs lenalidomide and dexamethasone in RRMM: POLLUX 3-year follow-up

DRd vs Rd: ORR 93% vs 76%; ≥CR 57% vs 23%. MRD neg rate: 30% vs 5%

Median follow-up: 44.3 months
D-Rd significantly prolonged PFS vs Rd in the ITT population (median: 44.5 months vs 17.5 months; HR, 0.44; 95% CI, 0.35-0.55; P<0.0001)

56% reduction in the risk of progression or death in patients receiving D-Rd

Median PFS has not been reached with DRd in first relapse

*The upper bound 95% CI is currently not estimable; median PFS may change with additional follow-up once the upper bound 95% CI estimate is reached.

DRd: Daratumumab, lenalidomide and dexamethasone; Rd: Lenalidomide and dexamethasone; HR: Hazard ratio ORR: Overall response rate; CR: Complete response; MRD: Minimal residual disease; NE: Not-estimated; CI: Confidence Interval; PFS: Progression free survival; ITT: Intention to treat

Bahlis et al., ASH 2018; abstract 1996
ELOQUENT-2: EloRd vs Rd
4-year follow-up: Progression-free survival

A 29% reduction in the risk of progression or death (sustained over time)
50% in the PFS rate at 4 years (21% vs 14%) in favor of EloRd

- Minimum follow-up: 48 months

Ixazomib-Rd vs Rd in RRMM patients: Tourmaline-MM1: PFS with IRd vs placebo-Rd

Number of pts at risk:

<table>
<thead>
<tr>
<th>IRd</th>
<th>Placebo-Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>360</td>
<td>362</td>
</tr>
<tr>
<td>345</td>
<td>340</td>
</tr>
<tr>
<td>332</td>
<td>325</td>
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<td>288</td>
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<td>254</td>
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<td>248</td>
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<td>95</td>
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<td>72</td>
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<td>58</td>
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<td>44</td>
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<td>26</td>
<td>22</td>
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<td>14</td>
<td>15</td>
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<td>9</td>
<td>5</td>
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<tr>
<td>1</td>
<td>3</td>
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<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median follow-up: 14.8 months in the IRd group and 14.6 months in the placebo-Rd group

**Log-rank test p=0.01**

**Hazard ratio (95% CI): 0.74 (0.59, 0.94)**

**Number of events:** IRd 129; placebo-Rd 157

IRd: Ixazomib, lenalidomide and dexamethasone; Rd: Lenalidomide and dexamethasone
Patient-based factors are highly influential in treatment decision-making.

Frailty
- Age
- Performance status
- Disability
- Co-morbidities

Disease morbidity
- Refractory disease
- Renal impairment
- Bone disease

Risk assessment
- ISS
- Cyto-genetics

Treatment history
- Previous therapies

Lifestyle
- Patient preference
- Travel / infusion time

Quality of life

ISS, International Staging System.
Treatment sequencing

- **Type of relapse:** Indolent/biochemical relapse vs aggressive relapse
  
  All combinations are feasible in both situations

- **Age of the patients:**
  
  All combinations are effective and well tolerated by elderly patients

- **Number and type of prior lines:**
  
  All studies were conducted in lenalidomide-naïve or sensitive patients and we are seeing now more patients lenalidomide-refractory
Aspire: PFS by prior lines of therapy

HR, hazard ratio; KRd, carfilzomib with lenalidomide and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

Phase 3 POLLUX study: DRd vs Rd in RRMM
Subgroup analyses

DRd improved PFS versus Rd regardless of the number of prior lines of therapy

HR, hazard ratio; CI, confidence interval. PFS: Progression free survival DRd: Daratumumab, lenalidomide and dexamethasone Rd: Lenalidomide and dexamethasone
*Kaplan-Meier estimate.

Eloquent-2: PFS in patients with ≥ median time from diagnosis (≥ 3.5 yrs) after 1PL or > 1PL


PI: previous line; Eld: Elotuzumab, lenalidomide and dexamethasone Ld: lenalidomide and dexamethasone
TOURMALINE-MM1: PFS according to the number of prior lines of therapy

Pts with 2 or 3 PL or 1PL without trx seemed to have greater benefit than pts after 1PL and trx

Pl: Previous line; Trx: transplant; Pts: patients; HR: Hazard ratio; CI: Confidence Interval

Treatment sequencing

- **Type of relapse:** Indolent/biochemical relapse vs aggressive relapse
  All combinations are feasible in both situations
- **Age of the patients:**
  All combinations are effective and well tolerated by elderly patients
- **Number and type of prior lines:**
  All studies were conducted in lenalidomide-naïve or sensitive patients and we are seeing now more patients lenalidomide-refractory
  Would it be possible to use Rd-based combinations in patients already exposed to len but no len-refractory?
## Which patients fit the ESMO guidelines 2017?

### 1st line
- **Bortezomib-based combinations**
- **Exposed or not to lenalidomide but not progressing under lenalidomide therapy**

### First relapse after Bortezomib-based induction

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<tr>
<th>Efficacy</th>
<th>POLLUX DaraRd vs Rd²⁻⁴</th>
<th>ASPIRE KRd vs Rd⁵⁻⁷</th>
<th>ELOQUENT-2 ERd vs Rd⁸</th>
<th>TOURMALINE-MM1 IRd vs Rd⁹⁻¹⁰</th>
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<td>0.78 (0.63–0.96)</td>
<td>NE</td>
</tr>
<tr>
<td>48 m vs 40 m</td>
<td>48.3 m vs 39.6 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS HR (95% CI), median</strong></td>
<td>0.38 (0.21–0.66)</td>
<td>0.796 (0.522–1.215)</td>
<td>Only 5 pts</td>
<td>0.58</td>
</tr>
<tr>
<td>In len-exposed</td>
<td>38.8 m vs 18.6 m</td>
<td>19.4 m vs 13.9 m</td>
<td>NR vs 17.5 m</td>
<td></td>
</tr>
</tbody>
</table>

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• **Type of relapse:** Indolent/biochemical relapse vs aggressive relapse
  
  All combinations are feasible in both situations

• **Age of the patients:**

  All combinations are effective and well tolerated by elderly patients

• **Number and type of prior lines:**

  All studies were conducted in lenalidomide-naïve or sensitive patients

  and we are seeing now more patients lenalidomide-refractory

• **Cytogenetic abnormalities:**

  Combination of PIs and IMiD’s is the optimal choice

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**PIs:** Proteasome inhibitor; **IMiDs:** Immunomodulatory imide drugs
Aspire study: KRd vs Rd:
PFS by Cytogenetic Risk Status at Baseline

<table>
<thead>
<tr>
<th></th>
<th>KRd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 48)</td>
<td>(n = 52)</td>
</tr>
<tr>
<td>PFS, median months</td>
<td>23.1</td>
<td>13.9</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.70 (0.43–1.16)</td>
<td>0.66 (0.48–0.90)</td>
</tr>
</tbody>
</table>

Tourmaline MM1: IRd vs Rd: PFS in patients according to the cytogenetic risk

**Figure 2.** PFS with IRd vs placebo-Rd in high- and standard-risk patients

<table>
<thead>
<tr>
<th></th>
<th>High-risk</th>
<th>Standard-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test p-value</td>
<td>0.021</td>
<td>0.0070</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.543 (0.321, 0.916)</td>
<td>0.840 (0.462, 0.888)</td>
</tr>
<tr>
<td>Median, months</td>
<td>IRd: 21.4, placebo-Rd: 9.7</td>
<td>IRd: 20.6, placebo-Rd: 15.6</td>
</tr>
<tr>
<td>No. of events</td>
<td>IRd: 96, placebo-Rd: 35</td>
<td>IRd: 83, placebo-Rd: 91</td>
</tr>
</tbody>
</table>

**Figure 3.** PFS with IRd vs placebo-Rd in patients with del(17p) (alone or in combination with t(4;14) and/or t(14;16)) (A), and in patients with t(4;14) alone (B)

IRd: Ixazomib, lenalidomide and dexamethasone; Rd: Lenalidomide and dexamethasone; PFS: Progression free survival; HR: Hazard ratio
In the Tourmaline – MM1 the median PFS benefit with IRd versus placebo-Rd was consistent using different positivity cut-offs of del (17/17p) and t(4;14)

Richardson P et al. ASCO 2016

IRd: Ixazomib, lenalidomide and dexamethasone; Rd: Lenalidomide and dexamethasone
Treatment sequencing

- **Type of relapse**: Indolent/biochemical relapse vs aggressive relapse
  
  All combinations are feasible in both situations

- **Age of the patients**: 
  
  All combinations are effective and well tolerated by elderly patients

- **Number and type of prior lines**: 
  
  All studies were conducted in lenalidomide-naïve or sensitive patients
  
  and we are seeing now more patients lenalidomide-refractory

- **Cytogenetic abnormalities**: 
  
  Combination of PIs and IMiD’s is the optimal choice

- **Toxicity profile/comorbidities**: 
  
  Renal impairment: K/I/Elo/Dara can be used in renal impairment and R should be adjusted.
  
  Cardiovascular toxicity/severe COPD/ skin sensitivity....... 

- **Patients preferences/lifestyle/ visits to the hospital....**

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Pis: Proteasome inhibitor; IMiDs: Immunomodulatory drugs; COPD: Chronic Obstructive Pulmonary Disease
Minimum number of planned hospital visits required for administration/collection of MM treatments over 18 cycles¹⁻⁵*

*Patients are treated until progression or unacceptable toxicity. Calculation excludes visits for monitoring. Standard carfilzomib (IV) regimen is 18 cycles; number of administrations of carfilzomib per cycle: cycle 1-12 = 6 doses (2 consecutive doses each week for 3 weeks), cycle 13-18 = 4 doses (2 consecutive doses during 1st and 3rd week). Treatment with carfilzomib + Rd for longer than 18 cycles should be based on an individual benefit-risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited.²⁻⁴ Daratumumab is administered (IV) in, weekly for the first 8 weeks, then once every two weeks throughout weeks 9–24, followed by every 4 weeks from week 25 until disease progression or unacceptable toxicity. Calculation: 18 x 4 = 72 weeks in 18 cycles. (1 x 8) + (1 x 16/2) + (1 x 64/2) = 28 doses.⁵

IRd, ixazomib-lenalidomide-dexamethasone; MM, multiple myeloma; Rd, lenalidomide-dexamethasone.

IV treatments require regular clinic visits and involve infusion times which place a substantial burden on patients.

IV regimens are associated with substantially higher administration costs than oral regimens.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>IRd</th>
<th>KRd</th>
<th>ERd</th>
<th>DaraRd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimum clinic visits</strong>&lt;br&gt; based on 18 cycles</td>
<td>18</td>
<td>96</td>
<td>44</td>
<td>28</td>
</tr>
<tr>
<td><strong>Dosing schedule</strong>&lt;br&gt;Days 1, 8, and 15 of 28-day cycle</td>
<td>Days 1, 2, 8, 9, 15, and 16 of 28-day cycle. Additional IV hydration needed especially before each dose in Cycle 1, but may be in other cycles also</td>
<td>Days 1, 8, 15, 22 of 28-day cycles 1 &amp; 2 then Days 1 and 15 cycle 3+. Premedication required 45-90 minutes prior to Elo</td>
<td>Days 1,8,15, 22 of 28-day cycles 1&amp;2 then Days 1 and 15 cycles 3-6 then Day 1 of each cycle. Premedication required</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital/clinic visit</strong>&lt;br&gt;Every 4 weeks</td>
<td>Twice a week</td>
<td>Weekly x 8 then twice weekly</td>
<td>Weekly x 8 then twice weekly cycles 3-6 then monthly</td>
<td></td>
</tr>
<tr>
<td><strong>Premedication</strong>&lt;br&gt;N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td><strong>Prehydration</strong>&lt;br&gt;N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td><strong>Minimum administration time in clinic/hospital per visit</strong>&lt;br&gt;0 hours</td>
<td>Over 2 hours (130 minutes)</td>
<td>About 5 hours (290 minutes)</td>
<td>About 8 hours 1st infusion (3-4 hours the subsequent-ones)</td>
<td></td>
</tr>
</tbody>
</table>

1- RCM Ixazomib, 2- RCM carfilzomib; 3 – RCM elotuzumab; 4- RCM Daratumumab

DaraRd: Daratumumab, lenalidomide and dexamethasone; KRd: Carfilzomib, lenalidomide and dexamethasone; IRd: Ixazomib, lenalidomide and dexamethasone; ERd: Elotuzumab, lenalidomide and dexamethasone; iv: Intravenous administration ; PO: Oral administration
There are significant resource implications of combination treatments.

- Median time from check-in to administration: 120 minutes
- Median travel time: 120 minutes
- Median travel distance: 100 Kms
- Patients requiring hospital transport: 40%
PFS/TTNT of PI-based regimens in RRMM: Results of phase 2/3 studies vs RWE

PFS*/TTNT** (patients with 1-3 previous treatment lines)

**Real world data presented as PFS/TTNT intervals.
PFS, progression free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; RWE, real world evidence; TTNT, time to next treatment; VRd, bortezomib, lenalidomide and dexamethasone; Rd, Lenalidomide and dexamethasone

DOT and TTNT values in IRd vs KRd and VRd patients

**DOT and TTNT of VRd, KRd, or IRd in patients with RRMM: Clinical practice in the US vs clinical trial experience**

**Retrospective cohort study design:** Patients who initiated KRd, VRd, or IRd (index regimen) as treatment line 2, 3, or 4 between January 2008 and December 2016 in Humedica, a large US-based EMR database

**Endpoints:** DOT, TTNT, discontinuation rates

<table>
<thead>
<tr>
<th></th>
<th>VRd</th>
<th>KRd</th>
<th>IRd</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>343</td>
<td>139</td>
<td>49</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>69</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>17.3</td>
<td>8.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Median DOT (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI component alone</td>
<td>5.4</td>
<td>6.1</td>
<td>NR</td>
</tr>
<tr>
<td>Entire regimen</td>
<td>8.7</td>
<td>6.3</td>
<td>NR</td>
</tr>
<tr>
<td>Median TTNT (months)</td>
<td>12.9</td>
<td>8.7</td>
<td>NR</td>
</tr>
</tbody>
</table>

Discontinuation rates for PI component (%)

<table>
<thead>
<tr>
<th></th>
<th>VRd</th>
<th>KRd</th>
<th>IRd</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months</td>
<td>63</td>
<td>71</td>
<td>40</td>
</tr>
<tr>
<td>12 months</td>
<td>72</td>
<td>76</td>
<td>NR</td>
</tr>
<tr>
<td>18 months</td>
<td>83</td>
<td>89</td>
<td>NR</td>
</tr>
</tbody>
</table>

- This study suggests that patients were able to stay on the PI component of an oral PI-Rd triplet for longer than patients receiving IV PI-Rd triplets; this may translate into improved TTNT

VRd – Bortezomib, lenalidomide dexamethasone; KRd – Carfilzomib, lenalidomide, dexamethasone; IRd – Ixazomib, lenalidomide, dexamethasone; DOT – Duration of treatment; TTNT – Time to next treatment; PI – Proteassome Inhibitor; Rd – Lenalidomide and dexamethasone

Comparative Effectiveness of Triplets Containing Bortezomib (B), Carfilzomib (C), Daratumumab (D), or Ixazomib (I) in Relapsed/Refractory Multiple Myeloma (RRMM) in Routine Care in the US

Retrospective cohort study design: 1432 adults with RRMM with at least 1 prior line of therapy (LOT) and initiating a triplet regimen containing B, C, D, or I.

Endpoints: DOT, TTNT

- In RRMM patients, median TTNT was longer for Ixazomib based regimens vs B-, C-, and D-based triplets.
- The median TTNT (months) results were 11.1 for I-, and 9.8 for B-, 6.7 for C-, and 7.2 for D-based triplets.

DOT – Duration of treatment; TTNT – Time to next treatment

Adapted from Davies F et al. EHA Poster #PS1419
**Real-world data on the efficacy and safety of IRd in RRMM: Data from the Czech RMG**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>66 (41–84)</td>
</tr>
<tr>
<td>Bortezomib-refractory, %</td>
<td>18.9</td>
</tr>
<tr>
<td>Lenalidomide-refractory, %</td>
<td>7.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1st line treatment†</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>94.5</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>40.9</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>18.9</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>5.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IRd use per line of treatment</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second</td>
<td>58.5</td>
</tr>
<tr>
<td>Third</td>
<td>23.7</td>
</tr>
<tr>
<td>Fourth</td>
<td>7.6</td>
</tr>
<tr>
<td>Fifth and beyond</td>
<td>10.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR), %</td>
<td>67.1</td>
</tr>
<tr>
<td>CR</td>
<td>11.4</td>
</tr>
<tr>
<td>VGPR</td>
<td>16.5</td>
</tr>
<tr>
<td>PR</td>
<td>39.2</td>
</tr>
<tr>
<td>MR</td>
<td>10.1</td>
</tr>
<tr>
<td>≤SD</td>
<td>22.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFS after 1 line, months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>After 2 lines</td>
<td>23.1</td>
</tr>
<tr>
<td>After 3 lines</td>
<td>8.7</td>
</tr>
<tr>
<td>After ≥4 lines</td>
<td>4.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade ≥3 toxicities</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>35.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22.8</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12.3</td>
</tr>
<tr>
<td>Infection</td>
<td>19.3</td>
</tr>
</tbody>
</table>

*Risk status undeterminable in 34 patients. †By individual drugs.

CR, complete response; IRd, ixazomib, lenalidomide, dexamethasone; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RMG, registry of monoclonal gammopathies; RRMM, relapsed/refractory multiple myeloma; SD, stable disease; VGPR, very good PR

CASE REPORT

Este caso clínico foi desenvolvido por um perito em Hematologia para fins formação médica contínua refletindo a sua experiência clínica e pessoal.
Patient history*

Initial diagnosis

- Diagnosed with MM IgG-kappa (ISS-2; R-ISS-2) in April 2012
- Myeloma-defining event: anaemia (Hb: 10.9 g/dL)
- No high-risk cytogenetic abnormalities
- No extramedullary disease

Prior medical history

- Medication for hypertension and hypercholesterolaemia

Lifestyle

- Generally active; plays tennis and golf
- Regularly looked after two grandsons

* This patient case represents an individual patient experience only and does not represent all patients.

Hb, haemoglobin; IgG, immunoglobulin G; ISS, International Staging System; MM, multiple myeloma; R-ISS, Revised International Staging System.
First-line therapy

May 2012

- Patient received VMP x 9 cycles, followed by Rd x 9 cycles (Spanish trial GEM-2010):
  - He was able to continue playing tennis and golf
  - He achieved sCR after 18 cycles, but MRD remained positive
  - Good tolerability without significant AE/SAEs
Biochemical relapse

January 2015

- In a follow-up visit (1 year and 2 months after treatment end), while the patient was asymptomatic, IF results tested positive (confirmed twice)

May 2015

- Serum protein electrophoresis showed an M-spike of 0.6 g/dL
- 2 months later, M-spike was still 0.5 g/dL

IF, immunofixation.
# Clinical relapse

**January 2015**  
- In a follow-up visit (1 year and 2 months after treatment end), while the patient was asymptomatic, IF results tested positive (confirmed twice)

**May 2015**  
- Serum protein electrophoresis showed an M-spike of 0.6 g/dL  
- 2 months later, M-spike was still 0.5 g/dL

**December 2015**  
- **Mild fatigue:**  
  - Hb level decreased to 11 g/dL  
  - PET-CT positive uptake observed in right hip with no lytic lesions  
  - No high-risk features

*PET-CT, Positron emission tomography–computed tomography. Hb: Hemoglobin*
The first question Alexander asked us was about the duration of the treatment

1. Continuous therapy
2. Fixed-duration therapy (as per first-line therapy)
Prolonged duration of therapy is associated with improved OS in patients undergoing second-line therapy.

Real-world US data in RRMM\(^1,2\)

<table>
<thead>
<tr>
<th>Duration of therapy in 2L (months)</th>
<th>Increase in 1-year OS relative to median duration of therapy in 2L</th>
</tr>
</thead>
<tbody>
<tr>
<td>7m to &lt;8m</td>
<td>3.7%</td>
</tr>
<tr>
<td>8m to &lt;9m</td>
<td>6.7%</td>
</tr>
<tr>
<td>9m to &lt;10m</td>
<td>9.2%</td>
</tr>
<tr>
<td>10m to &lt;11m</td>
<td>11.1%</td>
</tr>
<tr>
<td>11m to &lt;12m</td>
<td>12.7%</td>
</tr>
<tr>
<td>≥12m</td>
<td>14.0%</td>
</tr>
</tbody>
</table>

OS: Overall survival; RRMM, relapsed/refractory multiple myeloma; m, months; 2L, second line.

Treatment at first relapse: What is the best choice for Alexander?

- The patient agreed with the recommendation to receive continuous therapy:
  - As he previously received VMP and Rd for 18 months with subsequent treatment-free interval, he could be a candidate for either PI- or IMiD-based combinations
  - Alexander stated a preference for an IMiD-based regimen for convenience, and because he had a more positive experience with the last 9 cycles than with the first 9 cycles of his first-line therapy
  - He also wanted to maintain an active lifestyle

IMiD, immunomodulatory imide drugs; PI, proteosome inhibitor. VMP: Bortezomib, Melfalan, Prednisolone; Rd: Lenalidomide and dexamethasone
**How to make the right choice?**

1st line
- Bortezomib-based combinations
- Exposed to lenalidomide but no progressing under lenalidomide therapy

**First relapse after Bortezomib-based induction**

<table>
<thead>
<tr>
<th></th>
<th>POLLUX</th>
<th>ASPIRE</th>
<th>ELOQUENT-2</th>
<th>TOURMALINE-MM1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DaraRd vs Rd²⁻⁴</td>
<td>KRd vs Rd⁵⁻⁷</td>
<td>ERd vs Rd⁸</td>
<td>IRd vs Rd⁹,¹⁰</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.44 (0.35–0.55)</td>
<td>0.670 (0.558–0.803)</td>
<td>0.71 (0.59–0.86)</td>
<td>0.74 (0.59–0.94)</td>
</tr>
<tr>
<td>44.5 m vs 17.5 m</td>
<td>26.3 m vs 17.6 m</td>
<td>19.4 m vs 14.9 m</td>
<td>20.6 m vs 14.7 m</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>93</td>
<td>87</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>≥ CR, %</td>
<td>57 (MRDneg 30%)</td>
<td>32</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>DOR, months</td>
<td>NE</td>
<td>28.6</td>
<td>21.2</td>
<td>20.5</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.63 (0.42–0.95)</td>
<td>0.79 (0.63–0.99)</td>
<td>0.78 (0.63–0.96)</td>
<td>NE</td>
</tr>
<tr>
<td>48 m vs 40 m</td>
<td>48.3 m vs 39.6 m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS HR (95% CI), median</td>
<td>0.38 (0.21–0.66)</td>
<td>0.796 (0.522–1.215)</td>
<td>Only 5 pts</td>
<td>0.58</td>
</tr>
<tr>
<td>In len-exposed</td>
<td>38.8 m vs 18.6 m</td>
<td>19.4 m vs 13.9 m</td>
<td></td>
<td>NR vs 17.5 m</td>
</tr>
</tbody>
</table>

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Rd: Lenalidomide and dexamethasone; DaraRd: Daratumumab, lenalidomide and dexamethasone; KRd: Carfilzomib, lenalidomide and dexamethasone; IxaRd: Ixazomib, lenalidomide and dexamethasone; EloRd: Elotuzumab, lenalidomide and dexamethasone. PFS: Progression free survival; HR: Hazard ratio; ORR: Overall response rate; CR: Complete response; DOR: Duration of treatment; OS: Overall Survival; CI: Confidence interval; MRDneg: Minimal residual disease; NE: Non-estimated.
Patient-based factors are highly influential in treatment decision making

- Frailty
  - Age\(^1,2\)
  - Performance status\(^3\)
  - Disability\(^1\)
  - Comorbidities\(^1,2\)

- Disease morbidity
  - Refractory disease\(^3\)
  - Renal impairment\(^4\)
  - Bone disease\(^5\)

- Risk assessment
  - ISS\(^6\)
  - Cytogenetics\(^6,7\)

- Treatment history
  - Previous therapies\(^3\)

- Lifestyle
  - Patient preference\(^8\)
  - Travel/infusion time\(^9\)

- Quality of life\(^10,11\)

Patient-based factors are highly influential in treatment decision making

Treatment at first relapse

- Patient received IRd:
  - VGPR achieved for over 2 years
  - ECOG PS 0
  - Patient visits clinic on monthly basis
  - Active lifestyle maintained on treatment

ECOG PS, Eastern Cooperative Oncology Group Performance Status; VGPR, very good partial response.
Experience with treatment regimens can enhance practical guidance and management recommendations

- Experience in routine clinical practice can identify practical challenges that are not present in the trial setting, thereby helping to optimise treatment in real-world practice.
- Practical learnings from experience with IRd include:
  - Use following indolent or biochemical relapses
  - Use at first relapse in elderly after bortezomib-based combinations
  - Use at second and third relapses in patients who received ASCT in the first line
  - The extension of PFS irrespective of cytogenetic profile
  - Opportunities for patients who want to maintain their regular activity
  - Options for patients who do not want to or cannot come to the hospital every week

When patients are asked for their preference they usually prefer the oral administration.

Information is based on the personal experience of Dr Mateos.
Patient history*

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