Treatment Advances in Multiple Myeloma: Expert Perspectives on Translating Clinical Data to Practice

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San Diego, California

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Brian G.M. Durie, MD, has disclosed that he has received consulting fees from Celgene, Johnson & Johnson, Onyx, and Takeda
Faculty

Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota

Shaji Kumar, MD, has disclosed that he has received consulting fees from Kesios Therapeutics and SkylineDx.
Philippe Moreau, MD
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Philippe Moreau, MD, has disclosed that he has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, and Takeda.
Should We Be Using Risk-Adapted Therapy in Clinical Practice?

Moderator
Brian G.M. Durie, MD

Faculty Presenter
Shaji Kumar, MD
Pt Case Example

- A 42-yr-old male was diagnosed with multiple myeloma when he presented with back pain of several months’ duration
  - Initial imaging showed compression fracture of T12 vertebral body; spine MRI showed marrow signal abnormality involving most of the spine

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.8 mg/dL</td>
</tr>
<tr>
<td>WBC</td>
<td>4200/μL</td>
</tr>
<tr>
<td>Platelets</td>
<td>162,000/μL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.2 mg/dL</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>9.1 mg/dL</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.7 g/dL</td>
</tr>
<tr>
<td>LDH</td>
<td>378 IU/dL</td>
</tr>
<tr>
<td>Serum β₂-M</td>
<td>5.8 mg/dL</td>
</tr>
</tbody>
</table>
Pt Case Example

- Additional exam reveals
  - Serum protein electrophoresis: M spike of 3.2 g/dL, IgA kappa
  - Serum free light chain: kappa of 34 mg/dL, lambda of 0.12 mg/dL
  - 24-hr urine with protein electrophoresis showed an M spike of 80 mg, kappa light chain and IgG-kappa fragments
  - PET scan showed diffuse lesions involving the axial skeleton with no extramedullary disease
  - Bone marrow evaluation: 40% plasma cells, kappa light chain restricted
  - FISH studies showed monosomy 13, t(4;14), and del(17p)

- He was started on a combination of bortezomib, lenalidomide, and dexamethasone. After 4 cycles, he was in a CR, and MRD assessment by flow did not detect any residual disease
Which of the following would you recommend next for this pt?

A. Stop bortezomib and continue with lenalidomide maintenance
B. Stop lenalidomide and continue with bortezomib maintenance
C. Stop therapy and observe since the disease is MRD negative
D. Single autologous SCT followed by bortezomib maintenance
E. Proceed to a tandem autologous SCT
F. Start a donor search and consider allogeneic SCT
G. Unsure
## Expert Recommendations

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Tandem autologous SCT</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Tandem autologous SCT</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Tandem autologous SCT</td>
</tr>
<tr>
<td>Bruno Paiva, PhD</td>
<td>Tandem autologous SCT</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Single autologous SCT followed by bortezomib maintenance</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Tandem autologous SCT</td>
</tr>
</tbody>
</table>
Risk Assessment in Myeloma

Shaji Kumar, MD  
Professor of Medicine  
Mayo Clinic

Scottsdale, Arizona  
Rochester, Minnesota  
Jacksonville, Florida
Myeloma Is Not One Disease


~ 25% pts dead in 3 yrs

~ 50% pts alive at 5 yrs
What Makes Them Different?

• **Tumor clone:**
  • Genetic abnormalities
  • Proliferation, circulating cells, etc

• **Host:**
  • Age, performance status

• **Host and tumor:**
  • International staging system (ISS)
  • Immune parameters

• **Variety of other “prognostic factors” have been described**
Why Risk Stratify?

• *Two important goals*
  
  • *Counsel:* Need to provide pt with realistic expectations based on the currently available treatments
  
  • *Therapy:* Decide if particular therapies can be chosen based on their differential effects on the high-risk and standard-risk disease
## Genetic Abnormalities in Myeloma

Deletions involving chromosomes 1, 13, 14, 17

<table>
<thead>
<tr>
<th>FISH Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy(ies) without IgH abnormality</td>
<td>201 (42)</td>
</tr>
<tr>
<td>IgH abnormality without trisomy(ies)</td>
<td>146 (30)</td>
</tr>
<tr>
<td>IgH abnormality with trisomy(ies)</td>
<td>74 (15)</td>
</tr>
<tr>
<td>Monosomy 14 in absence of IgH translocations or trisomy(ies)</td>
<td>22 (4.5)</td>
</tr>
<tr>
<td>Other cytogenetic abnormalities</td>
<td>26 (5.5)</td>
</tr>
<tr>
<td>Normal</td>
<td>15 (3)</td>
</tr>
</tbody>
</table>

Impact of FISH-Based Stratification

Follow-up From Diagnosis (Yrs)

- FISH high risk
  - (14 %, median OS: 3 yrs)
  - $P < .001$
  - FISH standard risk
  - (86%, median OS: NR)

<table>
<thead>
<tr>
<th>High-Risk Abnormalities</th>
<th>In the absence of trisomies</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14), t(14;16), t(14;20)</td>
<td></td>
</tr>
<tr>
<td>Deletion 13q/monosomy 13 (metaphase cytogenetics)</td>
<td></td>
</tr>
<tr>
<td>Del 17p</td>
<td></td>
</tr>
<tr>
<td>Del 1p/Amp 1q</td>
<td></td>
</tr>
</tbody>
</table>

Revised ISS Staging System

**Standard Risk Factors for MM and the R-ISS**

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Serum β2M &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>Not ISS Stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2M ≥ 5.5 mg/L</td>
</tr>
<tr>
<td>CA by iFISH</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Presence of del(17p) and/or t(4;14) and/or t(14;16)</td>
</tr>
<tr>
<td>Std risk</td>
<td>No high risk CA</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Serum LDH &lt; ULN</td>
</tr>
<tr>
<td>High</td>
<td>Serum LDH &gt; ULN</td>
</tr>
</tbody>
</table>

A new model for risk stratification for MM

**R-ISS Stage**

| I     | ISS stage I and standard risk CA by iFISH and normal LDH |
| II    | Not R-ISS stage I or III |
| III   | ISS Stage II and high-risk CA by iFISH or high LDH |

Gene Expression–Based Classifications

Signatures

- GEP70
- GEP17
- HOVON
- IFM

Evolving Genome of MM

Mutations and Outcomes

**P53 mutations**

![Graphs showing survival probability vs. time for PFS and OS with different P53 mutation statuses.](Image)

**ATM/ATR mutations**

![Graphs showing survival probability vs. time for PFS and OS with different ATM/ATR mutation statuses.](Image)

Increasing Number of Tools

The old

- Alkylators
- Anthracyclines
- Corticosteroids

And the new....

- Proteasome inhibitors
- IMiDs
- HDAC inhibitors
- Monoclonal antibodies
Tailoring the Intervention

• Use of a specific *drug* or drug class

• Use of multidrug *combinations*
  • eg, PI + IMiD

• Varying the *duration* of therapy
  • Continuous vs fixed

• Targeting a particular level of *response*
  • Eg, CR or MRD negativity
Bortezomib and t(4;14): OS Analysis

OS in pts with t(4;14) with induction

Log-rank $P < 0.001$

OS by GEP-defined FGFR3/MMSET subgroup

Bortezomib/dexamethasone vs.
Vincristine/doxorubicin/dexamethasone (VAD)

Bortezomib and del(17p)

HOVON-65/GMMG-HD4: VAD induction, tandem SCT, and thalidomide maintenance vs PAD induction, tandem SCT, and bortezomib maintenance

VRD Consolidation and Maintenance

Tandem ASCT: del(17p) ± t(4;14)

Kaplan-Meier survival estimates

Log rank test: 
$P = 0.0001$

HR 0.22 (0.10-0.50) 
$P < 0.001$

2 ASCT 
76%

1 ASCT 
33%

Phase III Trial Comparing Single ASCT alone vs ASCT with Consolidation vs Tandem ASCT

- Phase III staMINA trial in transplant-eligible pts with symptomatic MM without progression on induction therapy (N = 758)

  - No differences observed in PFS, OS, or PD in overall pt population at 38 mo follow-up

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACM</td>
<td>57%</td>
<td>86%</td>
<td>42%</td>
</tr>
<tr>
<td>TAM</td>
<td>56%</td>
<td>82%</td>
<td>42%</td>
</tr>
<tr>
<td>AM</td>
<td>52%</td>
<td>83%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Stratification by cytogenetic risk, β2M, and center

# Effect of Treatment Duration

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.69</td>
<td>0.54 to 0.88</td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIMEMA-MM-03-05</td>
<td>0.63</td>
<td>0.44 to 0.90</td>
<td>0.703</td>
</tr>
<tr>
<td>RV-MM-Pi-209 (Mel200x2)</td>
<td>0.55</td>
<td>0.22 to 1.40</td>
<td></td>
</tr>
<tr>
<td>RV-MM-Pi-209 (MPR)</td>
<td>0.66</td>
<td>0.34 to 1.29</td>
<td></td>
</tr>
<tr>
<td>CC-5013-MM-018</td>
<td>0.87</td>
<td>0.54 to 1.39</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 65</td>
<td>0.62</td>
<td>0.38 to 1.03</td>
<td>0.871</td>
</tr>
<tr>
<td>66–75</td>
<td>0.73</td>
<td>0.52 to 1.02</td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td>0.68</td>
<td>0.38 to 1.20</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.93</td>
<td>0.63 to 1.37</td>
<td>0.054</td>
</tr>
<tr>
<td>Male</td>
<td>0.56</td>
<td>0.40 to 0.78</td>
<td></td>
</tr>
<tr>
<td>Karnofsky PS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–70</td>
<td>0.49</td>
<td>0.31 to 0.76</td>
<td>0.059</td>
</tr>
<tr>
<td>80</td>
<td>0.58</td>
<td>0.34 to 0.99</td>
<td></td>
</tr>
<tr>
<td>90–100</td>
<td>0.96</td>
<td>0.66 to 1.39</td>
<td></td>
</tr>
<tr>
<td>ISS stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.75</td>
<td>0.33 to 1.69</td>
<td>0.992</td>
</tr>
<tr>
<td>II</td>
<td>0.71</td>
<td>0.43 to 1.19</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0.66</td>
<td>0.39 to 1.01</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>0.69</td>
<td>0.45 to 1.06</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del17, or t(4;14) or t(14;16)</td>
<td>0.73</td>
<td>0.55 to 0.96</td>
<td>0.358</td>
</tr>
<tr>
<td>No Del17, or t(4;14) or t(14;16)/missing</td>
<td>0.54</td>
<td>0.30 to 0.97</td>
<td></td>
</tr>
</tbody>
</table>
CR is Particularly Important for HR MM

Risk adapted therapy?

- We have good risk stratification tools
- We have several treatment choices
- Emerging data supports use of specific approaches to address risk
- Prospective trials need to incorporate these questions into the design
How Should We Be Adapting Therapy for Elderly Patients With Comorbidities?

Moderator
Brian G.M. Durie, MD

Faculty Presenter
Philippe Moreau, MD
Pt Case Example

- 78-yr-old male with a prior history of:
  - Hypertension, diabetes, and peripheral neuropathy (grade 1)
  - Bone pain refractory to acetaminophen, with ECOG PS of 2 (due to pain)

- Current exam reveals:
  - Hemoglobin of 9.8 g/dL, creatinine clearance of 40 mL/min, $\beta_2$-microglobulin of 5.8 µg/L
  - X-rays show lytic lesions in skull, vertebral collapse (T11)
  - Electrophoresis: M-spike IgG kappa 52 g/L
  - Bone marrow aspiration: 42% plasma cells

- Diagnosed with symptomatic multiple myeloma ISS 3
For this pt, do you need a cytogenetic profile or LDH level before selecting therapy?

A. Yes, you need to obtain cytogenetic information
B. Yes, you need to know his LDH value
C. Yes, you need both cytogenetics and LDH
D. No
E. Unsure
When asked this question, faculty indicated that this information is important for prognosis but not for treatment decisions.

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Yes, both cytogenetics and LDH</td>
</tr>
<tr>
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<td>Yes, both cytogenetics and LDH</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Yes, both cytogenetics and LDH</td>
</tr>
</tbody>
</table>
For this pt, would you complete a geriatric assessment before initiating therapy?

A. Yes
B. No
C. Unsure
## Expert Recommendations

<table>
<thead>
<tr>
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</tr>
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<td>Yes</td>
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<td>No</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Yes</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>No</td>
</tr>
</tbody>
</table>
Now, how would you treat this pt?

A. Bortezomib, lenalidomide, dexamethasone
B. Bortezomib, melphalan, prednisone
C. Carfilzomib, lenalidomide, dexamethasone
D. Cyclophosphamide, lenalidomide, dexamethasone
E. Cyclophosphamide, bortezomib, dexamethasone
F. Cyclophosphamide, ixazomib, dexamethasone
G. Lenalidomide and dexamethasone
H. Unsure
## Expert Recommendations

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Lenalidomide/(very) low-dose dex</td>
</tr>
<tr>
<td>Bruno Paiva, PhD</td>
<td>Lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Lenalidomide/dexamethasone</td>
</tr>
</tbody>
</table>
Treating Elderly/Frail Patients With MM

Philippe Moreau, MD
Myeloma: Age Distribution

Median Age Is 69

SEER Data, 2013.
Eligibility for ASCT

Yes

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

200 mg/m² melphalan followed by ASCT

Short-term consolidation
- VTD
- RVD

Maintenance
- Lenalidomide
- Bortezomib

No

First option: VMP, Rd, (MPT), RVD

Second option: VCD, VD, VTD

Other option: BP, CTD

FRONTLINE THERAPY
MPT vs MP: Meta-Analysis of 1685 Individual-Patient Data From 6 Randomized Trials

**PFS**

HR: 0.68 in favor of MPT, \( P < .0001 \)

Median 20.3 mos (18.8-21.6)

Median 14.9 mos (14.0-16.6)

**OS**

HR: 0.83 in favor of MPT, \( P = .004^* \)

Median 39.3 mos (35.6-44.6)

Median 32.7 mos (30.5-36.6)

* Cox model for treatment, with analysis stratified by study using a random effects (frailty) model

VMP vs MP: OS (ITT)
31% Reduced Risk of Death With VMP

Abstract #8524 / Facon, ASCO 2015 – Updated OS and PFS analysis of MM020 trial
**Future**

*MP based:*
VMP ± daratumumab: Alcyone

*RD based:*
Ixazomib-RD vs RD: Tourmaline 1
Elotuzumab-RD vs RD: Eloquent 2
Daratumumab-RD vs RD: Maia

*VMP/RD alternating, Mateos 2015*

*VRD, SWOG, Durie ASH 2015*
Total Therapy Approach for Elderly MM: GEM2010: VMP/Rd

Symptomatic newly diagnosed MM pts > 65 yrs

Sequential scheme

MPV x 9 cycles

Len/dex x 9 cycles

Alternating scheme*

MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd

Hypothesis:
- Higher efficacy for the alternating scheme
- Less probability of cell tumor scape
- Lower cumulative toxicity

74 wks

N = 233 pts

Phase III GEM05 Trial: Sequential vs Alternating VMP and Rd

Sequential arm
Alternating arm

Overall Survival (%)

Seq 72% at 3 years, 95% CI 66-75 months
Alt 74% at 3 years, 95% CI 70-76 months
p=0.63

Number at risk
Seq 117 104 98 48 10 0
Alt 114 107 101 51 8 0

Follow-up (months)

SWOG S0777 Study Design

Randomization
N = 525

Stratification:
• ISS (I, II, III)
• Intent to transplant @ progression (yes/no)

Eight 21-Day Cycles of VRd

Bortezomib 1.3/mg² IV
Days 1, 4, 8, and 11
Lenalidomide 25 mg/day PO
Days 1-14
Dexamethasone 20 mg/day PO
Days 1, 2, 4, 5, 8, 9, 11, 12

Six 28-Day Cycles of Rd

Lenalidomide 25 mg/day PO
Days 1-21
Dexamethasone 40 mg/day PO
Days 1, 8, 15, 22

Overall Survival By Assigned Treatment Arm

Log-rank P value = 0.0250 (two sided) *

HR = 0.709 (0.516, 0.973) *

Deaths / N
VRd 76 / 242
Rd 100 / 229

Median In Months
VRd 75 (66, .)
Rd 64 (56, .)

*Stratified

The Issue of Frailty
## Recommendations for Adjusting Therapy

<table>
<thead>
<tr>
<th>Autologous stem cell transplantation</th>
<th>Full dose novel agent–based therapy</th>
<th>Reduced dose novel agent–based therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 yrs In good clinical condition AND no comorbidities</td>
<td>65-75 yrs In good clinical condition AND no comorbidities</td>
<td>&gt; 75 yrs In good clinical condition AND no comorbidities</td>
</tr>
<tr>
<td>Frail AND/OR with comorbidities</td>
<td>Frail AND/OR with comorbidities</td>
<td>Frail AND/OR with comorbidities</td>
</tr>
</tbody>
</table>

Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report

Antonio Palumbo,1 Sara Bringhen,1 Maria-Victoria Mateos,2 Alessandra Larroca,1 Thierry Facon,3 Shaji K. Kumar,4 Massimo Offidani,5 Philip McCarthy,6 Andrea Evangelista,7 Sagar Lonial,8 Sonja Zweegman,9 Pellegrino Musto,10 Evangelos Terpos,11 Andrew Belch,12 Roman Hajek,13 Heinz Ludwig,14 A. Keith Stewart,15 Philippe Moreau,16 Kenneth Anderson,17 Hermann Einsele,18 Brian G. M. Durie,19 Meletios A. Dimopoulos,11 Ola Landgren,20 Jesus F. San Miguel,21 Paul Richardson,22 Pieter Sonneveld,23 and S. Vincent Rajkumar4

Blood. 2015;125:2068.
# Frailty score

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (CI 95%)</th>
<th>P</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Age 75-80 years</td>
<td>1.37 (0.93-2.03)</td>
<td>0.114</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>2.75 (1.81-4.18)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td><strong>CHARLSON INDEX</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson ≤1</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Charlson ≥2</td>
<td>1.6 (1.07-2.39)</td>
<td>0.021</td>
<td>1</td>
</tr>
<tr>
<td><strong>ADL SCORE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADL &gt;4</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>ADL ≤4</td>
<td>1.76 (1.14-2.71)</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td><strong>IADL SCORE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IADL &gt;5</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>IADL ≤5</td>
<td>1.53 (1.03-2.27)</td>
<td>0.036</td>
<td>1</td>
</tr>
</tbody>
</table>

### ADDITIVE TOTAL SCORE  PATIENT STATUS

<table>
<thead>
<tr>
<th>Total</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>FIT</td>
</tr>
<tr>
<td>1</td>
<td>UNFIT</td>
</tr>
<tr>
<td>≥2</td>
<td>FRAIL</td>
</tr>
</tbody>
</table>


Overall Survival
Subgroup analysis in all patients

Age

Chromosomal abnormalities

Frailty

1-yr OS

< 75yr  92%
≥ 75yr  86%

1-yr OS

SR Fish  91%
HR Fish  83%

1-yr OS

Fit  96%
Frail  78%

≥75yr vs <75yr, HR=1.72 p=0.001

HR vs SR Fish, HR=1.86 p=0.001

Frail vs Fit, HR=3.53 p<0.001

Fit defined as: score=0   Frail defined as: score≥2
HR Fish: presence of t(4;14) or t(14;16) or del 17q13

Discontinuation of Therapy

Nonhematologic Adverse Events

ADL activity daily living: 0/1
(Katz JAMA 1963)
Maximum score total 6 (cutoff > 4)

- Bathing
- Dressing
- Toileting
- Transferring
- Continence
- Feeding
IADL instrumental activity daily living: 0/1
Maximum score total 8 (cutoff > 5)
Lawton Psychopharmacol Bull 1988

- Ability to use the telephone
- Shopping
- Food preparation
- Housekeeping
- Laundry
- Mode of transportation
- Responsability for own medications
- Ability to handle finances
**Charlson CCI: From 0 to 37 (J Chronic Dis 1987)**

**Cutoff ≥ 2**

1. Myocardial infarction; congestive heart failure; cerebrovascular disease; dementia; chronic pulmonary disease; connective tissue disease; peptic ulcer disease; mild liver disease; diabetes without end-organ damage

2. Hemiplegia; moderate or severe renal disease; diabetes with end-organ damage; tumor without metastasis; leukemia; lymphoma

3. Moderate or severe liver disease

6. Metastatic solid tumor; AIDS
**Conclusion 1**

<table>
<thead>
<tr>
<th>PATIENT STATUS ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (score 0 – 1 – 2)</td>
</tr>
<tr>
<td>ADL (score 0 – 1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIT</th>
<th>UNFIT</th>
<th>FRAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive total score = 0</td>
<td>Additive total score = 1</td>
<td>Additive total score ≥ 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GO-GO</th>
<th>MODERATE-GO</th>
<th>SLOW-GO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-dose</td>
<td>Reduced-dose</td>
<td>Further reduced dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose level 0</th>
<th>Dose level -1</th>
<th>Dose level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>25 mg/d</td>
<td>15 mg/d</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m^2/wk</td>
<td>1.0 mg/m^2/wk</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/wk</td>
<td>20 mg/wk</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300 mg/m^2 d 1,8,15</td>
<td>50 mg/d</td>
</tr>
</tbody>
</table>

## Risk factors

- Age over 75 years
- Mild, moderate or severe frailty: patients needing help for household tasks and personal care
- Comorbidities: cardiac dysfunction, pulmonary dysfunction, hepatic dysfunction, renal dysfunction

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>DOSE LEVEL 0</th>
<th>MODERATE-DOSE LEVEL</th>
<th>SLOW-DOSE LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>DOSE LEVEL 0</td>
<td>At least one risk factor</td>
<td>At least one risk factor plus occurrence of grade 3-4 non-hematologic AE</td>
</tr>
</tbody>
</table>

### Agent | DOSE LEVEL 0 | DOSE LEVEL 1 | DOSE LEVEL 2 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>40 mg/d</td>
<td>20 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg or 9 mg/m²</td>
<td>0.18 mg/kg or 7.5 mg/m²</td>
<td>0.13 mg/kg or 5 mg/m²</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>100 mg/d</td>
<td>50 mg/d</td>
<td>50 mg qod</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg/d</td>
<td>15 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² twice weekly</td>
<td>1.3 mg/m² once weekly</td>
<td>1.0 mg/m² once weekly</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² d 1-4 or 50 mg qod</td>
<td>30 mg/m² d 1-4 or 25 mg qod</td>
<td>15 mg/m² d 1-4 or 12.5 mg qod</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>100 mg/d d1-21/4 wks or 300 mg/m²/d</td>
<td>50 mg/d d 1-21/4 wks or 150 mg/m²/d</td>
<td>50 mg qod d 1-21/4 wks or 75 mg/m²/d</td>
</tr>
</tbody>
</table>
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clinicaloptions.com/oncology
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