Multiple myeloma: New aspects in diagnosis and therapy

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Medical Oncology
Hospital Münsterlingen
Monoclonal gammopathy of unknown significance

- Serum M-Protein < 30 g/l
- Clonal plasma cells bone marrow < 10%
- No evidence of another B-cell-neoplasia
- No endorgan damage, no bone lesions

The International Myeloma Working Group: Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders

British Journal of Haematology, 2003, 121, 749-757
MGUS – multiple myeloma

Risk of progression to multiple myeloma or a related disorder

1 % per year

Diagnosis
Diagnostic criteria multiple myeloma

- M-Protein in serum and/or urine

Serum protein electrophoresis

<table>
<thead>
<tr>
<th>Fraktion</th>
<th>%</th>
<th>g/l</th>
<th>Int. rif. g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>40.9</td>
<td>36.8</td>
<td>43.0 - 51.0</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>4.8</td>
<td>4.3</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>17.6</td>
<td>15.8</td>
<td>5.0 - 8.0</td>
</tr>
<tr>
<td>Beta</td>
<td>11.7</td>
<td>10.5</td>
<td>6.0 - 9.0</td>
</tr>
<tr>
<td>Gamma</td>
<td>25.0</td>
<td>22.5</td>
<td>6.0 - 11.0</td>
</tr>
<tr>
<td>1</td>
<td>23.1</td>
<td>20.8</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic criteria multiple myeloma

- M-Protein in serum and/or urine
- ≥10% clonal plasma cells in the bone marrow or extramedullary plasmocytoma
Diagnostic criteria multiple myeloma

- M-Protein in serum and/or urine
- $\geq 10\%$ clonal plasma cells in the bone marrow or extramedullary plasmocytoma
- Endorgan damage including bone lesions

Endorgan damage „CRAB“ criteria

- Calcium
- Renal
- Anemia
- Bone
**Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma**

**Definition of multiple myeloma**

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 ml per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

**Definition of smouldering multiple myeloma**

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis
Magnetic Resonance Imaging in Multiple Myeloma: Diagnostic and Clinical Implications

FDG-PET-CT
Initial diagnostic workup
- History and physical examination
- Complete blood count
- Creatinine, calcium, albumin, LDH
- Beta2-microglobulin
- Serum free light chain assay
- Serum quantitative immunoglobulins (IgG, IgA, IgM)
- Serum protein electrophoresis, serum immunofixation
- 24 h urine for total protein, urine protein electrophoresis, urine immunofixation
- Skeletal survey, MRI in special situations
- Bone marrow aspirate and biopsy
- Cytogenetics
- FISH (Fluorescence in situ hybridization)
Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3


**FISH**
- del 17p, t(4;14), t(14;16) [del 13, t(11;14), 1q amplification]

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International staging system

<table>
<thead>
<tr>
<th></th>
<th>ISS I</th>
<th>ISS II</th>
<th>ISS III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta2-MG</td>
<td>&lt; 3.5 mg/l</td>
<td>Neither I nor III</td>
<td>≥ 5.5 mg/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>≥ 35 g/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medianes OS</td>
<td>62 months</td>
<td>44 months</td>
<td>29 months</td>
</tr>
</tbody>
</table>

### IMWG consensus on risk stratification in multiple myeloma

WJ Chng, A Dispenzieri, C-S Chim, R Fonseca, H Goldschmidt, S Lentzsch, N Munshi, A Palumbo, JS Miguel, P Sonneveld, M Cavo, S Usmani, BGM Durie, and H Avet-Loiseau on behalf of the International Myeloma Working Group

#### ISS and FISH

<table>
<thead>
<tr>
<th>Parameters</th>
<th>High-risk</th>
<th>Standard-risk</th>
<th>Low-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS II/III and t(4;14) or 17p13 del</td>
<td>Others</td>
<td>ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age &lt;55 years</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>2 years</td>
<td>7 years</td>
<td>&gt;10 years</td>
</tr>
<tr>
<td>% Patients</td>
<td>20%</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>Therapeutic questions</td>
<td>There is a need for novel therapeutic approaches e.g. Allogeneic stem cell transplant or immune therapy approaches</td>
<td>Do these patients benefit from maintenance therapy? Is VGPR a good enough response in these patients, as they may revert to an MGUS state</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ISS, International staging system; MGUS, monoclonal gammopathy of undetermined significance; OS, overall survival; VGPR, very good partial response. *Survival of t(4;14) patients is improved with the use of velcade-based therapy.
# IMWG Consensus 2013

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Standard risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS</td>
<td>I / II</td>
<td>Neither low nor high</td>
<td>II / III</td>
</tr>
<tr>
<td>FISH</td>
<td>No t(4;14)</td>
<td>Neither low nor high</td>
<td>t(4;14) or del 17p13</td>
</tr>
<tr>
<td></td>
<td>No del 17p13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No +1q21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 55 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>&gt; 10 years</td>
<td>7 years</td>
<td>2 years</td>
</tr>
<tr>
<td>% patients</td>
<td>20%</td>
<td>60%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Chng WJ et al, Leukemia 2013; 1-9
Therapy
„Novel“ drugs

- Thalidomide
- Bortezomib (Velcade®)
- Lenalidomide (Revlimid®)
Improved survival in multiple myeloma and the impact of novel therapies

Shaji K. Kumar,¹ S. Vincent Rajkumar,¹ Angela Dispenzieri,¹ Martha Q. Lacy,¹ Suzanne R. Hayman,¹ Francis K. Buadi,¹ Steven R. Zeldenrust,¹ David Dingli,¹ Stephen J. Russell,¹ John A. Lust,¹ Philip R. Greipp,¹ Robert A. Kyle,¹ and Morie A. Gertz¹

¹Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

n = 2981

44.8 vs. 29.9 months

Kumar SK et al. Blood 2008; 111: 2516-20
Improved survival in multiple myeloma and the impact of novel therapies

Shaji K. Kumar,¹ S. Vincent Rajkumar,¹ Angela Dispenzieri,¹ Martha Q. Lacy,¹ Suzanne R. Hayman,¹ Francis K. Buadi,¹ Steven R. Zelenrust,¹ David Dingli,¹ Stephen J. Russell,¹ John A. Lust,¹ Philip R. Greipp,¹ Robert A. Kyle,¹ and Morie A. Gertz¹

¹Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

30.9 vs. 14.8 months

n = 387

Kumar SK et al. Blood 2008; 111: 2516-20
Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial

Jesus San Miguel, Katja Weisel, Philippe Moreau, Martha Lacy, Kevin Song, Michel Delforge, Lionel Karlin, Hartmut Goldschmidt, Anne Banos, Albert Oriol, Adrian Alegre, Christine Chen, Michele Cavo, Laurent Garderet, Valentina Ivanova, Joaquin Martinez-Lopez, Andrew Belch, Antonio Palumbo, Stephen Schey, Pieter Sonneveld, Xin Yu, Lars Sternas, Christian Jacques, Mohamed Zaki, Meletios Dimopoulos

4th «new drug»
Pomalidomide (Imnovid®)

Median PFS 4.0 vs 1.9 months

Imnovid®: Dosage

• 4 mg per day p.o., day 1 –21, 7 days break

• In combination with dexamethasone 40 mg p.o. 1x per week; patients > 75 years 20 mg p.o. 1x per week

• Cycle duration 28 days

• Only after previous treatment with Revlimid® and Velcade®
Imnovid®: Side effects

- Anemia, leucopenia, thrombocytopenia
- Infections
- Fatigue
- Diarrhea, constipation
- Increased risk for thrombo-embolic events
Many combinations

- MPT: Melphalan, prednisone, thalidomide
- VMP: Velcade, melphalan, prednisone
- VCD: Velcade, cyclophosphamide, dexamethasone
- VTD: Velcade, thalidomide, dexamethasone
- MPR: Melphalan, prednisone, Revlimid
- Rd, RD, Rev-Dex: Revlimid, dexamethasone
- Velcade, Caelyx
Criteria for the choice of drugs

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Thalidomide</th>
<th>Velcade</th>
<th>Revlimid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Increased thrombo-embolic risk</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>+</td>
<td>++</td>
<td>(+)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Drugs with known efficacy

- Doxorubicin = Adriblastin®
- Bendamustin = Ribomustin®
- Carfilzomib = Kyprolis® (proteasome inhibitor)
- MLN 9708 (oral proteasome inhibitor)
- Panobinostat (pan-deacetylase inhibitor)
- Elotuzumab (monoclonal antibody; anti CS1)
- Daratumumab (monoclonal antibody; anti CD38)
Eligibility for autologous stem-cell transplantation (ASCT)

Yes

Induction: 3-drug regimens
- VTD
- VCD
- PAD
- RVD

↓
200 mg/m² Melphalan followed by ASCT

No

First option: MPT or VMP

Second option: Bendamustine–Prednisone

Other options: CTD, MP
mSMART – Off-Study
Transplant Eligible

**Standard-Risk**
- **Trisomies only**
  - 4 cycles of Rd\(^a\)
  - Collect Stem Cells\(^b\)
  - Autologous stem cell transplant
  - Continue Rd\(^c\)

- **T(11;14), t(6;14), Trisomies + IgH**
  - 4 cycles CyBorD
  - 2 cycles of Rd consolidation; then Len maintenance if not in VGPR but Len responsive\(^*\)

**Intermediate-Risk**
- **t(4;14)**
  - 4 cycles of CyBorD
  - Bor based therapy for minimum of 1 year

**High-Risk**
- **Del 17p, t(14;16), t(14;20)**
  - 4 cycles of VRd
  - Autologous stem cell transplant, especially if not in CR
  - Bor or CyBorD for minimum of 1 year

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\(^a\) Bortezomib containing regimens preferred in renal failure or if rapid response needed
\(^b\) If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor
\(^c\) Continuing Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year

\(^*\) Consider risks and benefits; if used, consider limited duration 12-24 months

mSMART – Off-Study
Transplant Eligible

Standard-Risk

Trisomies only
4 cycles of Rd
Collect Stem Cell

Intermediate-Risk

T(11;14), t(6;14), Trisomies + IgH
4 cycles CyBorD

T(4;14), t(14;20), Trisomies + IgH

4 cycles of VRd

Autologous stem cell transplant, especially if not in CR

Bor based therapy for minimum of 1 year

Bor or CyBorD for minimum of 1 year

Risk adapted therapy

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a) Bortezomib containing regimens preferred in renal failure or if rapid response needed
b) If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor
c) Continuing Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year

* Consider risks and benefits; if used, consider limited duration 12-24 months

mSMART 2.0: Classification of Active MM

High-Risk

- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- GEP
  - High risk signature

Intermediate-Risk

- FISH
  - t(4;14)
  - 1q gain
  - Complex karyotype
  - Metaphase Deletion 13 or hypodiploidy
- High PC S-phase

Standard-Risk

- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

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\[\text{Note:} \quad a \text{ Note that a subset of patients with these factors will be classified as high-risk by GEP.} \]
\[\text{b} \quad \text{LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis; e} \text{Trisomies may ameliorate.} \]
\[\text{c} \quad \text{Prognosis is worse when associated with high beta-2 M and anemia.} \]
\[\text{d} \quad \text{t(11;14) may be associated with plasma cell leukemia; f Cut-offs vary.} \]
Transplant eligible patients

Induction | HDCT | Consolidation | Maintenance
The key elements of modern treatment strategies: sequential treatment approach for myeloma. Ongoing treatment with an induction phase, followed by intensification (transplant), consolidation, and a maintenance phase.

Morgan GJ et al. Blood 2013; 122: 1332-34
The impact of consolidation will be clarified by ongoing trials.

**Clinical practice guidelines**

**Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

P. Moreau¹, J. San Miguel², H. Ludwig³, H. Schouten⁴, M. Mohty⁵,⁶,⁷, M. Dimopoulos⁸, M. Dreyling⁹, on behalf of the ESMO Guidelines Working Group

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**Eligibility for autologous stem-cell transplantation (ASCT)**

- **Yes**
  - Induction: 3-drug regimens
    - VTD
    - VCD
    - PAD
    - RVD
  - ↓ 200 mg/m² Melphalan followed by ASCT

- **No**
  - First option: MPT or VMP
  - Second option: Bendamustine–Prednisone
  - Other options: CTD, MP

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Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

P. Moreau¹, J. San Miguel², H. Ludwig³, H. Schouten⁴, M. Mohty⁵,⁶,⁷, M. Dimopoulos⁸ & M. Dreyling⁹, on behalf of the ESMO Guidelines Working Group*

... systematic maintenance therapy is not recommended.
Autologous Transplantation and Maintenance Therapy in Multiple Myeloma


Induction

n=402
Rd (four 28-d cycles)
Lenalidomide 25 mg/d, d1-21
Low-dose dex 40mg/d, d 1,8,15,22

Consolidation

n=202
MPR (six 28-d cycles)
Melphalan 0.18 mg/kg/d, d 1-4
Prednisone 2 mg/kg/d, d 1-4
Len 10 mg/d, d 1-21

Maintenance

n=200
MEL 200
Tandem Mel 200mg/m² plus stem cell support

No maintenance

Maintenance
Len 10 mg/d, d 1-21
28-d course until relapse

Primary end point: PFS

B  From Start of Consolidation

- **High-dose melphalan** vs **MPR**

  - **Probability of Progression-free Survival**
    - Hazard ratio for progression or death with high-dose melphalan, 0.44 (95% CI, 0.32–0.61); P<0.001
    - Ages at risk:
      - High-dose melphalan: 141 131 114 105 92 82 67 49 21 3
      - MPR: 132 128 98 76 57 41 32 25 7 1

  - **Probability of 4 Yr Overall Survival**
    - Hazard ratio for death with high-dose melphalan, 0.55 (95% CI, 0.32–0.93); P=0.02
    - Ages at risk:
      - High-dose melphalan: 141 136 129 121 115 111 105 88 42 7
      - MPR: 132 131 124 121 117 106 94 82 27 5
C  From Start of Maintenance

Hazard ratio for progression or death with lenalidomide maintenance, 0.47 (95% CI, 0.33–0.65); P<0.001

Hazard ratio for death with lenalidomide maintenance 0.64 (95% CI, 0.36–1.15); P=0.14

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide maintenance</th>
<th>No maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>126 112 100 86 73 62 51 15 2 0</td>
<td>125 96 78 64 51 37 20 9 2 1</td>
</tr>
</tbody>
</table>

**Probability of Progression-free Survival**

- Lenalidomide maintenance
- No maintenance

**Probability of 3-Yr Overall Survival**

- Lenalidomide maintenance
- No maintenance

**Months**

- 0 6 12 18 24 30 36 42 48 54 60

- 0 1 2 3 4 5 6 7 8 9 10

Conclusion

MPR vs MEL 200

<table>
<thead>
<tr>
<th></th>
<th>MPR (n=202)</th>
<th>MEL 200 (n=200)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>22.4 months</td>
<td>43.0 months</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>4-year OS</td>
<td>65.3%</td>
<td>81.8%</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

Lenalidomide maintenance vs no maintenance

<table>
<thead>
<tr>
<th></th>
<th>R-maintenance (n=198)</th>
<th>No maintenance (n=204)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>41.9 months</td>
<td>21.6 months</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>3-Jahres OS</td>
<td>88.0 %</td>
<td>79.2%</td>
<td>P=0.14</td>
</tr>
</tbody>
</table>

Median follow up 51.2 months

Therapy of elderly patients
Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN)

Antonio Palumbo,¹ Sara Bringhen,¹ Heinz Ludwig,² Meletios A. Dimopoulos,³ Joan Bladé,⁴ Maria V. Mateos,⁵ Laura Rosiñol,⁶ Mario Boccadoro,¹ Michele Cavo,⁷ Henk Lokhorst,⁸ Sonja Zweegman,⁹ Evangelos Terpos,³ Faith Davies,¹⁰ Christoph Driessen,¹¹ Peter Gimsing,¹² Martin Gramatzki,¹³ Roman Hájek,¹⁴ Hans E. Johnsen,¹⁵ Fernando Leal Da Costa,¹⁶ Orhan Sezer,¹⁷ Andrew Spencer,¹⁸ Meral Bekșac,¹⁹ Gareth Morgan,¹⁰ Hermann Einsele,²⁰ Jesus F. San Miguel,⁵ and Pieter Sonneveld²¹

5 year overall survival rates

Co-morbidity

CR

Toxicity
To consider in elderly patients

- High doses are not always optimal
- Severe toxicities and treatment discontinuations should be avoided!
- Careful surveillance of therapy, especially in patients ≥ 75 years
- Consider dose reductions
  - Especially in patients with bad performance status and at the start of therapy
## Age adjusted dosage recommendations

<table>
<thead>
<tr>
<th></th>
<th>&lt;65 years</th>
<th>65-75 years</th>
<th>&gt;75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>40 mg/d, d 1-4 and 15-18</td>
<td>40 mg/d, d 1, 8, 15, 22</td>
<td>20 mg/d, d 1, 8, 15, 22</td>
</tr>
<tr>
<td><strong>Melphalan</strong></td>
<td>0.25 mg/kg, d 1-4</td>
<td>0.18 - 0.25 mg/kg, d 1-4</td>
<td>0.13 - 0.18 mg/kg, d 1-4</td>
</tr>
<tr>
<td><strong>Thalidomide</strong></td>
<td>200 mg/d</td>
<td>100 - 200 mg/d</td>
<td>50 - 100 mg/d</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td>25 mg/d, d 1-21</td>
<td>15 - 25 mg/d, d 1-21</td>
<td>10 - 25 mg/d, d 1-21</td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
<td>1.3 mg/m², d 1, 4, 8, 11</td>
<td>1.3 mg/m², d 1, 4, 8, 11 or</td>
<td>1.0 – 1.3 mg/m², d 1, 8, 15, 22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
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<tbody>
<tr>
<td>MPT</td>
<td>&gt;</td>
<td>MP</td>
</tr>
<tr>
<td>VMP</td>
<td>&gt;</td>
<td>MP</td>
</tr>
<tr>
<td>MPR-R</td>
<td>&gt;</td>
<td>MP</td>
</tr>
<tr>
<td>VMPT-VT</td>
<td>&gt;</td>
<td>VMP</td>
</tr>
<tr>
<td>Len-Dex</td>
<td>&gt;</td>
<td>MPT</td>
</tr>
</tbody>
</table>
Conclusion: Transplant eligible

- Induction with bortezomib-containing 3 drug regimen
- High dose chemotherapy and autologous stem cell transplant is still part of the therapy
- Consolidation is an option
- Lenalidomide maintenance is still in controversy
Conclusion: Transplant ineligible

• Lenalidomide and low dose dexamethasone is another treatment option for patients with newly diagnosed multiple myeloma
Thank you for your attention