The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
TABLE OF CONTENTS

SUMMARY OF TREATMENT RECOMMENDATIONS 4

Background 5
GUIDELINE GOALS AND OBJECTIVES
GUIDELINE QUESTIONS
DEVELOPMENT PANEL
SEARCH STRATEGY
TARGET POPULATION

GUIDELINES

I. MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS) 6
Diagnostic Criteria
Prognosis
Investigation and Management

II. SMOULDERING (ASYMPTOMATIC) MYELOMA 8
Diagnostic Criteria
Prognosis
Treatment

III. MULTIPLE MYELOMA 9
Diagnostic Criteria & Staging 9
Initial Investigations 10
Prognosis 11
Treatment Guidelines for Newly Diagnosed Multiple Myeloma 12

Patients ≤ 65 Years Old and Transplant-Eligible: 12
1. Induction Regimens 12
2. Stem Cell Transplant 14
3. Post Transplant Therapy 16
4. Summary of Recommendations 18

Patients > 65 Years Old or Transplant Ineligible 20
Summary of Recommendations 24

Treatment Guidelines for Relapsed and Refractory Multiple Myeloma 25

Assessment of Response to Therapy 27
Follow-Up After Treatment 29
Supportive Therapy 30
1. Bisphosphonates 31
2. Osteonecrosis of the Jaws (ONJ) 32
3. Percutaneous Vertebral Augmentation or Kyphoplasty 32
4. Radiation Therapy 32
5. Viral Prophylaxis 33
6. Orthopedic Surgery

IV. SOLITARY PLASMACYTOMA

V. AMYLOIDOSIS

GLOSSARY OF ABBREVIATIONS

IMPLEMENTATION STRATEGY
EVALUATION STRATEGY
DECLARATION OF CONFLICT OF INTEREST

REFERENCES

APPENDIX A:
EVIDENCE TABLES FOR TREATMENT REGIMENS IN MULTIPLE MYELOMA

APPENDIX B:
TREATMENT REGIMENS FOR MULTIPLE MYELOMA
Pamidronate (30-90mg) or zoledronate (4mg) IV monthly for 2 years

Transplant Eligible
Standard Risk Disease

CyBorD (4-6 cycles)
- Cyclophosphamide 300mg/m² orally weekly for 4 weeks
- Bortezomib 1.5mg/m² IV/sc weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks

Stem Cell Mobilization: High dose cyclophosphamide and GCSF

High Dose Melphalan Bortezomib and Autologous Stem Cell Transplant

VRD x 2 cycles

Transplant Eligible
High Risk Disease
(17p deletion of t(4;14))

CyBorD (4-6 cycles) or VRD (4-6 cycles)
- Lenalidomide* 25mg orally daily for 21/28 days
- Bortezomib 1.5mg/m² IV/sc weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks

Transplant Ineligible

CyBorD (9-12 cycles)

Lenalidomide*
(25mg orally daily for 21/28 days)
and Dexamethasone
(40mg weekly until progression)

Bortezomib 1.3mg/m² every 2 weeks for 2 years

*CURRENTLY NOT FUNDED for FIRST LINE USE in ALBERTA

17p del or t(4:14)

NO

Lenalidomide
10mg daily for 21/28 days until progression

YES

Bortezomib
1.3mg/m² IV/sc every 2 weeks for 2 years
BACKGROUND

Multiple myeloma (MM) is an aggressive malignant neoplasm of plasma cells that accumulates in the bone marrow and contributes to approximately 15 percent of all hematologic malignancies. In Canada, MM makes up 1.2 percent of all new cancer cases and 1.8 percent of all cancer deaths.\(^1\) Seventy-five percent of all myeloma cases are in patients over the age of 60 years, and the incidence increases steadily with age.\(^2\)

MM is not considered curable with current approaches; however, 5-year survival rates have increased over the past few decades due to a variety of newer and more effective treatment options. The clinical course of MM is heterogeneous and survival times range widely, depending on critical factors such as the disease stage and the presence of prognostic indicators.\(^3\) Patients are classified initially as having asymptomatic or symptomatic disease; those with symptomatic disease are then classified further according to the stage of their disease. Treatment options are heterogeneous, and may include therapies such as standard or high-dose chemotherapy regimens, alone or in combination with autologous or allogeneic stem cell transplantations.

GUIDELINE GOALS AND OBJECTIVES

- To outline the diagnostic criteria for multiple myeloma, monoclonal gammopathy, smoldering myeloma, and amyloidosis
- To describe current treatment strategies for multiple myeloma, monoclonal gammopathies, smoldering myeloma, and amyloidosis

GUIDELINE QUESTIONS

- What are the diagnostic and prognostic criteria for multiple myeloma and related disorders?
- What are the most suitable management strategies of multiple myeloma and related disorders?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of the Alberta Provincial Hematology Tumour Team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit.

SEARCH STRATEGY

The MEDLINE (1966 through July 2012), PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases were searched. In addition, the ASCO and ASH Abstracts and Proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials.

TARGET POPULATION

The following guidelines apply to adults over the age of 18 years. Different principles may apply to pediatric patients.
I. MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

Diagnostic Criteria

- M-protein in serum < 30 g/L
- Bone marrow clonal plasma cells (PC) < 10%
- No CRAB or ROTI (myeloma Related Organ or Tissue Impairment):
  - Ca (corrected) >0.25 mmol/L upper limit of normal or >2.75 mmol/L
  - Renal impairment: Creatinine > 176 µmol/L
  - Anemia: Hemoglobin < 100g/L or 20g/L below lower limit of normal
  - Bone lesions: lytic lesions or osteoporosis with compression fractures
  - Others: symptomatic hyper-viscosity, amyloidosis, recurrent bacterial infections (> 2/year)

The incidence of MGUS is 1% for patients over the age of 50 years, and approximately 3% for patients over the age of 70 years.

Prognosis

- Actuarial rate of progression to multiple myeloma or other lymphoproliferative disorder:
  - 17% at 10 years, 34% at 20 years, and 39% at 25 years
  - Approximately 1.5% per year
- Three risk factors for progression to multiple myeloma:
  1) Non-IgG monoclonal protein
  2) Serum M-protein > 15 g/L
  3) Abnormal free light chain (FLC) ratio (FLC ratio < 0.26 or > 1.65)
- Risk of progression at 20 years based on number of risk factors:
  - High 3/3: 58%
  - High-Intermediate 2/3: 37%
  - Low-Intermediate 1/3: 21%
  - Low risk 0/3: 5%
- Cumulative annual rate of progression based on FLC ratio:
  - Normal FLC ratio (0.26-1.65) vs. Abnormal: 0.6% vs. 1.8%
  - FLC ratio 0.25-4: 0.8%
  - FLC ratio 0.125-0.25 or 4-8: 2%
  - FLC ratio < 0.125 or >8: 3%

Investigation and Management

Patients with MGUS do not require any treatment unless they have evidence of organ or tissue impairment (i.e. CRAB or ROTI) and thus should be classified as symptomatic myeloma rather than MGUS. Patients with MGUS are at risk to develop lymphoproliferative diseases such as myeloma, amyloidosis or malignant lymphomas. Those with low risk MGUS do not require follow up with hematology. Instead, they can be monitored by their primary care physician with annual CBC, chemistry, creatinine and calcium. All others should have an annual hematology assessment.
At diagnosis the following tests should be completed:

- CBC
- Creatinine
- Calcium
- Total protein
- Albumin
- Quantitative immunoglobulin levels (IgG, IgA, IgM)
- Serum and urine (24-hour collection) protein electrophoresis
- FLC studies
- Bone marrow aspirate and biopsy
- Skeletal survey

The following tests should be obtained yearly thereafter:

- CBC
- Serum creatinine
- Calcium,
- Serum, and 24-hour urine protein electrophoresis
- Quantitative immunoglobulins
- Free light chains
- Skeletal survey
II. SMOULDERING (ASYMPTOMATIC) MYELOMA

Diagnostic Criteria

- M-protein in serum ≥ 30g/L, and/or
- Bone marrow plasmacytosis ≥10%
- No CRAB or ROTI
- No high risk features

Prognosis

For the purpose of predicting progression to symptomatic myeloma, smoldering myeloma can be divided into 3 risk groups:

- High Risk: serum M protein ≥30 g/L and bone marrow PC ≥ 10%
- Intermediate Risk: serum M protein < 30 g/L and bone marrow PC ≥ 10%
- Low Risk: serum M protein ≥30 g/L and bone marrow PC < 10%

The serum free light chain ratio can be used to further define the risk of progression for those with high or intermediate risk disease.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression</td>
<td>5.5 years</td>
<td>2.4 years</td>
<td>9.2 years</td>
<td>19 years</td>
</tr>
<tr>
<td>Rate of progression @ 10 years</td>
<td>62%</td>
<td>76%</td>
<td>59%</td>
<td>32%</td>
</tr>
<tr>
<td>FLC ratio 0.125 – 8.0</td>
<td>59%</td>
<td>58%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>FLC ratio &lt;0.125 or &gt;8.0</td>
<td>84%</td>
<td>69%</td>
<td>33%</td>
<td></td>
</tr>
</tbody>
</table>

In addition, certain features can identify patients at high risk of progression to multiple myeloma. These include:

- Bone marrow plasmacytosis ≥ 60%. (median time to progression to symptomatic myeloma of 7 months; 95% progression within 2 years)
- T(4;14) or p53 deletion (median time to progression <2 years)
- Two or more focal bone lesions detected by CT, MRI, or PET scan. (median time to progression 13 months)
- Ratio of involved/uninvolved free light chains > 100. (median time to progression 15 months)

Treatment

Patients with high-risk features are considered as having overt myeloma and should receive front-line myeloma therapy. Otherwise, no treatment is required for smoldering myeloma until progression to multiple myeloma or other lymphoproliferative disorder. Patients should be followed every 3-4 months and monitored for “myeloma-related” symptoms (CRAB) or organ damage.
III. MULTIPLE MYELOMA

Diagnostic Criteria

- M-protein in serum and/or urine as detected by SPEP, UPEP or FLC
- Clonal bone marrow plasma cells or plasmacytoma
- Presence of organ dysfunction: CRAB [Ca >2.75 mmol/L, Creatinine > 176 µmol/L, Hgb < 100g/L, Bone lesions or osteopenia with compression fractures] or ROTI
- High risk features including bone marrow plasmacytosis ≥ 60%, t(4;14) or p53 deletion, two or more focal bone lesions detected by CT, MRI, or PET scan, or ratio of involved/uninvolved free light chains > 100

Staging

The Alberta Provincial Hematology Tumour Team as the standard staging system has adopted the International Staging System, rather than Durie-Salmon, for myeloma patients.

Table 1. International Staging System (ISS) for Multiple Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>β2M (mg/L)</th>
<th>Albumin (g/L)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt; 3.5</td>
<td>and</td>
<td>≥ 35</td>
</tr>
<tr>
<td>II</td>
<td>≥ 3.5 to &lt; 5.5</td>
<td>and /or</td>
<td>&lt; 35</td>
</tr>
<tr>
<td>III</td>
<td>β2M ≥ 5.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Durie-Salmon Staging for Multiple Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Myeloma Cell Mass (x10^{12} cells/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following:</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td></td>
<td>• Hgb &gt;100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Calcium normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No lytic bone lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG &lt;50 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA &lt;30 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Urine M-protein &lt;4 g/24 h</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Neither I nor III</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>III</td>
<td>One or more of the following:</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td></td>
<td>• Hgb &lt; 85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Calcium &gt; 3 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG &gt;70 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA &gt;50 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Urine M-protein &gt;12 g/24 h</td>
<td></td>
</tr>
</tbody>
</table>

Sub-classification: 'A' Creatinine Normal / 'B' Creatinine Elevated
Initial Investigations

- History and physical exam
- CBC, albumin, total protein, creatinine, β2-microglobulin, LDH, calcium, ALP, ALT, LDH, bili
- SPEP with immunofixation (IFE)
- 24 hour UPEP with quantification of M-protein and IFE. Consider possibility of amyloidosis in those with significant albuminuria
- Quantitative immunoglobulins (IgG, IgA, IgM)
- FLC studies (κ, λ and FLC ratio)
- NT-proBNP, troponin
- Bone survey of the axial and appendicular skeleton (CT scan, MRI, and/or PET scan are occasionally required for accurate measurements of plasmacytomas)
- Bone marrow aspirate and biopsy including flow cytometry
- Cytogenetics: (tests in **bold font** are required and strongly recommended at diagnosis)
  - **FISH** for:
    - t(14;16)
    - t(4;14)
    - Deletion 17 (17p-)
  - 1q21 amplification; t(14;20) (currently not available through Calgary Lab Services)
  - **Conventional band karyotyping at diagnosis.** To indicate ploidy status and presence of del13q. Full karyotyping not required.
- MRI may be indicated in special circumstances (i.e., to rule out cord compression, CNS involvement, non-secretory multiple myeloma, smouldering myeloma and solitary bone or soft tissue plasmacytoma)
- PET scan is not currently indicated for the diagnosis or follow-up of multiple myeloma patients
- Echocardiogram or cardiac MRI is only indicated if there is clinical suspicion of cardiac amyloidosis

Myeloma associated AL amyloidosis is reported in 12-30% of multiple myeloma patients. These patients typically fulfill the diagnostic criteria for multiple myeloma and have evidence of amyloid light chain deposition confirmed by Congo red staining. Amyloidosis should be suspected in the presence of nephrotic range proteinuria with predominant albuminuria; non-hypertensive congestive heart failure without coronary artery disease; low voltage, bradycardia or A-V block on EKG, organomegaly, autonomic neuropathy and carpal tunnel syndrome.

The following investigations should be ordered if the diagnosis of myeloma-associated AL amyloidosis is suspected in order to confirm the diagnosis:
- Congo red staining of the bone marrow
- Fat pad aspirate, biopsy, or punch biopsy and Congo red staining if bone marrow is negative
- Direct biopsy of suspected involved organ if Congo red stain is negative in bone marrow and fat pad.
- Congo red positive biopsies should be forwarded for mass spectroscopy analysis and typing.

Patients with biopsy-proven amyloidosis should be classified as “Myeloma with Documented Amyloidosis” if they have ≥ 10% plasma cells and/or myeloma-related bone disease. For the management of these patients, please refer to the section on **Amyloidosis** below.
Prognosis

Prognostic information reflects the treatment received during the era of a specific publication and may not reflect improvements in outcome expected with the introduction of novel agents, triple induction therapy, maintenance, consolidation, etc.

Table 3. Survival Outcomes for Multiple Myeloma According to Stage

<table>
<thead>
<tr>
<th>ISS Stage</th>
<th>Median OS from initiation of chemotherapy (months)</th>
<th>Median OS* from initiation of chemotherapy (months)</th>
<th>Median OS* post SDT (months)</th>
<th>Median OS* post HDT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>62</td>
<td>55</td>
<td>111</td>
<td>69</td>
</tr>
<tr>
<td>II</td>
<td>44</td>
<td>40</td>
<td>66</td>
<td>41</td>
</tr>
<tr>
<td>III</td>
<td>29</td>
<td>25</td>
<td>45</td>
<td>33/22</td>
</tr>
</tbody>
</table>

*Median OS from the time of initiation of chemotherapy
SDT = standard dose chemotherapy, HDT = high dose therapy.

Table 4. Survival Outcomes According to Recurrent Genomic Aberrations as Detected by FISH

<table>
<thead>
<tr>
<th>Genomic Aberrations‡</th>
<th>Incidence</th>
<th>Event Free Survival*† (months)</th>
<th>Overall Survival*† (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delete 13q</td>
<td>48%</td>
<td>29 vs. 41 (p=1.10^-8)</td>
<td>68% vs. 83% (p=9.10^-7)</td>
</tr>
<tr>
<td>t(4;14)(p16;q32)</td>
<td>14%</td>
<td>20.6 vs. 36.5 (p=1.10^-12)</td>
<td>41.3 vs. 79% (p=2.10^-10)</td>
</tr>
<tr>
<td>Delete 17p</td>
<td>11%</td>
<td>15 vs. 35 (p=5.10^-10)</td>
<td>22 vs. 75% (p=4.10^-12)</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>39%</td>
<td>37 vs. 33 (p=0.02)</td>
<td>82% vs. 70% (p=0.006)</td>
</tr>
</tbody>
</table>

‡ In a multivariate analysis only del 17p (>60%), t(4;14) and β2m >4mg/L impacted OS.
*Median survival at a median follow-up of 41 months for patients with versus without genomic aberration.
**t(11;14)(q13;q32) and MYC translocations did not impact EFS or OS.
†All patients received tandem transplantation in IFM99 studies (auto/auto or auto/allo).
†Numbers reflect survival post single ASCT.

Flow Cytometry: Flow cytometry should be performed on bone marrow biopsies at diagnosis, and on subsequent biopsies in order to confirm complete remission or detect minimal residual disease. The presence or absence of immunophenotypic evidence of clonal plasma cells on bone marrow samples following therapy is a strong predictor of PFS and survival.

Progression-free survival according to the response status after six cycles of induction therapy in patients with negative immunofixation plus normal serum free light chain (sFLC) ratio (stringent complete response [CR]; n = 31), immunofixation negative plus abnormal sFLC ratio (CR; n = 13), immunofixation positive plus normal sFLC ratio (partial response [PR]/normal sFLC ratio; n = 26), or immunofixation positive plus abnormal sFLC ratio (PR/abnormal sFLC ratio; n = 32)²¹.
Treatment Guidelines for Newly Diagnosed Multiple Myeloma

Goal of therapy:

The goals of therapy for young patients with multiple myeloma is to achieve the deepest possible response, ideally a complete remission, and to then maintain that response for as long as possible.

For elderly patients, the goal of therapy is to minimize symptoms and maximize response with as little toxicity as possible.

These guidelines identify effective, evidence based treatment regimes (as opposed to single agents) to be utilized. These treatment regimens can include multi-drug and multi-step approaches, radiation therapy, or single agents when appropriate.

Patients ≤ 65 Years Old and Transplant-Eligible:

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, patients who are 65 years old or younger and are transplant-eligible should receive a course of therapy consisting of:

- Pre-transplant induction with a 3-drug regimen that includes a novel agent
- High dose melphalan +/- bortezomib followed by autologous stem cell transplantation
- Post transplant consolidation
- Maintenance lenalidomide and/or bortezomib until disease progression.

Induction Regimens:

Induction regimens should contain at least one novel agent (e.g. bortezomib, lenalidomide, thalidomide). There is consensus amongst the myeloma physicians that a triple drug based induction regimen results in superior outcomes with improved rate and depth of responses (higher CR and sCR rates). Four randomized trials comparing doublet versus triplet-based regimen are in favor of triplet-based regimen since the latter results in improved responses as well as progression free survival\textsuperscript{20-25}. The following figure shows the overall, VGPR, and nCR/CR rates for a selection of phase 2 and phase 3 trials incorporating novel agents. A continuous improvement in response is seen with the combination of newer agents. However many of these are small single-center experiences, and evidence that early responses translate into longer-term survival is not yet available.

(References: VAD\textsuperscript{26}, TD\textsuperscript{27}, RD\textsuperscript{28}, PAD\textsuperscript{29}, VTD\textsuperscript{30}, CV\textsuperscript{31}, RVD\textsuperscript{32}, CVRD\textsuperscript{26}).
Bortezomib-based induction regimens:
Numerous studies have shown that the depth of response achieved following ASCT is predictive of outcome. Patients achieving CR, nCR, and/or VGPR after transplantation have longer remissions and survival times than those with lesser responses. It has been suggested that if induction regimens with higher initial response rates were used prior to transplant, this should produce deeper responses post transplant, resulting in better PFS and OS. Until recently, this potential benefit of more effective induction had not been shown. A large meta-analysis failed to demonstrate any survival advantage for combination chemotherapy (i.e. VAD, VBMCP) compared to melphalan + prednisone. A randomized trial comparing induction with TD versus VAD showed higher response rates to TD induction, but similar response rates (VGPR 42% vs 44%) after transplant.

However, recent studies of bortezomib based regimens suggest the choice of induction regimen may indeed affect outcome post transplant. They showed an improvement in response with higher CR/near CR post transplant, and superior progression free survival for those receiving bortezomib based regimens, with an improvement in overall survival seen in one study. The findings of these three studies are summarized in appendix A, table1.

Bortezomib and dexamethasone based regimens for 3-4 cycles are well tolerated and shown to be more effective than older regimens, improving response rate, PFS, and OS post transplant. Bortezomib and dexamethasone should be included as part of multi-drug regimens as standard induction therapy prior to stem cell transplantation, along with a third agent such as cyclophosphamide (CyBorD) and lenalidomide* (VRD). Patients refractory to initial therapy with VCD (fail to achieve at least PR) should be switched to second line therapy with lenalidomide and dexamethasone or VRD for several cycles prior to stem cell mobilization.

CYBORD:
Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days. Each cycle consists of:
- Cyclophosphamide 300mg/m² orally weekly for 4 weeks
- Bortezomib 1.5mg/m² intravenously or subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

A twice-weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy.

VRD*:
Patients should receive no more than 4 cycles prior to attempted stem cell mobilization. Cycles are repeated every 28 days. Each cycle consists of:
- Lenalidomide 25mg orally daily for 21 days
- Bortezomib 1.5mg/m² subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

A 21-day schedule can be used for sicker patients requiring a more rapid initial response to therapy:
- Lenalidomide 25mg orally daily for 14 days
- Bortezomib 1.3mg/m² subcutaneously twice weekly for 2 weeks
- Dexamethasone 40mg orally twice weekly for 2 weeks.

*This is an evidence based recommendation. Lenalidomide is currently NOT funded for front line use in ALBERTA.
Thalidomide-based regimens:

Several large randomized trials have compared induction therapy with thalidomide to dexamethasone.\[^{38-46}\] Trial details can be found in Table 2 of Appendix A. In patients eligible for SCT, a thalidomide-based induction regimen resulted in a significantly higher response rate (CR and VGPR) and PFS/TTP/EFS. The impact on OS of induction therapy with thalidomide followed by autologous stem cell transplant remains a matter of debate. Only one study did demonstrate an overall survival advantage with thalidomide – VADoxili\[^{38}\]. Randomized controlled trials of thalidomide have demonstrated higher incidence of adverse events with thalidomide as compared to standard therapy. In particular, VTE, peripheral neuropathy, & constipation are increased. Risk of VTE (between 4 and 20%) is greater when thalidomide is combined with steroid &/or chemo but less when thalidomide used as maintenance.

Lenalidomide-based induction regimen:

The combination of lenalidomide and dexamethasone is a well tolerated and convenient oral regimen resulting in high response rates when followed by ASCT, with 3 year PFS and OS of 64% and 94% respectively.\[^{47}\] Two large randomized trials comparing an induction therapy with a lenalidomide-based regimen have reported high rates of CR/VGPR and high 2-year PFS and OS rates.\[^{48,49}\] Table 3 in Appendix A outlines the details of these trials. Lenalidomide with low-dose dexamethasone (40 mg PO weekly) (Ld) is superior to lenalidomide with standard-dose dexamethasone (LD) (40 mg PO days 1-4, 9-12, 17-20). The impact of a lenalidomide-based induction regimen on survival post-ASCT is unclear since transplant is often deferred until relapse in these studies. Patients treated with 4 cycles of lenalidomide followed by ASCT had a 2 year OS of 93%, similar to those treated with Ld until disease progression.

Because prolonged therapy with lenalidomide can impair stem cell mobilization, consider stem cell collection within 4 cycles of induction lenalidomide.

Other Regimens:

Single agent dexamethasone is associated with suboptimal response and should not be used as the only therapy for myeloma.

The VAD regimen should not be used due to the toxicity of this regimen (neurotoxicity, cardiac toxicity, myelosuppression) and its inferior outcomes compared to bortezomib containing regimens.

High Risk Myeloma:

Patients with high risk cytogenetic aberrations such as del17p or t(4;14) and t(14;16) have a worse outcome with ASCT than patients without these findings. They should be considered for clinical trials with novel frontline agents with or without SCT. However, in the absence of a clinical trial, patients with high risk myeloma should receive similar treatment as other myeloma patients including induction with a bortezomib based regimen and should be considered for initial therapy with a combination of bortezomib, lenalidomide and dexamethasone (VRD), followed by ASCT.

2. Stem Cell Transplantation:

Autologous Stem Cell Transplant (ASCT):

Four large randomized trials have demonstrated the superiority of autologous stem cell transplantation to standard dose chemotherapy with significant prolongation of TTP and OS.\[^{50-53}\] Other trials, with several
caveats, have failed to demonstrate the same benefit from ASCT.\textsuperscript{54-57} Details of these trials are outlined in Table 4 of Appendix A.

Patients are considered transplant eligible if they are under the age of 65, meet minimal requirements for underlying organ function and all other transplant eligibility requirements of the Calgary or Edmonton transplant programs. There is no proven benefit to transplant over standard therapy for patients over the age of 65. These patients can be considered for ASCT if they meet all transplant eligibility criteria, are physiologically very fit, and have no significant comorbid illnesses.

Transplant eligible patients should receive 3-4 cycles of induction therapy before proceeding to ASCT. The achievement of CR is not required to proceed to transplant. Patients who fail to achieve CR after 3-4 cycles of induction, including those with primary refractory disease, can still benefit from high dose therapy and ASCT and should still be referred for transplant evaluation. Patients with renal failure on dialysis are candidates for autologous stem cell transplant and should be referred without significant delays for transplant evaluation. Twenty to twenty-five percent of patients do recover their renal function and become dialysis-independent up to 6 months post-transplant.

**Stem cell collection:**

The standard regimen includes cyclophosphamide 2.5 mg/m\textsuperscript{2} with G-CSF starting on day 7. The goal is to collect at least 5 x 10\textsuperscript{6} CD34 cells/kg for each planned transplant.

**Conditioning regimen:**

The standard transplant conditioning regimen is high dose Melphalan 200 mg/m\textsuperscript{2} on day -1. The incorporation of bortezomib (1.3mg/m\textsuperscript{2} day -5, -2, +1, and +4) with high dose melphalan conditioning has been shown to improve CR rates and should be considered in those without a contraindication to bortezomib\textsuperscript{58-60}.

**Tandem Autologous Transplantation:**

Tandem autologous transplant should not be routinely performed. Four large randomized trials have addressed the role of tandem transplantation in multiple myeloma, and have shown that tandem transplantation improves survival in patients who fail to achieve a VGPR after the first transplant\textsuperscript{61-64}. Details of these trials are outlined in Table 5 of Appendix A. However, considerable benefit is also seen with continuous post transplant therapy that includes novel agents.

**Allogeneic Stem Cell Transplant:**

Four studies have been conducted to date comparing tandem autologous to tandem autologous-allogeneic stem cell transplant. The details of these trials are outlined in Table 6 of Appendix A. In a French study trial (IFM99-03) of high risk patients (del13 and high β2), no difference in outcome was seen between the two approaches. However it should be noted that only patients with high risk disease were enrolled into this study and high dose ATG was used in the conditioning regimen.\textsuperscript{65} In a study by Bruno and colleagues, allogeneic transplant was by far superior however in this study the results of the tandem autologous arm were lower than expected and the study had several reporting caveats.\textsuperscript{66} Early results from the PETHEMA group suggest superior results with allogeneic transplant; however they only report a trend for better PFS, not OS.\textsuperscript{68} The largest study comparing autologous to transplantation was performed by the US Blood and Marrow Clinical Trials Network. 625 patients were biologically assigned to receive either a tandem ASCT with melphalan 200 mg/m\textsuperscript{2} (n = 436) or ASCT with melphalan 200 mg/m2 followed by an allogeneic SCT conditioned with fludarabine and 200 cGy of total body irradiation (n = 189). The 3-year PFS was 46% for the tandem autologous arm versus 43% for the autologous-allogeneic arm (P =
.67). OS at 3 years was also not significantly different between the groups: 80% for the tandem autografts versus 77% for the autologous-allogeneic arm. Assignment to the autologous-allogeneic arm was associated with worsened survival in patients with stage I and II disease, but not in those with stage III disease68. At this point, allogeneic transplant is not considered a standard part of therapy for newly diagnosed or relapsed myeloma and should be performed only in the setting of a clinical trial.

3. Post Transplant Therapy:

Consolidation:

All patients should receive 2 cycles of consolidation therapy in addition to maintenance therapy. Both bortezomib23 and lenalidomide69 based regimens have been used. Compared to thalidomide and dexamethasone, the combination of bortezomib, thalidomide, and dexamethasone as consolidation after ASCT significantly improved CR (46% vs 60%) and CR/nCR rates (61% vs 73%). With a median follow-up of 30.4 months from start of consolidation, 3-year progression-free survival was significantly longer for the VTD group (60% vs 48% for TD). Grade 2 or 3 peripheral neuropathy (8.1% vs 2.4%) was more frequent with VTD (grade 3, 0.6%) versus TD consolidation.

Our recommendation is for 2 cycles of consolidation with VRD* in all patients post ASCT. Lenalidomide in place of thalidomide should be used to minimize risk of neuropathy.

- Bortezomib 1.3 mg/m² on days 1, 8, 15, and 22
- Lenalidomide 10mg/d, days 1-21/28 (or Thalidomide 100 mg daily)
- Dexamethasone 40 mg on days 1, 8, 15, 22

*This is an evidence based recommendation. Bortezomib based consolidation is currently funded only for those not achieving VGPR post-ASCT

Maintenance Therapy:

Lenalidomide:

Two phase III trials have examined the role of lenalidomide maintenance following ASCT. The CALGB 100104 (n=460) trial compared a strategy of maintenance with lenalidomide (10mg daily) to placebo following ASCT69. At a median follow up of 34 months, maintenance resulted in an improved TTP of 46 months versus 27 months for placebos (p<0.001). Overall survival was also improved, with HR for death 0.62 (p<0.03). Lenalidomide maintenance was associated with an increase in second primary malignancies (SPM) (7.8% vs 2.6%). However event free survival analysis including SPM as study related events continued to show improved survival outcomes in favor of the maintenance arm.

The IFM 2005-02 trial70 randomized 614 patients to maintenance with lenalidomide 10-15mg daily following ASCT. All patients received two cycles of consolidation with lenalidomide 25mg daily for 21 of 28 days prior to starting maintenance. With a median follow up of 45 months, the 4 year PFS was 43% for lenalidomide compared to 22% for placebo (p<0.001). There was no difference in OS (73% vs 75%). There were 23 second primary malignancies in the lenalidomide group and 9 in the placebo group.

A retrospective analysis of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma including 3846 patients reported an incidence rate of second primary malignancies (SPMs) of 3.6271. Incidence rate of invasive (hematologic and solid tumor) SPMs was 2.08, consistent with the background incidence of developing cancer. In a separate analysis of pooled data from pivotal phase 3
trials of relapsed or refractory MM (n = 703), the overall IR of SPMs was 3.98 (2.51-6.31) with lenalidomide/dexamethasone and 1.38 (0.44-4.27) with placebo/dexamethasone. IRs of non-melanoma skin cancers were 2.40 (1.33-4.33) and 0.91 (0.23-3.66), respectively. IRs of invasive SPMs were 1.71 (0.86-3.43) and 0.91 (0.23-3.66), respectively.

**Bortezomib:**
The phase III HOVON-65/ GMMG-HD4 trial randomized 827 patients to receive VAD induction followed by ASCT and maintenance therapy with thalidomide (arm A) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by ASCT and maintenance with bortezomib every 2 weeks for 2 years (arm B). The strategy of bortezomib-based induction with bortezomib maintenance resulted in superior response rates (≥ VGPR 76% vs 56%, p<0.001) and PFS (35 vs 28 months, p=0.02). The study was not designed to evaluate the benefit of bortezomib maintenance on its own. However, the number of patients achieving a response upgrade after starting maintenance was similar between the thalidomide and bortezomib maintenance arms suggesting similar effects of these two strategies. An analysis of PFS calculated from the time of last HDM showed a significant difference in favor of the bortezomib arm (31 versus 26 months). This indicates that although post-transplantation bortezomib and thalidomide both achieved similar response upgrades, bortezomib contributed more to improvement of PFS. Importantly in this study, for patients with del17p, PAD followed by bortezomib maintenance significantly improved PFS (mPFS in arm B vs arm A: 26.2 vs 12.0 months; P=0.024) and overall survival (3-year OS rate in arm B vs arm A: 69% vs 17% P=0.028)

**Thalidomide:**
Thalidomide maintenance has consistently been associated with an improvement in PFS with a variable effect on OS. However it does lead to reduction in quality of life, and is frequently discontinued due to side effects and toxicity. Four large randomized trials have reported an improvement in TTP and OS with the use of thalidomide maintenance, and a summary of these trials is presented in Table 7 of Appendix A. The four trials used different doses (100-400 mg) of thalidomide as well as different durations of therapy (6-48 months). The median duration of therapy in the IFM99-02 study was approximately 18 months, with a median thalidomide dose of 200 mg. The IFM99-02 trial compared no maintenance (arm A), maintenance pamidronate (arm C) or maintenance thalidomide (<400 mg) + pamidronate (arm B), 2 months post-tandem autologous transplant in myeloma patients with only one risk factor (β2 microglobulin >3 mg/L or del13). Thalidomide improved response rate (higher CR and VGPR rate with thalidomide: 55% arm A, 57% arm B, 67% arm C) Thalidomide improved 3-year EFS: 36% arm A, 37% arm B and 52% arm C Thalidomide improved 4-year OS: 77% arm A, 74% arm B, 87% arm C Pamidronate did not decrease the incidence of bone events Patients with del13 or those who achieved a VGPR or better did not benefit from thalidomide.

α-Interferon (IFN):
Clinical trials of IFN maintenance produce conflicting results. However it has considerable toxicity and very poor tolerance. With the availability of better tolerated, more effective therapies, the use of IFN is not recommended. Please refer to Table 8 in Appendix A for a review of studies that have reported on the use of IFN.

Prednisone:
In non-transplant patients, one randomized study by Berenson and the SWOG group showed better EFS (14 vs. 5 months; p=0.03) and OS (37 vs. 26 months; p=0.05) with prednisone 50 mg compared to prednisone 10 mg.\textsuperscript{78} Prednisone is not recommended for maintenance following ASCT.

Members of the Alberta Provincial Hematology Tumour Board recommend maintenance therapy with lenalidomide or bortezomib for patients without progressive disease following ASCT. The risk of SPMs must be taken into account before initiating lenalidomide treatment. In the context of the observed progression free survival benefit after ASCT, the benefit/risk profile of lenalidomide/dexamethasone remains positive. Maintenance with bortezomib (with or without lenalidomide) should be considered in patients with del17p.

**Summary of Recommendations:**
Regimens containing bortezomib and dexamethasone as well as a third agent (cyclophosphamide, lenalidomide) are the standard induction regimen prior to stem cell transplantation for transplant eligible patients with standard risk or high risk myeloma requiring treatment. VAD or single agent dexamethasone should not be used.

- CYBORD is the recommended regimen for initial therapy of newly diagnosed transplant eligible patients. Patients should receive 4-6 cycles prior to stem cell collection. Cycles are repeated every 28 days. A twice weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy.
- High risk patients (17p deletion, t(4;14)) should receive a bortezomib based regimen and should be considered for initial therapy with a combination of bortezomib, lenalidomide and dexamethasone (VRD)*. **Lenalidomide is not currently funded for up front treatment of myeloma.**
- Patients refractory to VCD (fail to achieve at least PR) should be switched to second line therapy with lenalidomide and dexamethasone or VRD (bortezomib days 1,4,8,11, Lenalidomide days 1-14, weekly dexamethasone) for several cycles prior to stem cell mobilization
- Cyclophosphamide 2.5g/m\textsuperscript{2} followed by growth factor administration is used for stem cell collection
- The standard stem cell transplant regimen consists of a single transplant conditioned with high dose (200mg/m\textsuperscript{2}) Melphalan with bortezomib (1.3mg/m\textsuperscript{2} day -5, -2, +1, and +4)
- Following transplant:
  - All patients should receive 2 cycles of VRD*
  - Following consolidation, patients with 17p deletion or t(4;14) should receive bortezomib (1.3mg/m\textsuperscript{2}) every 2 weeks for 2 years. All others should receive lenalidomide 10mg daily for 21-28/28 days every 4 weeks until disease progression

\*This is an evidence based recommendation. Lenalidomide is currently NOT funded for front line use in ALBERTA. Bortezomib based consolidation is currently funded only for those not achieving VGPR post-ASCT
This is an evidence based recommendation. Lenalidomide is currently NOT funded for front line use in ALBERTA. Bortezomib based consolidation is currently funded only for those not achieving VGPR post-ASCT.
Patients > 65 Years Old or Transplant Ineligible:

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, combinations of melphalan and prednisone with novel agents (thalidomide, lenalidomide, or bortezomib) have been shown to be superior to melphalan and prednisone alone as initial therapy for transplant ineligible patients. The standard therapy for these patients should therefore include a novel agent, alkylator, and steroids. However, in frail patients, and those with significant comorbidities or advanced age (>75 years), there is an increased risk of toxicities. For these patients, consideration should be given to dose reductions of the initial regimen, and/or the use of two-drug combinations such as RD or VD.

Bortezomib-Based Regimens:
The VISTA trial randomized patients to bortezomib + melphalan + prednisone (VMP) versus MP for 9 cycles. Regimens:

- MP (melphalan + prednisone) cycles 1-9 (6 week cycles)
  - melphalan 9mg/m² days 1-4
  - prednisone 60mg/m² days 1-4
- VMP (bortezomib + melphalan + prednisone)
  - cycles 1-4 (6 week cycles): MP plus bortezomib 1.3mg/m² IV days 1,4,8,11,22,25,29,32
  - cycles 5-9 (6 week cycles): MP plus bortezomib 1.3mg/m² IV days 1,8,22,29

The mean response duration was 19.9 months in the bortezomib group versus 13.1 months in the control group. Median TTP was 24.0 months in the bortezomib group versus 16.6 months in the control group (HR= 0.48). OS after a median follow-up of 16.3 months was not reached in either group: 45 patients (13%) in the bortezomib group and 76 patients (22%) in the control group died. The hazard ratio for overall survival was 0.61 for the bortezomib group (p=0.008)

A modified VISTA regimen has also been used, with 6 cycles of VMP followed by VP maintenance:

- Cycle 1 (6 week cycle):
  - bortezomib 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32
  - melphalan 9 mg/m² on days 1-4
  - prednisone 60 mg/m² on days 1-4
- Cycle 2-5 (5 week cycles):
  - bortezomib 1.3 mg/m² on days 1, 8, 15, and 22
  - melphalan 9 mg/m² on days 1-4
  - prednisone 60 mg/m² on days 1-4
- Maintenance (up to 3 years):
  - bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 every 3 months
  - plus either prednisone (50 mg every other day) or thalidomide (50 mg per day)

The VMP regimen was compared to VMP plus thalidomide followed by maintenance with bortezomib plus thalidomide (VMPT-VT). VMPT followed by VT as maintenance was superior to VMP alone in patients with multiple myeloma who are ineligible for autologous stem-cell transplantation. The 3-year PFS was 56% in patients receiving VMPT-VT and 41% in those receiving VMP (P = .008). Complete response were 38% in the VMPT-VT group and 24% in the VMP group (P < .001). The 3-year overall survival was 89% with VMPT-VT and 87% with VMP (HR, 0.92; 95% CI, 0.53 to 1.60; P = .77). Grade 3 to 4 neutropenia (38% v 28%; P = .02), cardiologic events (10% v 5%; P = .04), and thromboembolic events (5% v 2%; P = .08) were more frequent among patients assigned to the VMPT-VT group than among those assigned to the VMP group; treatment-related deaths were 4% with VMPT-VT and 3% with VMP.
VMP-VT regimen:
Cycles 1-4 (42 day cycles):
- Melphalan 9 mg/m² on days 1 to 4
- Prednisone 60 mg/m² on days 1 to 4
- Bortezomib 1.3 mg/m² iv on days 1, 4, 8, 11, 22, 25, 29, and 32
- Thalidomide 50 mg per day continuously.

Cycles 5-9
- Melphalan 9 mg/m² on days 1 to 4
- Prednisone 60 mg/m² on days 1 to 4
- Bortezomib 1.3 mg/m² iv on days 1, 8, 22, and 29
- Thalidomide 50 mg per day continuously.

Maintenance:
- After the last VMPT course, patients received maintenance therapy with bortezomib 1.3 mg/m² every 14 days and thalidomide 50 mg per day for 2 years or until progression or relapse.

The combination of cyclophosphamide, bortezomib and dexamethasone has been shown in a number of phase II trials to be well tolerated, and produces superior response rates. It is currently the regimen of choice for first line therapy for non-transplant eligible myeloma patients.

- Cyclophosphamide 300mg/m² orally weekly for 4 weeks
- Bortezomib 1.5mg/m² intravenously or subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

Patients should receive 9-12 cycles followed by maintenance bortezomib (1.3mg/m²-every 2 weeks for 2 years).

Lenalidomide-Based Regimens:

Lenalidomide is currently not funded for first-line use in multiple myeloma.

In the MM015 trial, 459 patients were randomly assigned to receive melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R) therapy until a relapse or disease progression or to receive MPR or MP without maintenance therapy. The median progression-free survival was significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio, 0.49; P<0.001) or MP (13 months; hazard ratio, 0.40; P<0.001). Response rates were superior with MPR-R and MPR (77% and 68%, respectively, vs. 50% with MP; P<0.001 and P=0.002, respectively, for the comparison with MP). The progression-free survival benefit associated with MPR-R was noted in patients 65 to 75 years of age but not in those older than 75 years of age (P=0.001 for treatment-by-age interaction). The 3-year rate of second primary tumours was 7% with MPR-R, 7% with MPR, and 3% with MP.

MPR-R regimen: Nine 28-day cycles of
- Melphalan 0.18 mg/kg days 1 through 4
- Prednisone 2 mg per kilogram days 1 through 4
• Lenalidomide 10 mg on days 1 through 21
• Followed by lenalidomide maintenance (10 mg on days 1 through 21 of each 28-day cycle) until disease progression or the development of unacceptable adverse effects

The FIRST study compared MPT for 12 cycles (18 months) to lenalidomide and dexamethasone for 18 cycles (18 months) and len/dex until disease progression in newly diagnosed myeloma patients not eligible for stem cell transplant.\(^8^5\) The continuous Rd strategy was superior to MPT with improved response rate, PFS and duration of response. Overall survival at 4 years was improved with continuous Rd, but this did not reach statistical significance (4-year OS 59% vs 51%, \(p=0.0168\)).

Thalidomide-Based Regimens:

Table 9 in Appendix A described the results of three randomized trials which reported a higher response rate and EFS with melphalan + prednisone + thalidomide (MPT) when compared to melphalan + prednisone alone.\(^8^6-8^8\)

• The IFM99-06 and IFM 01-01 trials also reported higher OS rates.\(^8^6, 8^7\)
• MPT was also shown in one trial (IFM99-06) to be superior to tandem transplant with reduced intensity melphalan conditioning (100 mg/m\(^2\) x 2).\(^8^6\)
• Increased toxicity (DVT/pulmonary embolism 12% versus 4% with MP) and higher rates of neutropenia have been reported with MPT therapy.

### Table 5. Melphalan + Prednisone + Thalidomide (MPT) Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM99-06 Regimen(^8^6)</td>
<td>Melphalan 0.25 mg/kg on days 1–4 q 6 weeks x 12 cycles</td>
</tr>
<tr>
<td></td>
<td>Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles</td>
</tr>
<tr>
<td></td>
<td>Thalidomide at the maximum tolerated dose, but &lt; 400 mg/day, x 12 cycles.</td>
</tr>
<tr>
<td>IFM01-01 Regimen(^8^7) (patients &gt;75 years)</td>
<td>Melphalan 0.20 mg/kg on days 1–4 q 6 weeks x 12 cycles</td>
</tr>
<tr>
<td></td>
<td>Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles</td>
</tr>
<tr>
<td></td>
<td>Thalidomide 100 mg PO daily, x 12 cycles.</td>
</tr>
<tr>
<td>Palumbo Regimen(^8^8)</td>
<td>Melphalan 4 mg/m(^2) on days 1–7 q 4 weeks x 6 cycles</td>
</tr>
<tr>
<td></td>
<td>Prednisone 40 mg/m(^2) on days 1–7 q 4 weeks x 6 cycles</td>
</tr>
<tr>
<td></td>
<td>Thalidomide 100 mg /day continuously until relapse or progressive disease</td>
</tr>
</tbody>
</table>

• Thrombosis prophylaxis is required with the use of thalidomide or lenalidomide. There is no consensus at the present time regarding the optimal DVT/pulmonary embolism prophylaxis. Acceptable options include:
  o Daily ASA (81 or 325 mg)
  o Prophylactic dose of low molecular weight heparin (LMWH)
  o Coumadin with therapeutic INR (2-3)

**Dose Adjustment for Elderly Patients:**

When therapy is started in elderly patients, frail patients, the very elderly (over 75 years of age) and those with significant co-morbidities are at an increased risk of toxicity from combination regimens. As a result of such toxicity, therapy is often terminated early resulting in poorer outcomes than if less intense but more tolerable therapy were to be given for a longer period of time. It is suggested that dose reductions be considered for patients with one or more of these risk factors.\(^7^9\) In addition, initial therapy with a novel agent plus dexamethasone may be better tolerated than triple drug regimens.
Some suggested dose reductions are as follows (adapted from Palumbo et al.):

<table>
<thead>
<tr>
<th>Dose Level 0</th>
<th>Dose level -1</th>
<th>Dose Level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO RISK FACTORS</strong></td>
<td><strong>At least one risk factor</strong></td>
<td><strong>At least one risk factor and any grade 3/4 non hematologic toxicity</strong></td>
</tr>
<tr>
<td><strong>Lenalidomide 25 mg/day, d 1-21</strong></td>
<td>15 mg/day, d 1-21</td>
<td>10 mg/day, d 1-21</td>
</tr>
<tr>
<td><strong>Thalidomide 100 mg/day</strong></td>
<td>50 mg/day</td>
<td>50 mg every 2 days</td>
</tr>
<tr>
<td><strong>Bortezomib 1.3mg/m² d1,8,15,22 q5weeks</strong></td>
<td>1.0mg/m² d1,8,15,22</td>
<td>1.3 mg/m² d1, 15 q 4 weeks</td>
</tr>
<tr>
<td><strong>Melphalan 0.2 mg/kg d1-4 q5weeks</strong></td>
<td>0.15mg/kg d1-4</td>
<td>0.1 mg/kg d1-4</td>
</tr>
<tr>
<td><strong>Dexamethasone 40 mg/ week</strong></td>
<td>20mg/week</td>
<td>10mg/week</td>
</tr>
<tr>
<td><strong>Prednisone 2mg/kg d1-4</strong></td>
<td>1.5mg/kg d1-4</td>
<td>1 mg/kg d1-4</td>
</tr>
</tbody>
</table>
Summary:

- CYBOR-D, VMP, and lenalidomide* plus dexamethasone (given until disease progression) are suitable options for newly diagnosed, transplant ineligible myeloma patients. However, lenalidomide is currently not approved for initial therapy.
- Therefore, CYBORD for 9-12 cycles is the recommended therapy for newly diagnosed, transplant ineligible patients. Alternatively, patients may be treated with VMP for 9 cycles. Following initial therapy, all patients should receive maintenance with bortezomib 1.3 mg/m² every 2 weeks for 2 years.
- Bortezomib based therapy is preferred over lenalidomide based therapy for patients with 17p deleted myeloma.

*This is an evidence based recommendation. Lenalidomide is currently NOT funded for front line use in ALBERTA.
Treatment Guidelines for Relapsed and Refractory Multiple Myeloma

Whenever possible, patients with relapsed multiple myeloma should be considered for a clinical trial. In the absence of a suitable trial, treatment of relapsed disease should be determined on individual basis depending on timing of relapse, age, prior therapy, bone marrow function, co-morbidities, and patient preference.

Repeat bone-marrow examination with cytogenetic testing should be performed at relapse as high-risk features frequently develop as the disease evolves, and may affect the choice of therapy. A short duration of last response is also a high risk feature, with poor long term prognosis for those with initial remission lasting less than 1 year.

The choice of the salvage therapy is mostly guided by the preference of the patient and the treating physician. The following guidelines can help guide treatment decisions:

1. **Renal failure**: Lenalidomide dose adjustment is required for patients in renal failure or on hemodialysis in order to minimize the risk of cytopenia. No such adjustment is required for bortezomib.
2. **Peripheral neuropathy**: Bortezomib is neurotoxic and should not be the first choice of salvage therapy in patients with grade 2 sensory neuropathy, or grade 1 with pain.
3. **Prior exposure to thalidomide**: Prior exposure to thalidomide does not preclude patients from responding to lenalidomide. While a shorter TTP was reported in the MM009 and MM010 studies in patients previously exposed to thalidomide, their mTTP was 8.6 months.
4. **Prior history of DVT**: IMIDs are known to have a prothrombotic effect. Risk of thrombosis with thalidomide and lenalidomide varies between 10-15% and can be as high as 25% when these drugs are used with erythropoietin. Prophylaxis of DVT with aspirin or therapeutic Coumadin or LMWH is mandatory. Bortezomib is the agent of choice over IMIDs for patients with prior life-threatening thrombotic events. If IMIDs are to be used, patients should receive prophylactic LMWH.
5. **Distance from hospital**: IMIDs offer the advantage of being orally administered and therefore require less frequent visits to the hospital. Nevertheless, in non-compliant patients bortezomib is preferable.

**Autologous Stem Cell Transplant:**
A second high dose chemotherapy treatment with autologous stem cell transplantation for those patients who have had a disease free interval of > 2 years following their initial high dose therapy is a reasonable consideration. The median time to progression after a salvage second autologous stem cell transplant is typically 1-2 years. Re-induction may increase the efficacy of the procedure but prospective data does not exist. The transplant related mortality (TRM) varies between 2 and 10%. No data currently exists on the role of maintenance or post-ASCT consolidation after a second transplant. When a patient with relapsed myeloma is being considered for a salvage second transplant, the TRM and the activity of novel agents should be clearly discussed and reviewed with the patient.

**Non-transplant based options:**
The majority of patients relapsing with myeloma will not be candidates for high dose chemotherapy and autologous stem cell transplant. Standard approaches generally incorporate a novel-agent containing regimen.
Bortezomib:
Bortezomib has long been accepted as a standard for the treatment of relapsed disease\textsuperscript{101}. It is widely available in Canada and approved for use in this setting in Alberta. Based on the design of the initial phase III trials in this setting treatment should be continued to progression or intolerance. Although the initial trials generally examined bortezomib naïve patients, it is important to note that the majority of patients will now have been exposed to this agent in the upfront setting. Thus, the decision to pursue retreatment will be influenced on the response during prior exposure to the drug. When at all possible treatment with a triplet based combination should be considered.

Immunomodulatory drugs:

Thalidomide
The bulk of the evidence for the use of thalidomide in the relapse setting is phase II data Minimal phase III data to guide its use in the relapse setting\textsuperscript{102,103}. There is minimal monotherapy activity and thus is best used in conjunction with other agents in a doublet or triplet combination when other IMIDs are contraindicated (ex VTD or CTD). While neuropathy continues to be the major limiting side-effect its advantage is that there is minimal myelosuppression.

Lenalidomide
Initial trials examined its use in combination with dexamethasone showing improved activity compared with dexamethasone alone and should be delivered as continuous therapy\textsuperscript{104}. Durable responses can be achieved and continuous therapy is generally well tolerated. Phase II data supports the use of additional agents such as bortezomib (RVD)\textsuperscript{105} or alkylator\textsuperscript{106} especially if initial responses with steroid based doublet regimens are sub-optimal.

Pomalidomide
This third generation immunomodulatory agent is indicated for use in patients with previous exposure to bortezomib and lenalidomide. At present, it is funded through a drug company sponsored compassionate access program. Inclusion in the provincial formulary is pending review. Phase III data supports its use over single agent dexamethasone\textsuperscript{107}. Similar to other IMIDs pomalidomide should be combined with dexamethasone and continued to progression.

- IMIDs (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib), either as single agents or combination with other drugs (dexamethasone, prednisone, melphalan, cyclophosphamide), have been shown to be active in the treatment of relapsed and refractory myeloma. Table 10 in Appendix A summarizes the results of randomized phase III trials in relapsed and refractory myeloma.
- When lenalidomide and dexamethasone are used for relapsed or refractory myeloma, treatment should continue until disease progression
- Pomalidomide (4mg for 21/28 days every 4 weeks) with dexamethasone 40mg weekly can be considered for myeloma that is refractory to both lenalidomide and bortezomib.
Assessment of Response to Therapy:
The response criteria and disease progression/relapse criteria of the International Myeloma Working Group, shown in Tables 7 and 8, have been adopted to assess response to therapy, progression, and other survival parameters.

As part of response assessment, all patients should have a repeat bone marrow aspirate at the time of maximum response.

Table 7. International Response Criteria for Multiple Myeloma

<table>
<thead>
<tr>
<th>Response</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response (sCR)</td>
<td>• CR as defined below +</td>
</tr>
<tr>
<td></td>
<td>• Normal FLC ratio</td>
</tr>
<tr>
<td></td>
<td>• Absence of clonal cells in BM(^b) by IHC or immuno-fluorescence(^c)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>• Negative immunofixation on the serum and urine</td>
</tr>
<tr>
<td></td>
<td>• Disappearance of any soft tissue plasmacytomas</td>
</tr>
<tr>
<td></td>
<td>• ≤ 5% plasma cells in bone marrow(^b)</td>
</tr>
<tr>
<td></td>
<td>• Normal FLC ratio of 0.26 to 1.65, on 2 consecutive assessments.</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>• Serum / urine M-protein detectable by IF but not on electrophoresis</td>
</tr>
<tr>
<td></td>
<td>• ≥90% decrease in serum M-protein plus urine M-protein level &lt;100mg per 24h</td>
</tr>
<tr>
<td></td>
<td>• ≥90% decrease in the difference between involved and uninvolved FLC levels on 2 consecutive assessments.</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>• &gt;50% reduction of serum M-protein and reduction in 24h urinary M-protein by ≥ 90% or to &lt; 200mg per 24h</td>
</tr>
<tr>
<td></td>
<td>• If the serum and urine M-protein are unmeasurable(^d) a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria</td>
</tr>
<tr>
<td></td>
<td>• If serum and urine M-protein and serum free light assay are unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cells were ≥30%</td>
</tr>
<tr>
<td></td>
<td>• In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>• Not meeting criteria for CR, VGPR, PR or progressive disease</td>
</tr>
<tr>
<td></td>
<td>• Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)</td>
</tr>
</tbody>
</table>

\(^a\) All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required.

\(^b\) Confirmation with repeat bone marrow biopsy not needed.

\(^c\) Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by IHC and/or immuno-fluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of 4:1 or o1:2.

\(^d\) Definitions of measurable disease: Response criteria for all categories and subcategories of response except CR are applicable only to patients who have ‘measurable’ disease defined by at least one of the following three measurements:

1) Serum M-protein ≥ 10 g/L
2) Urine M-protein ≥ 200 mg/24h
3) Serum FLC assay: involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal
Table 8. International Disease Progression/Relapse Criteria

<table>
<thead>
<tr>
<th>Relapse Subcategory</th>
<th>Relapse Criteria</th>
</tr>
</thead>
</table>
| **Progressive Disease**
  (used to calculate PFS and TTP; includes patients in CR) | - Increase of ≥25% from baseline in:
  - Serum M-component (absolute increase must be ≥ 5g/L) and/or
  - Urine M-component (absolute increase must be ≥ 200mg/24h) and/or
  - In patients without measureable serum and urine M-protein levels, an absolute increase in the difference between involved and uninvolved FLC levels ≥ 10mg/dL
  - % Bone marrow plasma cells: the absolute % must be ≥10%
  - Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
  - Development of hypercalcemia (corrected serum calcium >2.65mmol/L) that can be attributed solely to the plasma cell proliferative disorder |
| **Clinical Relapse**
  Requires one or more of:
  - Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice
  - Development of new soft tissue plasmacytomas or bone lesions
  - Definite increase in the size of plasmacytomas or bone lesions as defined by a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
  - Hypercalcemia >2.65 mmol/L
  - Decrease in Hb of ≥ 1.25 mmol/L
  - Rise in serum creatinine by 177 mmol/L or more |
| **Relapse from CR**
  (used only to study DFS) | Any one or more of the following:
  - Reappearance of serum or urine M-protein by IF or electrophoresis
  - Development of ≥ 5% plasma cells in the bone marrow
  - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia) |

*a All relapse categories require 2 consecutive assessments before classification as relapse or disease progression and/or the institution of any new therapy.

*b For progressive disease, serum M-component increases of ≥ 10 gm/L are sufficient to define relapse if starting M-component is ≥ 50 g/L.

*c Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

*d For purposes of calculating time to progression and PFS, CR patients should also be evaluated using criteria listed above for progressive disease.
Follow-Up After Treatment

Myeloma patients **should not** be discharged from the Cancer Centre as they are rarely cured of their disease. Patients should be seen at intervals varying from 1 to 3 months depending on their disease status, and whether they are receiving monthly bisphosphonate. Each visit should include:

- A clinical assessment
- CBC, creatinine, calcium, albumin, total protein, quantitative immunoglobulins, and measurement of M-protein (SPEP and UPEP)
- FLC studies are also required in patients with non-measurable disease, oligosecretory and light chain disease, and to monitor for light chain escape which can occur in 6% of IgG myeloma and up to 10% of IgA myeloma
- Immuno-fixation on SPEP and UPEP and BM biopsy are required to confirm CR
- FLC is required to confirm sCR (stringent CR)
- A skeletal survey should be obtained once per year

The recommended follow-up plan as outlined by the International Response Criteria\(^{112}\) includes:

- Patients undergoing therapy should be tracked monthly for the first year of new therapy and every other month thereafter.
- Patients with 'measurable disease' need to be followed by both SPEP and UPEP for response assessment and categorization.
- Except for assessment of CR, patients with measurable disease restricted to the SPEP will need to be followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP.
- Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR.
- To be considered CR, both serum and urine immuno-fixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; patients with negative UPEP values pre-treatment still require UPEP testing to confirm CR and exclude light chain or Bence–Jones escape.
- A skeletal survey is not required for assessment of response unless clinically indicated (e.g. to investigate new bone pain)
- Bone marrow is required for categorization of CR, and for patients with non-secretory disease. Bone marrow aspirate should be performed at the time of maximum response to therapy. Bone marrow flow cytometry should be used to detect minimal residual disease for those otherwise in CR.
Supportive Therapy

1. Bisphosphonates:

The first study to show a benefit for bisphosphonate use in preventing skeletal events in myeloma reported new events in 24% of those treated with pamidronate versus 41% in those receiving placebo (p<0.001) with a trend to improved survival in the treatment arm (28 vs 23 months, p=0.082). The MRC Myeloma IX trial compared zoledronate to oral clodronate in 1960 newly diagnosed myeloma patients with and without bone lesions, and showed a lower incidence of skeletal related events (27% versus 35%, HR=0.74, p=0.0004). This benefit was seen in those with pre-existing bone lesions (35% versus 43% new events, HR=0.77, p=0.0004) and those with no bone lesions at diagnosis (10% versus 17%, HR=0.53, p=0.007). Vertebral fractures were reduced (5 versus 9%, p=0.0008), as were other fractures (5 versus 7%, p=0.04) and new lytic lesions (5% versus 10%, p<0.0001). There was also an improvement in overall survival (median 50 versus 45.5 months, p=0.04) that may be due to slightly better disease control in the treatment arm.

A recent randomized controlled trial compared the effect of two doses of pamidronate (30mg versus 90 mg) on health-related quality of life and skeletal morbidity in patients with newly diagnosed multiple myeloma. There was no difference seen in mean physical function or time to first skeletal-related event. Eight patients in the pamidronate 90 mg group developed osteonecrosis of the jaw compared with two patients in the 30 mg group. This group suggests that monthly infusion of pamidronate 30 mg as the recommended dose for prevention of bone disease in patients with multiple myeloma.

A Cochrane meta-analysis evaluated the role of bisphosphonates in the treatment of bone disease in multiple myeloma. Twenty trials (n= 6692) were included in this meta-analysis, and the authors concluded that the beneficial effects of bisphosphonates are:

- Reduction of vertebral fractures (RR=0.74)
- Reduction in skeletal related events (RR=0.80)
- Reduction in pain (RR = 0.75)
- No direct effect of bisphosphonates on overall survival (HR=0.95, 95% CI-0.82-1.13, p=0.64).

However, a potency effect is seen, with superior overall survival observed with zoledronate compared with etidronate or placebo, but no difference when compared with other agents.

The IFM 99-02 study assessed the role of maintenance pamidronate post-tandem ASCT and found no reduction in the incidence of bone events and no impact on survival compared to no maintenance. The guidelines for the treatment of bone disease in multiple myeloma are summarized in Table 9.
Table 9. Guidelines for the Treatment of Bone Disease in Multiple Myeloma

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Guidelines</th>
</tr>
</thead>
</table>
| Symptomatic MM            | • Intravenous bisphosphonates with either pamidronate 30 - 90 mg every 4 weeks or zoledronate 4mg iv every 4 weeks for 2 years is recommended.  
                          | • Clodronate 1600 mg daily for 2 years is an acceptable alternative if intravenous treatment with pamidronate or zoledronate is not possible.  
                          | • The use of vitamin D (1000 - 2000 I.U. / day) is recommended with a daily calcium intake of 1500 mg/day in the absence of hypercalcemia. |
| Smoldering MM             | • Bisphosphonates are not recommended for patients with smoldering MM.      |
| Age-related osteoporosis  | • Treatment doses appropriate for osteoporosis                              |
| Duration of therapy with bisphosphonates | • Patients should receive bisphosphonates monthly for 2 years. If after 2 years the patient has achieved remission and is in stable plateau phase off treatment, the bisphosphonates can be discontinued. However, if the MM still requires active treatment, the bisphosphonate treatments can be decreased to every 3 months. |

Bisphosphonates and renal function:
All myeloma patients receiving bisphosphonates should have closely monitoring of renal function before administration of each intravenous infusion by measuring urinary albumin, serum electrolytes, and CrCl. Patients with mild to moderate renal impairment (CrCl 30 to 60 mL/min) should receive reduced doses of zoledronic acid and clodronate. No change to zoledronic acid infusion time is recommended. Pamidronate should be administered via 4-hour infusion in patients with mild to moderate renal impairment. Pamidronate and zoledronic acid are not recommended for patients with CrCl < 30 mL/min, whereas clodronate can be safely given in patients with a CrCl > 12 mL/min. Bisphosphonate therapy should be discontinued in patients experiencing changes in renal function until CrCl returns to within 10% of baseline values.

2. Osteonecrosis of the Jaws (ONJ):

The strongest correlation for the occurrence of ONJ is reported with use of pamidronate and/or zoledronate and less commonly reported with oral clodronate. The incidence varies between 4% and 11.4% with the higher incidence observed with the use of zoledronate and with prolonged duration of therapy. ONJ is often precipitated by a dental intervention that involves manipulation the mandibular and maxillary bones (i.e. root canal, dental extraction).

Table 10. Staging of ONJ

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Exposed bone without symptoms</td>
</tr>
<tr>
<td>Stage II</td>
<td>Exposed bone with symptoms such as pain, swelling and foul taste</td>
</tr>
<tr>
<td>Stage III</td>
<td>Exposed bone with clinical evidence of extension of the disease, including large (&gt;3cm) or multiple areas of exposed bone, osteolysis or sequestrum formation, orocutaneous fistulas, or pathologic fracture</td>
</tr>
</tbody>
</table>

In order to minimize the risk of ONJ, the following prophylactic and therapeutic guidelines should be followed:
• Prior to initiating therapy with bisphosphonates, a comprehensive dental evaluation should be performed and all invasive dental procedures be completed.
• Annual dentist visits and maximal preventive care.
• Avoid dental extractions if possible.
• Withhold bisphosphonates for at least one month before dental extraction and do not resume until recovery and healing is complete. The use of prophylactic antibiotic is recommended after dental extraction to promote healing and prevent infection.
• Treatment of ONJ should be conservative (oral Peridex swish and spit, antibiotics to treat infection, hold bisphosphonates indefinitely) and avoid extensive surgical manipulations. Non-randomized trials suggest a possible beneficial role for hyperbaric oxygen therapy.

3. Percutaneous Vertebral Augmentation or Kyphoplasty:

Percutaneous balloon kyphoplasty involves the inflation of a balloon prior to polymethyl methacrylate (PMMA) injection into a vertebral compression fracture (VCF). This procedure restores vertebral height and reduces kyphotic deformity in addition to reducing the pain level and stabilizing the fractured vertebral body. The first prospective trial evaluating the role of balloon kyphoplasty in multiple myeloma showed that over 80% of the treated patients experienced significant pain control. In addition, there was an overall 30% height restoration with improvement of 60–70% of height restoration when the procedure was performed for fractures less than 6 month old. A consensus statement from the International Myeloma Working Group regarding the role of kyphoplasty in multiple myeloma was recently published.87 Summary of the indications and contraindications for this procedure are outlined in Table 11.

Table 11. Indications and Contraindications for Kyphoplasty in Multiple Myeloma117

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong></td>
<td><strong>Absolute:</strong></td>
</tr>
<tr>
<td>Severe pain present (pain &gt; 7/10) with:</td>
<td>• Contraindication to general or local anesthesia</td>
</tr>
<tr>
<td>• Collapse of one or more vertebra or</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Bone destruction (osteolytic / osteopenic)</td>
<td>• Bleeding disorder</td>
</tr>
<tr>
<td>with high risk of collapse of one or more</td>
<td>• Active Infection</td>
</tr>
<tr>
<td>vertebra</td>
<td>• Pain unrelated to vertebral collapse</td>
</tr>
<tr>
<td></td>
<td>• Cord compression</td>
</tr>
<tr>
<td></td>
<td>• Presence of overt Instability</td>
</tr>
<tr>
<td></td>
<td>• Severe cardiopulmonary insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Allergy to contrast</td>
</tr>
<tr>
<td><strong>Secondary:</strong></td>
<td><strong>Relative:</strong></td>
</tr>
<tr>
<td>Severe pain absent (pain ≤ 7/10 on VAS) with</td>
<td>• Lesions above T3</td>
</tr>
<tr>
<td>significant loss of height and/or structural</td>
<td>• Vertebra plana</td>
</tr>
<tr>
<td>integrity or stability.</td>
<td>• Fracture with obstructing plasmacytoma</td>
</tr>
<tr>
<td></td>
<td>• Retro-pulsed bone</td>
</tr>
</tbody>
</table>

Referrals for kyphoplasty should be made within six months from the occurrence of the compression fracture, as early referrals appear to yield the maximum benefit from this procedure.

4. Radiation Therapy

**Isolated Plasmacytoma:** see section IV
Spinal cord compression: Suggest consultation with radiation oncology for dosage and initiation of therapy. The phase 3 clinical trial\textsuperscript{156} specifically excluded patients with multiple myeloma therefore caution in extrapolating these results onto the multiple myeloma population is suggested.

Painful lesions: Radiotherapy may be useful to prevent further osteolysis and reduce pain.\textsuperscript{157} Low-dose radiation therapy (10-30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression. Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude stem cell collection in potential candidates for high-dose therapy and hematopoietic SCT.

5. Viral Prophylaxis

**Autologous stem cell transplant patients:** See Alberta Transplant Guidelines Guidelines.

**Vaccination:** There is little evidence to support a documented response to vaccination in this population,\textsuperscript{158} but with little harm documented, it is generally suggested that patients and their immediate family members and care providers receive yearly vaccination for Influenza. It may be suggested that vaccination for streptococcus pneumonia and Haemophilus influenza is recommended but efficacy is not guaranteed.

**Viral prophylaxis:** Herpes zoster is a possible complication related to bortezomib administration. Antiviral prophylaxis, such as acyclovir or valacyclovir, is recommended against zoster reactivation during bortezomib treatment and for 30 to 60 days after its discontinuation.\textsuperscript{159} Viral primary prophylaxis is not recommended for other therapies.

6. Orthopedic Surgery: Orthopedic consultation for impending or actual long bone fracture or bone compression/vertebral column instability is suggested. Prophylactic pinning of impending fractures should be discussed on a case by case basis.
IV. SOLITARY PLASMACYTOMA

The location of the solitary plasmacytoma is crucial to predicting its natural history. The majority of patients with extra-osseous (non-bone-involving) plasmacytoma have localized disease which is potentially curable with irradiation. The majority of patients with solitary plasmacytoma of bone will eventually manifest overt multiple myeloma (> 50% will progress to multiple myeloma).

Solitary Plasmacytoma of Bone:
- Typically no M-protein in serum / urine (a small M-component is present in 50%)
- Single area of bone destruction due to clonal plasma cells
- Bone marrow not consistent with multiple myeloma
- Normal skeletal survey (and MRI of spine and pelvis if done)
- No CRAB or ROTI (no end organ damage other than solitary bone lesion)

Extramedullary Plasmacytoma:
- Typically no M-protein in serum / urine (a small M-component is present in 50%)
- Extramedullary tumour of clonal plasma cells
- Normal bone marrow
- Normal skeletal survey
- No CRAB or ROTI (no end organ damage including bone lesions)

Staging

Patients should undergo all the usual tests for multiple myeloma. CT scan of the plasmacytoma should be obtained prior to radiation therapy. An MRI of the spine and pelvis may show unsuspected and asymptomatic skeletal lesions. This finding would place the patient in the smoldering myeloma category. PET scan could help determine the extent of bone or soft tissue involvement.

Treatment and Prognosis

Solitary Plasmacytoma of Bone:
- Treatment consists of radiation in the range of 40 Gy to 50 Gy
- Solitary plasmacytomas > 5 cm, the persistence of an M-protein after radiation or evidence of marrow involvement by MRI have a greater incidence of progression
- 50% of patients with solitary plasmacytoma are alive at 10 years
- 25–40% of patients survive disease-free at 10 years
- Overt multiple myeloma occurs in almost 50% of patients with solitary plasmacytoma of bone (progression may occur 15 years later)
- Recommend stem cell harvest in transplant eligible patients

Patients with solitary plasmacytoma have a higher risk of progression to myeloma if there is occult bone marrow involvement as detected by flow cytometry or a monoclonal light chain secretion in the urine.
- Progression in 72% of patients with and 12.5% without marrow disease, with a time to progression of 26 months vs not reached; (P = .003).
- Progression in 91% with and 44% without monoclonal urinary light chains, median TTP, 16 vs 82 months; P < .001
• If no marrow involvement and no urinary light chains, 7.7% progression at 3.7 years versus 75% if either is present.

Extramedullary Plasmacytoma:
• Treatment with localized radiation (40–50 Gy) and is often curative
• Plasmacytoma may recur locally or metastasize to regional nodes
• Symptomatic multiple myeloma occurs in only 15% of patients

Follow-Up
• CBC, serum creatinine, calcium, and serum protein electrophoresis should be done every 3 months for 1 year, then every 6 months for 2 years, then annually.
• A 24-hour urine protein electrophoresis and skeletal survey should be done annually, for at least 5 years for extra-osseous plasmacytomas, and for 5 to 10 years for osseous plasmacytomas.
V. AMYLOIDOSIS

All patients with suspected or biopsy proven amyloidosis should be immediately referred to an amyloid specialist at the Cross Cancer Institute (Edmonton) or Tom Baker Cancer Center (Calgary) for detailed work up and management.

Classification and Presentation:

Amyloidosis is a disease of protein misfolding giving rise to stable protein fibril deposits that accumulate in organs eventually causing them to malfunction and fail. Multiple subtypes exist each defined by the specific protein serving as the basis for the toxic fibril. The three most common amyloid subtypes are listed below with further details regarding other variants described in table 12120.

AL Type:
Most common subtype seen. Fibril subtype is clonal light chain. Often associated with a plasma cell dyscrasia but may also be seen other B-cell based lymphoproliferative disorders. Often presents with widespread organ involvement.

ATTR Type:
Most commonly manifesting as Senile Systemic Amyloidosis with no mutations noted in the transthyretin (TTR) gene. Also manifests as Familial Amyloid Polyneuropathy (FAP) and associated with a number of mutations in the TTR gene (REF). Almost exclusively presents with cardiac and nervous system involvement.

AA Type:
Fibril giving rise to the amyloid deposits is abnormal Serum Amyloid A (SAA) protein. This is an acute phase reactant and thus the disease is associated with systemic inflammation (autoimmune disorders, chronic infection, hereditary fever syndromes etc.). Almost exclusively presents with renal involvement.

Only AL amyloid falls under the category of plasma cell dyscrasia. Amyloidosis is a symptomatic plasma cell dyscrasia, fulfilling the criteria for ROTI, and requires therapy in the vast majority of cases. AL amyloid is the only subtype of amyloidosis that benefits from chemotherapy, highlighting the importance of confirming the diagnosis. As it is due to an underlying clonal population of cells (most often of plasma cell origin but is also associated with indolent B-cell based lymphoproliferative disorders) it is considered a malignancy.
Table 12. Amyloid subtype characteristics and manifestations

<table>
<thead>
<tr>
<th>Precursor Type</th>
<th>Abbreviation</th>
<th>Clinical Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal protein (Ig light chain or Ig heavy chain)</td>
<td>AL, AH</td>
<td>Mult-organ fibril deposition resulting in dysfunction. May present as localized disease (&lt;10% of cases).</td>
</tr>
<tr>
<td>Serum Amyloid A protein</td>
<td>AA</td>
<td>Associated with systemic inflammation. Primarily renal involvement.</td>
</tr>
<tr>
<td>Transthyretin</td>
<td>ATTR (wild type or mutant)</td>
<td>Nerve and Cardiac involvement. Presenting either SSA (ATTR wt) or FAP (ATTR mutated).</td>
</tr>
<tr>
<td>Fibrinogen A</td>
<td>Afib</td>
<td>Primarily renal involvement.</td>
</tr>
<tr>
<td>Apolipoprotein A</td>
<td>Aapo I</td>
<td>Cardiac and nerve.</td>
</tr>
<tr>
<td>Beta 2 microglobulin</td>
<td>Aβ2M</td>
<td>Associated with chronic dialysis.</td>
</tr>
</tbody>
</table>

Diagnostic Pathway for AL Amyloidosis

Consider AL amyloidosis in the differential if there is evidence of a clone by serology (SPEP, UPEP or sFLC assay) or tissue biopsy (bone marrow, or lymph node) an evidence of organ involvement such as:
- proteinuria/albuminuria (especially in context of nephrotic range proteinuria)
- non-ischemic cardiomyopathy with ventricular hypertrophy
- unexplained diastolic dysfunction
- unexplained raised HS-Troponin T, troponin I, BNP or NT-proBNP
- unexplained persistent elevation of Alkaline phosphatase +/- hepatomegaly
- Peripheral neuropathy
- Autonomic neuropathy

Confirmation by tissue biopsy is required to confirm the diagnosis and must be obtained before initiating therapy. Since MGUS is not uncommon, especially in patients with advanced age, the presence of a monoclonal protein in a patient with positive Congo red staining on a tissue biopsy is not adequate to make a diagnosis of AL amyloidosis. False positive diagnoses have been reported in between 7-25% of cases if only serologic methods are used to base the diagnosis of AL amyloid. In addition, some patients with AL amyloidosis will not have an abnormal SPEP or free light chain assay. Immunohistochemical staining is frequently unreliable and not able to accurately determine the type of amyloid present.

While obtaining a sample from the target tissue in question is the gold standard the diagnosis can sometimes be confirmed on more easily accessible surrogate tissue (bone marrow biopsy, fat pad biopsy or punch biopsy with sufficient subcutaneous adipose tissue).

All cases should be referred for hematopathology review. Subtyping should be done using immunohistochemistry with review by a pathologist with sufficient experience in confirming the diagnosis. Laser microdissection with mass spectrometry (LMD/MS) is now the gold standard for typing amyloid, enabling precise identification of type in over 98% of cases.121
Initial Tests:

All patients should have a complete plasma cell dyscrasia baseline workup if the underlying clone is thought to be secondary to clonal plasma cells (see section III above). If the underlying clonal disorder is thought to be lymphoma then appropriate disease specific testing should be undertaken as per current guidelines. Patients should also have baseline assessments of all potentially affected organs as outlined in table 13:

Table 13: Organ Assessment in Amyloidosis\textsuperscript{121}

<table>
<thead>
<tr>
<th>Organ</th>
<th>Baseline Investigations</th>
<th>Criteria for organ involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>NT-proBNP, HS Troponin T, echocardiogram and cardiac MRI</td>
<td>Mean wall thickness &gt;12 mm on echocardiogram, Increased cardiac biomarkers, no other cardiac disease responsible for findings</td>
</tr>
<tr>
<td>Renal</td>
<td>24hr urine for assessment of proteinuria, UPEP, Creatinine, Urea, albumin, lipid profile</td>
<td>24-hr urinary protein &gt;0.5 g/day, predominantly albumin</td>
</tr>
<tr>
<td>Liver</td>
<td>Alkaline phosphatase, Bilirubin, AST, ALT, ultrasound or CT</td>
<td>Liver span &gt;15 cm in the absence of heart failure, or ALP level &gt;1.5 times ULN</td>
</tr>
<tr>
<td>Coagulation</td>
<td>INR, PTT, specific factor levels (e.g. Factor X) if clinically indicated</td>
<td>Factor deficiency (predominantly factor X) in absence of other causes</td>
</tr>
<tr>
<td>Nerve</td>
<td>Nerve Conduction studies if clinically indicated</td>
<td>Symmetric sensorimotor peripheral neuropathy, gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration</td>
</tr>
<tr>
<td>Lung</td>
<td>High resolution CT scan to demonstrate interstitial infiltration or amyloidomas. In absence of other tissue, proof of amyloid by biopsy is recommended.</td>
<td>In presence of of radiographic findings PFTs should be performed at baselin and in followup examining for alterations in diffusion capacity.</td>
</tr>
<tr>
<td>Liver</td>
<td>No specific imaging test. May note hepatomegaly with non specific infiltrative changes on US, CT or MRI.</td>
<td>Total liver span &gt;15 cm in the absence of heart failure, or alkaline phosphatase level &gt;1.5 times upper limit of normal</td>
</tr>
<tr>
<td>GI</td>
<td>No specific lab test. If symptoms suggest, and in absence of other tissue proof of amyloid, biopsy is highly recommended.</td>
<td>Based on symptoms and/or biopsy proof</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>No specific lab test. If symptoms suggest, and in absence of other tissue, proof of amyloid biopsy is highly recommended.</td>
<td>Based on symptoms and/or biopsy proof</td>
</tr>
</tbody>
</table>

Staging and Prognosis:

Outcome in AL amyloid is primarily determined by the presence and degree of cardiac involvement. Even with modern novel agent containing regiments the early death rate remains as high as 20% within the first 6 weeks. The Mayo staging system, defined by elevations in Troponin T and NT-proBNP, is the most widely used staging system\textsuperscript{122}. Even amongst Mayo stage III patients, further stratification can be performed using an NT-proBNP of > 8500 ng/L and a systolic blood pressure of < 100mmHg to identify ultra-high-risk patients requiring aggressive supportive care and urgent initiation of therapy under the auspices of a dedicated specialists\textsuperscript{123}. 
Threshold values: cTnT < 0.035 µg/L; cTnI < 0.1 µg/L and NT-proBNP < 332 ng/L

• Stage I (low risk): both troponin and NT-proBNP are below the threshold
• Stage II (intermediate risk) if only one marker is below the threshold
• Stage III (high risk) if both are equal to or above the threshold

The median overall survival rates for stages I, II and III are 27.2, 11.1 and 4.1 months respectively.

A. Survival according to “cardiac stage” in 242 patients with cardiac AL. (Thresholds for cTnT and NT-proBNP are 0.035 µg/L and 332 ng/L).122
B. Survival according to response.123

Treatment of AL Amyloidosis

Most hematological responses will result in clinical improvement of some degree even up to 12 months after the hematological responses have been recorded. The goal of the therapy is to halt the production of the amyloid protein (hematological remission, response criteria below). It should be noted that the treatment of an amyloidosis patient is multidisciplinary and requires the active involvement of a nephrologist and cardiologist. A comprehensive list of the current therapeutic options in this disease is described in table 11, appendix A.

Combination Chemotherapy:

Bortezomib Based Regimens: While effective, high-dose chemotherapy is feasible in a minority of patients. Low-dose combination chemotherapy is the general approach pursued for the majority of patients.

Proteosome inhibitor-based regimens have evolved to be treatment of choice in AL amyloidosis. Prospective studies have shown deep and rapid response rates with the ability to treat those with advanced cardiac disease. Various groups have investigated triplet combinations using bortezomib with the classic steroid/alkylator backbone.124-127 In those surviving long enough to benefit from therapy CR rates of up to 65% are reported, especially when used in the upfront setting. A recent multi-institutional study focusing on the use of this combination in Mayo stage III patients demonstrated an unprecedented 1-year OS of over 50% in this poor-risk group of patients.128 Two recent case-control studies examining a bortezomib-alkylator-steroid combination compared with two standard regimens (melphalan and dexamethasone and CTD) have corroborated these findings, suggesting that bortezomib may be an important agent especially in the frontline setting.126, 127
In the absence of grade 2 neuropathy or grade 1 neuropathy with pain, a bortezomib based regimen should be considered first line of therapy:

- The standard initial therapy for amyloidosis is CyBorD (bortezomib 1.5 mg/m² weekly, cyclophosphamide 300 mg/m² orally weekly, and dexamethasone 40 mg weekly)

IMiDs: Immunomodulatory drugs such as thalidomide, lenalidomide and pomalidomide have emerged as important agents. Initial studies with thalidomide and dexamethasone demonstrateclonal responses of 48% (CR in 19%) and organ responses of 26%. However, 60% experienced ≥3 grade toxicity. The use of cyclophosphamide, thalidomide and dexamethasone (CTD) may result in more rapid responses (CR in 21% and PR in 53%) and organ responses in 33% but toxicity remains high.

Treatment with lenalidomide and dexamethasone has shown responses rates of up to 67% (CR = 29%). Recently pomalidomide has also shown activity in this disease with haematologic responses of 48% and median OS and PFS of 28 and 14 months respectively. Continuous therapy may be a key component to durable responses when IMiDs are used.

Alkylating Agents: Alkylating agents such as melphalan and cyclophosphamide, in conjunction with a steroid, have been used for over 40 years. While complete response (CR) rates of around 20-30% are achievable, responses are slow. Thus, unless a novel agent based strategy is contraindicated a double therapy with an alkylator and steroid is not recommended as a frontline option. If required the recommended standard regimen is melphalan 10 mg/m² days 1 to 4 plus high-dose oral dexamethasone (40 mg per day on days 1 to 4) for up to 18 treatment courses if no severe adverse effects have occurred.

Autologous Stem Cell Transplant:
Prior to the era of rigorous patient selection this modality of therapy resulted in unacceptable levels of transplant related morbidity (TRM). However, using modern patient selection criteria with a focus on cardiac involvement, the TRM now approaches that expected in myeloma. A recent publication demonstrates the durability of responses achieved with ASCT and highlights the improvements seen in TRM with modern patient selection criteria. The median overall survival (OS) was 6.3 years. Of the 34% achieving CR the median OS was 13.2 years. The TRM was 11.4% however in those treated in the modern era it was as low as 5.6%. Two recent series have corroborated these findings. Long-term outcomes may be similar irrespective of whether the transplant is done as first line therapy or at relapse.

An NT-proBNP>5000 pg/ml and troponin T >0.06ng/L are important predictors of outcome post-ASCT. With serum levels below these thresholds the TRM may be as low as of 1%.

When stem cell transplantation is performed, the following guidelines should be followed:
- Patients should be <65 years old, have <3 major organs involved, and no congestive heart failure and have a NT-proBNP < 5000 pg/ml and troponin T < 0.06ng/L.
- Three risk categories according to Comenzo and Gertz are as follows:
  1) good risk patients are of any age and have 1–2 organs involved, no cardiac involvement and creatinine clearance >50 mL/min
  2) intermediate risk patients are <71 years old and have 1–2 organs involved, one of which must include cardiac or renal with creatinine clearance <51 mL/min
  3) poor risk patients have either three organs involved or advanced cardiac involvement
• Stem cell mobilization with G-CSF alone (5-6 μg/kg q12 hours for 5 days)
• Debulking with VAD or other regimens pre-transplant is unnecessary and not recommended
• Conditioning with dose melphalan (140-200 mg/m²) adjusted according to number of organ involved and the degree of heart failure

Supportive Treatment

Supportive care is a fundamental part of an integrated treatment approach to AL amyloidosis patients and requires the coordinated expertise of several specialists. Table 14 summarizes the recommended supportive measures.

Table 14. Supportive Care Recommendations for AL Amyloidosis

<table>
<thead>
<tr>
<th>Organ Involved / Symptom</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid cardiomyopathy</td>
<td>Salt restriction</td>
</tr>
<tr>
<td></td>
<td>Low dose diuretics avoiding intravascular volume contraction</td>
</tr>
<tr>
<td></td>
<td>Digoxin not helpful and calcium channel blockers might aggravate heart failure, use ACE inhibitors with caution</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias: amiodarone or pacemaker if severe bradycardia</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Waist-high fitted elastic leotard</td>
</tr>
<tr>
<td></td>
<td>Midodrine 10 mg PO three times daily, start at 2.5 mg PO daily and slowly increase dose as tolerated</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Octreotide starting with 50 μg twice daily up to 100 μg three times daily</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Neuropathic pain is difficult to control</td>
</tr>
<tr>
<td></td>
<td>Gabapentin starting with 300 mg daily and with daily increments up to 1800 mg</td>
</tr>
</tbody>
</table>

Response Criteria and Disease Monitoring

Outcomes are assessed using both haematologic and organ response criteria. In addition to the traditional clonal assessments by serum and urine protein electrophoresis and immunofixation, the serum free light chain assay is also monitored. The difference between serum free light chains (dFLC) has become the predominant tool for clonal response assessment. The Consensus criteria for organ and haematologic response are described below. Attaining a dFLC-VGPR or better has emerged as being integral to long-term survival with this disease. Even in the setting of a PR ongoing excess of amyloidogenic free light chains will lead to further organ deterioration, making at least a dFLC-VGPR the ultimate goal of therapy.

Hematologic (Immunochemical) Response:
- Complete response: Serum and urine negative for a monoclonal protein by means of immuno-fixation, normal kappa:lambda free light-chain ratio, and normal absolute value of the involved serum free light-chain (in patients without renal insufficiency)
- Partial response: Serum M component >0.5 g/dL and 50% reduction; light chain in the urine with a visible peak >100 mg/day and 50% reduction; or free light chain >10 mg/dL and 50% reduction
- Progression after complete response: Any detectable monoclonal protein or abnormal free light-chain ratio (light chain must double)
- Progression after partial response or stable response: 50% increase in serum M protein to >0.5 g/dL or 50% increase in urinary M protein to >200 mg/day with a visible peak
Organ Response:
- **Heart:** Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by two New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness
- **Kidney:** 50% decrease (a decrease of at least 0.5 g/day) in 24-hr urinary protein (must be >0.5g/day before treatment), creatinine and creatinine clearance must not worsen by 25% over baseline level
- **Liver:** 50% decrease in abnormal alkaline phosphatase value, at least 2 cm decrease in liver size on radiographic imaging
- **Nerve:** Improvement in nerve conduction velocity on electromyogram (rare)

Disease Monitoring:
- Patients who are being actively treated should be monitored monthly for treatment-related toxicities (e.g. cytopenia, nausea). In addition, assessment of their organ involvement (e.g. heart failure, renal dysfunction, neuropathy) should be performed. Response to therapy should also be monitored on a monthly basis while actively treated, and every 8-10 weeks thereafter. Recommended laboratory tests include:
  - CBC, electrolytes, creatinine, alkaline phosphatase
  - SPEP, 24-hour UPEP, free light chain studies
- In addition, EKG and echocardiogram should be assessed every six months. Other investigations such as nerve conduction studies and abdominal ultrasounds will need to be repeated only if there is evidence of organ involvement at baseline and for the evaluation of response to therapy.
### GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCT</td>
<td>autologous stem cell transplant</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CRAB</td>
<td>Calcium, Renal insufficiency, Anemia, or Bone damage</td>
</tr>
<tr>
<td>DVT</td>
<td>deep venous thrombosis</td>
</tr>
<tr>
<td>EFS</td>
<td>event-free survival</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FLC</td>
<td>free light chain</td>
</tr>
<tr>
<td>G-CSF</td>
<td>granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>HDT</td>
<td>high dose chemotherapy</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IMID</td>
<td>immunomodulatory drug</td>
</tr>
<tr>
<td>ISS</td>
<td>International Staging System</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>Ld</td>
<td>lenalidomide + low-dose dexamethasone</td>
</tr>
<tr>
<td>LD</td>
<td>lenalidomide + standard-dose dexamethasone</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>MGUS</td>
<td>monoclonal gammopathy of undetermined significance</td>
</tr>
<tr>
<td>MM</td>
<td>multiple myeloma</td>
</tr>
<tr>
<td>MP</td>
<td>melphalan + prednisone</td>
</tr>
<tr>
<td>MPT</td>
<td>melphalan + prednisone + thalidomide</td>
</tr>
<tr>
<td>mDOR</td>
<td>mean duration of response</td>
</tr>
<tr>
<td>MR</td>
<td>minimal response</td>
</tr>
<tr>
<td>ONJ</td>
<td>osteonecrosis of the jaw</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PC</td>
<td>plasma cells</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
</tr>
<tr>
<td>PMMA</td>
<td>polymethyl methacrylate</td>
</tr>
<tr>
<td>PO</td>
<td>orally</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>ROTI</td>
<td>myeloma-related organ or tissue impairment</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>sCR</td>
<td>stringent complete response</td>
</tr>
<tr>
<td>SCT</td>
<td>stem cell transplant</td>
</tr>
<tr>
<td>SD</td>
<td>stable disease</td>
</tr>
<tr>
<td>SDT</td>
<td>standard-dose chemotherapy</td>
</tr>
<tr>
<td>SPEP</td>
<td>serum protein electrophoresis</td>
</tr>
<tr>
<td>TTP</td>
<td>time to progression</td>
</tr>
<tr>
<td>TRM</td>
<td>transplant related mortality</td>
</tr>
<tr>
<td>UPEP</td>
<td>urine protein electrophoresis</td>
</tr>
<tr>
<td>VAD</td>
<td>vincristine + doxorubicin + dexamethasone</td>
</tr>
<tr>
<td>VBMCP</td>
<td>vincristine + bleomycin + melphalan + cyclophosphamide + prednisone</td>
</tr>
<tr>
<td>VCF</td>
<td>vertebral compression fracture</td>
</tr>
<tr>
<td>VGPR</td>
<td>very good partial response</td>
</tr>
<tr>
<td>VMP</td>
<td>bortezomib + melphalan + prednisone</td>
</tr>
</tbody>
</table>
IMPLEMENTATION STRATEGY

- Present and review the guideline during local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review for new and updated evidence will be conducted in May 2018, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.
REFERENCES

16. Larsen, J. T. et al. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. Leukemia 27, 941-946
21. Paiva et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation BLOOD, 15 NOVEMBER 2008 VOLUME 112, NUMBER 10. 4017-2023


### Table 1. Bortezomib-Based Induction Regimens for Patients Aged < 65 Years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate (CR/nCR)</th>
<th>PFS</th>
<th>3 year OS</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTD vs TD</td>
<td>58% vs 41% *</td>
<td>68% vs 56% at 3y *</td>
<td>86% vs 84%</td>
<td>Cavo et al &lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>BD vs VAD</td>
<td>40% vs 23% *</td>
<td>Median 36 vs 30 months *</td>
<td>81% vs 77%</td>
<td>IFM 2005-01 &lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>PAD vs TAD</td>
<td>50% vs 38%</td>
<td>48% vs 42% at 3 years *</td>
<td>78% vs 71% *</td>
<td>HOVON-65 &lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>CVAD vs. CTD</td>
<td>37% vs 50% (CR)</td>
<td>Median 25 vs 27mo</td>
<td></td>
<td>MRC Myeloma IX &lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>KD vs. vTD</td>
<td>52% vs 61%</td>
<td></td>
<td></td>
<td>Moreau et al &lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*<sup>p<0.05;</sup> *(<sup>p>0.05;</sup> **<sup>case-match study</sup>)*

### Table 2. Thalidomide-Based Induction Regimens for Patients Aged ≤ 65 Years

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>Response Rate</th>
<th>EFS /PFS/TTP</th>
<th>OS</th>
<th>Reference/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD vs. D</td>
<td>63 % vs. 41%*</td>
<td>nr</td>
<td>nr&lt;sup&gt;−&lt;/sup&gt;</td>
<td>E1A00 (Rajkumar et al, 2006) &lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>TD vs. D</td>
<td>69.4% vs. 51.1%*</td>
<td>22.4 vs. 6.5 mo (mTTP)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>nr vs. 32 mo&lt;sup&gt;−&lt;/sup&gt;</td>
<td>MM-003 (Rajkumar et al, 2008) &lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>TD vs. MP</td>
<td>68 % vs. 51%*</td>
<td>25 vs.. 43 mo (mEFS)&lt;sup&gt;−&lt;/sup&gt;</td>
<td>45 vs. 58 mo*</td>
<td>(Ludwig et al, 2009) &lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>TD vs. VAD&lt;sup&gt;−&lt;/sup&gt;</td>
<td>76% vs. 52%*</td>
<td>nr</td>
<td>nr&lt;sup&gt;−&lt;/sup&gt;</td>
<td>(Cavo et al, 2005) &lt;sup&gt;41&lt;/sup&gt;</td>
</tr>
<tr>
<td>TD vs. VAD&lt;sup&gt;−&lt;/sup&gt;</td>
<td>25% vs. 7%*pre-SCT</td>
<td>44% vs. 42%&lt;sup&gt;−&lt;/sup&gt; post-SCT</td>
<td>nr&lt;sup&gt;−&lt;/sup&gt;</td>
<td>RR represents ≥VGPR (Macro et al, 2006) &lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>TAD vs. VAD&lt;sup&gt;−&lt;/sup&gt;</td>
<td>72% vs. 54%*pre-SCT</td>
<td>76% vs. 79%&lt;sup&gt;−&lt;/sup&gt; post SCT</td>
<td>49% vs. 32%&lt;sup&gt;−&lt;/sup&gt; (CR/VGPR)</td>
<td>HOVON50/GIMMGGHD3 (Lokhorst et al, 2008) &lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>TD vs. VAD&lt;sup&gt;−&lt;/sup&gt;</td>
<td>68% vs. 49%*</td>
<td>52 vs. 33 mo (mEFS)&lt;sup&gt;−&lt;/sup&gt;</td>
<td>nr vs. 68 mo&lt;sup&gt;−&lt;/sup&gt;</td>
<td>RR represents ≥VGPR Bologna 2002 vs. 96 (Zamagni et al, 2007) &lt;sup&gt;44&lt;/sup&gt;</td>
</tr>
<tr>
<td>T-VADoxil vs. VADoxil</td>
<td>81% vs. 63%*</td>
<td>59% vs. 45%* (2y PFS)</td>
<td>77% vs. 64%*</td>
<td>(Zervas et al, 2004) &lt;sup&gt;45&lt;/sup&gt;</td>
</tr>
<tr>
<td>TT-2 (−)Thai vs. (+)Thal</td>
<td>62% vs. 43%*</td>
<td>56% vs. 44%* (5y EFS)</td>
<td>68% vs. 63% (5y)</td>
<td>RR represents CR (Barlogie et al, 1999) &lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>p < 0.05; − p>0.05; −<sup>case-match study</sup> </sup>

### Table 3. Lenalidomide-Based Induction Regimens

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>Response Rate</th>
<th>EFS /PFS/TTP</th>
<th>OS</th>
<th>Reference/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide + low Dex vs. Lenalidomide + standard dose Dex</td>
<td>ORR at 4 cycles: 69 % vs. 79%*</td>
<td>not reported</td>
<td>2 year OS: 88% vs. 78%*</td>
<td>E4A03 (Rajkumar et al, 2005) &lt;sup&gt;48&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lenalidomide + Dex vs. Placebo + Dex</td>
<td>75 % vs. 48%*</td>
<td>12-mo PFS: 77% vs. 55%*</td>
<td>12 mo OS: 93% vs. 91%</td>
<td>SWOG S0232 (Zonder et al, 2007) &lt;sup&gt;49&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 4. Comparison of Autologous Stem Cell Transplantation to Standard Chemotherapy for Multiple Myeloma

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>N</th>
<th>Age</th>
<th>SDT vs. HDT/ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR (%)</td>
</tr>
<tr>
<td>IFM90</td>
<td>200</td>
<td>≤ 65</td>
<td>5 vs. 22 (p&lt;0.001)</td>
</tr>
<tr>
<td>MRC VII</td>
<td>401</td>
<td>≤ 65</td>
<td>8 vs. 44 (p&lt;0.001)</td>
</tr>
<tr>
<td>IMMSG M97G</td>
<td>194</td>
<td>50 to 70</td>
<td>6 vs. 25 (p=0.0002)</td>
</tr>
<tr>
<td>MAG</td>
<td>190</td>
<td>55 to 65</td>
<td>20 vs. 36 (p=NR)</td>
</tr>
<tr>
<td>PETHEMA</td>
<td>164</td>
<td>≤ 65</td>
<td>11 vs. 30 (p=0.002)</td>
</tr>
<tr>
<td>US Intergroup</td>
<td>510</td>
<td>≤ 65</td>
<td>15 vs. 17 (p=ns)</td>
</tr>
<tr>
<td>HOVON</td>
<td>261</td>
<td>≤ 65</td>
<td>13 vs. 29 (p=0.002)</td>
</tr>
<tr>
<td>Palumbo</td>
<td>524</td>
<td>≤ 65</td>
<td>22 vs 43 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

*22% Salvage transplant @ relapse in SDT arm.  †Only responding patients were randomized.  §Cross-over rate of 52% in US Intergroup study.

Table 5. Comparison of Single versus Tandem Stem Cell Transplantation for Multiple Myeloma

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>n</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM94: Single vs. Tandem SCT</td>
<td>61</td>
<td>399</td>
<td>7 yrs: 10% vs. 20% (p&lt;0.03)</td>
</tr>
<tr>
<td>Bologna 96: Single vs. Tandem SCT</td>
<td>62</td>
<td>321</td>
<td>median: 23 mo vs. 35mo (p&lt;0.001)</td>
</tr>
<tr>
<td>HOVON 24: Single vs. Tandem SCT</td>
<td>63</td>
<td>304</td>
<td>median: 22 movs. 21 mo</td>
</tr>
<tr>
<td>MAG 95: Single vs. Tandem SCT</td>
<td>64</td>
<td>193</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Table 6. Comparison of Tandem Autologous and Autologous-Allogeneic Stem Cell Transplantations for Multiple Myeloma

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>n</th>
<th>TRM</th>
<th>EFS</th>
<th>OS</th>
<th>Reference/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto mel 200/200 vs. Auto mel 200 &gt; Allo bu,flu,ATG</td>
<td>219</td>
<td>65</td>
<td>5%</td>
<td>11%</td>
<td>0% at 5 yrs</td>
</tr>
<tr>
<td>Auto mel 200/200 vs. Auto mel 200 &gt; Allo 2Gy TBI</td>
<td>80</td>
<td>82</td>
<td>4%</td>
<td>10%</td>
<td>20% at 4 yrs</td>
</tr>
<tr>
<td>Auto mel 200 &gt;&gt; cyclophosphamide, etoposide, BCNU- or melphalan-200 vs. Allo-RIC flu, mel</td>
<td>85</td>
<td>25</td>
<td>5%</td>
<td>16%</td>
<td>31 months</td>
</tr>
</tbody>
</table>

* survival for PFS p=0.08

Table 7. Studies of Thalidomide Consolidation Therapy Post Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>n</th>
<th>PFS</th>
<th>pValue</th>
<th>OS</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 99-02 (tandem ASCT):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No maintenance vs. Pamidronate vs. Thalidomide 100-400 mg</td>
<td>200</td>
<td>36%</td>
<td>37%</td>
<td>&lt;0.009</td>
<td>77% at 4 yrs</td>
</tr>
<tr>
<td>ALLG trial:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone 50 qod vs. Thalidomide 200mg x 12 mos + prednisone</td>
<td>129</td>
<td>23%</td>
<td>42%‡</td>
<td>&lt;0.001</td>
<td>75% at 3 yrs</td>
</tr>
<tr>
<td>Barlogie TT2: Control Thalidomide</td>
<td>345</td>
<td>4.1 yrs</td>
<td>6.0 yrs§</td>
<td>0.001</td>
<td>44% at 8 yrs</td>
</tr>
<tr>
<td>Cavo (pair-matched study):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandem ASCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandem ASCT + thalidomide until 2nd ASCT</td>
<td>31%</td>
<td>51%§§</td>
<td>0.001</td>
<td>53% at 5 yrs</td>
<td>69% at 5 yrs</td>
</tr>
</tbody>
</table>

* 3-year EFS  † 3-year PFS  ‡mEFS  §PFS at 4 years

Page 54 of 62
### Table 8. Studies of Interferon Maintenance Therapy Post Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Intergroup Trial S932115</td>
<td>25 vs. 21 (p=0.05)</td>
<td>58 vs. 53 (p=0.8)</td>
</tr>
<tr>
<td>Cunningham</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>EBMT</td>
<td>29 vs. 20 (p=0.006)</td>
<td>78 vs. 47 (p=0.007)</td>
</tr>
<tr>
<td>HOVON-50</td>
<td>13.5 vs. 8.5 (p=0.04)</td>
<td>41 vs. 88.4 (NS)</td>
</tr>
</tbody>
</table>

### Table 9. Thalidomide-Based Regimens for Patients Older than 65 Years or Transplant-Ineligible

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>Thalidomide Dose</th>
<th>EFS</th>
<th>OS</th>
<th>Reference/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 99-06:</td>
<td>≤400 mg/day</td>
<td>19 mo</td>
<td>30.3 mo</td>
<td>(Facon et al, 2007)</td>
</tr>
<tr>
<td>MP</td>
<td></td>
<td>17.1 mo</td>
<td>38.6 mo</td>
<td></td>
</tr>
<tr>
<td>MPT</td>
<td></td>
<td>29.5 mo (p&lt;0.001 for MP vs. MPT)</td>
<td>NR at 56 mo (p&lt;0.001 for M vs. MP)</td>
<td></td>
</tr>
<tr>
<td>IFM 01-01:</td>
<td>100 mg/day</td>
<td>19 mo</td>
<td>27.7 mo</td>
<td>(Hulin et al, 2009)</td>
</tr>
<tr>
<td>MP</td>
<td></td>
<td>24.1 mo (p=0.004)</td>
<td>45.3 mo (p=0.05)</td>
<td></td>
</tr>
<tr>
<td>MPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIMEMA:</td>
<td>100 mg/day</td>
<td>2 yrs EFS 27% vs. 54% (p=0.0006)</td>
<td>3yrs OS 64% vs. 80% (p=0.19)</td>
<td>(Palumbo et al, 2006)</td>
</tr>
</tbody>
</table>

### Table 10. Phase III Trials of Treatment Regimens for Relapsed and Refractory Myeloma

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>N</th>
<th>CR (%)</th>
<th>mTTP (months)</th>
<th>mOS (months)</th>
<th>Reference/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>APEX: Bortezomib + Dexamethasone vs. Dexamethasone</td>
<td>333</td>
<td>9 vs. &lt;1 (p&lt;0.001)</td>
<td>6.2 vs. 3.5 (p=0.001)</td>
<td>29.8 vs. 23.7* (p=0.027)</td>
<td>(Richardson et al, 2005)</td>
</tr>
<tr>
<td></td>
<td>336</td>
<td></td>
<td></td>
<td></td>
<td>*62% cross-over</td>
</tr>
<tr>
<td>MM009: Lenalidomide + Dexamethasone vs. Dexamethasone</td>
<td>177</td>
<td>14.1 vs. 0.6 (p&lt;0.001)</td>
<td>11.1 vs. 4.7 (p=0.001)</td>
<td>29.6 vs. 20.2 (p=0.001)</td>
<td>(Weber et al, 2006)</td>
</tr>
<tr>
<td></td>
<td>176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM010: Lenalidomide + Dexamethasone vs. Dexamethasone</td>
<td>176</td>
<td>15.9 vs. 3.4 (p&lt;0.001)</td>
<td>11.3 vs. 4.7 (p=0.001)</td>
<td>nr vs. 20.6 (p=0.03)</td>
<td>(Dimopoulos et al, 2007)</td>
</tr>
<tr>
<td></td>
<td>175</td>
<td></td>
<td></td>
<td></td>
<td>*nr= not reached</td>
</tr>
<tr>
<td>MMY-3001: Bortezomib + Peg.Doxorubicin vs. Bortezomib</td>
<td>324</td>
<td>4 vs. 2</td>
<td>9.3 vs. 6.5 (p=0.07)</td>
<td>76% vs. 65%* (p=0.03)</td>
<td>(Orlowski et al, 2007)</td>
</tr>
<tr>
<td></td>
<td>322</td>
<td></td>
<td></td>
<td></td>
<td>15-month survival</td>
</tr>
<tr>
<td>Thalidomide*</td>
<td>169</td>
<td>2</td>
<td>2-year EFS = 20% ± 6%</td>
<td>2-years OS = 48% ± 6%</td>
<td>(Barlogie et al, 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*phase II study</td>
</tr>
</tbody>
</table>

### Table 11. Combination chemotherapy regimens and ASCT use in systemic AL amyloidosis.

<table>
<thead>
<tr>
<th>Chemotherapy / Reference</th>
<th>Number of patients</th>
<th>Hematologic Response % (CR %)</th>
<th>Overall survival (months) or 1-3 year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclo/Thal/Dex (Wechalekar et al)</td>
<td>75</td>
<td>74 (21)</td>
<td>41</td>
</tr>
<tr>
<td>MDex (Palladini et al)</td>
<td>46</td>
<td>67 (33)</td>
<td>61</td>
</tr>
<tr>
<td>MDex (Jaccard et al)</td>
<td>50</td>
<td>68 (47)</td>
<td>56.9</td>
</tr>
<tr>
<td><strong>Bortezomib containing regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td>Participants</td>
<td>CR</td>
<td>1 yr OS</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td>----</td>
<td>---------</td>
</tr>
<tr>
<td>Bortezomib (Reece et al&lt;sup&gt;144&lt;/sup&gt;)</td>
<td>70</td>
<td>OW: 68.8 (37.5)&lt;br&gt;TW: 66.7 (24.2)</td>
<td>OW: 94%&lt;br&gt;TW: 84% (1 yr OS)</td>
</tr>
<tr>
<td>Bor/Dex (Kastritis et al&lt;sup&gt;145&lt;/sup&gt;)</td>
<td>94</td>
<td>71 (25)</td>
<td>76% (1 yr OS)</td>
</tr>
<tr>
<td>Cyclo/Bor/Dex (Venner et al&lt;sup&gt;24&lt;/sup&gt;)</td>
<td>43</td>
<td>81.4 (41.9)</td>
<td>97.7% (2 yr OS)</td>
</tr>
<tr>
<td>Bor/Mel/Dex – 33 (Palladini et al&lt;sup&gt;27&lt;/sup&gt;)</td>
<td>50</td>
<td>67 (27) stage I &amp; II&lt;br&gt;40 (5) stage III</td>
<td>Not reached&lt;br&gt;58% (1 yr OS projected)</td>
</tr>
<tr>
<td>Cyclo/Bor/Dex (Jaccard et al&lt;sup&gt;28&lt;/sup&gt;)</td>
<td>60 (all Mayo stage III)</td>
<td>68 (17)</td>
<td>57% (1 yr OS)</td>
</tr>
</tbody>
</table>

**Lenalidomide containing regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Participants</th>
<th>CR</th>
<th>1 yr OS</th>
<th>2 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len/Dex (Sanchorawala et al&lt;sup&gt;146&lt;/sup&gt;)</td>
<td>34</td>
<td>67 (29)</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Len/Dex (Dispenceri et al&lt;sup&gt;132&lt;/sup&gt;)</td>
<td>23</td>
<td>41</td>
<td>Not specified</td>
<td></td>
</tr>
<tr>
<td>Len/Dex (Mahmood et al&lt;sup&gt;134&lt;/sup&gt;)</td>
<td>84</td>
<td>58.3 (20)</td>
<td>84% (2 yr OS)</td>
<td></td>
</tr>
<tr>
<td>Cyclo/Len/Dex (Kastritis et al&lt;sup&gt;144&lt;/sup&gt;)</td>
<td>37</td>
<td>55 (8)</td>
<td>41% (2 yr OS)</td>
<td></td>
</tr>
<tr>
<td>Cyclo/Len/Dex (Kumar et al&lt;sup&gt;148&lt;/sup&gt;)</td>
<td>35</td>
<td>60 (11)</td>
<td>37.8</td>
<td></td>
</tr>
<tr>
<td>Mel/Len/Dex (Moreau et al&lt;sup&gt;149&lt;/sup&gt;)</td>
<td>26</td>
<td>58</td>
<td>80.8% (2 yr OS)</td>
<td></td>
</tr>
<tr>
<td>Mel/Len/Dex (Sanchorawala et al&lt;sup&gt;150&lt;/sup&gt;)</td>
<td>16</td>
<td>50 (7)</td>
<td>Not reached</td>
<td></td>
</tr>
</tbody>
</table>

**Other Regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Participants</th>
<th>CR</th>
<th>1 yr OS</th>
<th>2 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomalidomide/Dex (Dispenceri et al&lt;sup&gt;133&lt;/sup&gt;)</td>
<td>33</td>
<td>48 (3)</td>
<td>76% (1 yr OS)</td>
<td></td>
</tr>
<tr>
<td><strong>ASCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCT (Jaccard et al&lt;sup&gt;137&lt;/sup&gt;)</td>
<td>50</td>
<td>61% CR</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>ASCT (Cibeira et al&lt;sup&gt;138&lt;/sup&gt;)</td>
<td>421</td>
<td>34% CR</td>
<td>75.6&lt;br&gt;100 day TRM 11.4%</td>
<td></td>
</tr>
<tr>
<td>ASCT (Venner et al&lt;sup&gt;139&lt;/sup&gt;)</td>
<td>88</td>
<td>28% CR</td>
<td>Not reached&lt;br&gt;100 day TRM 6.8%</td>
<td></td>
</tr>
<tr>
<td>ASCT (Jimenez-Zepeda et al&lt;sup&gt;140&lt;/sup&gt;)</td>
<td>78</td>
<td>78 (50)</td>
<td>37% after mean follow-up of 122 months</td>
<td></td>
</tr>
<tr>
<td>ASCT &amp; Thal/Dex consolidation (Cohen et al&lt;sup&gt;151&lt;/sup&gt;)</td>
<td>45 total&lt;br&gt;31 TD</td>
<td>21% CR&lt;br&gt;39% CR (1 yr)</td>
<td>84% (2 yr OS&lt;br&gt;TRM 4.4%</td>
<td></td>
</tr>
<tr>
<td>ASCT &amp; Vel/Dex consolidation (Landau et al&lt;sup&gt;152&lt;/sup&gt;)</td>
<td>40 total&lt;br&gt;23 VD</td>
<td>27% CR&lt;br&gt;58% CR (1 yr)</td>
<td>82% (2 yr OS&lt;br&gt;100 day TRM 10%</td>
<td></td>
</tr>
</tbody>
</table>

Mel - melphalan; Pred - prednisolone; Dex - dexamethasone; Cyclo - cyclophosphamide; Bor - bortezomib; Thal - thalidomide; Len - lenalidomide; ASCT - autologous stem cell transplantation; TD - thalidomide and dexamethasone consolidation; VD - velcade and dexamethasone consolidation; OS - overall survival; yr - year; CR - complete remission; PR - partial remission; OW - once weekly; TW - twice weekly; TRM - transplant related mortality
APPENDIX B: TREATMENT REGIMENS FOR MULTIPLE MYELOMA

**Pamidronate**
- 30 - 90 mg IV every 28 days for 2 years
- Zometa 4 mg iv every 28 days for 2 years

**Melphalan/Prednisone**
- Melphalan 8-10 mg/m²/day PO days 1-4
- Prednisone 60mg/m²/day PO days 1-4
- Repeat cycles every 28-42 days

**Cyclophosphamide/Prednisone**
- Cyclophosphamide: 300mg/m² PO (approximately 500mg total dose) weekly
- Prednisone: 50-100mg PO q2d

**Thalidomide**
- Initiate at 100mg - 200 PO qhs, and
- Consider combining thalidomide with dexamethasone either 40mg once weekly, 40mg days 1-4, 9-12, 17-20 to increase response rate
- Avoid high dose dexamethasone in elderly patients > 65 years

*Note:* Monitor for DVT, pulmonary embolism, and prophylaxis with daily aspirin, therapeutic warfarin (INR 2-3) or LMWH. The use of therapeutic dose of warfarin or LMWH is recommended in patients with prior history of DVT or pulmonary embolism.
**Bortezomib (Velcade) ± Dexamethasone**

- **Induction:** 1.3 mg/m² IV or s/c days 1, 4, 8, 11 on a 21 days cycle x 8 cycles or until CR + 2 cycles
- **Maintenance:** 1.3 mg/m² IV push days 1, 8, 15, 22 followed by 1 week rest x 3

**Notes:**

1. Treatments on days 1, 8, 15 and 22 is to be administered if ANC ≥ 1.0 and platelets ≥ 30. If platelet count is <30, bortezomib should be held for that day and resumed on the following dosing day if platelet count is adequate. Missed dose should not be made up for. At the discretion of the treating physician, and if clinically indicated, patients with platelet < 30 may be transfused platelets to ≥ 30 and proceed with treatment.
2. Platelet count should be measured before each dose during cycle 1. For subsequent cycles, CBC should be repeated prior to each dose if platelet count on day 1 is <100 x 10⁹. Otherwise, dose 2, 3, and 4 can be given without additional monitoring.
3. Subcutaneous bortezomib (given at the same dose and concentration as iv bortezomib) is an acceptable alternative for patients who develop peripheral neuropathy or other intolerance, or who have significant neuropathy prior to the start of therapy.
4. A minimum of 72 hours should separate the doses of bortezomib.
5. Approximately 30% patients achieve a PR after 4 cycles; therefore do not discontinue treatment if only stable disease is seen after 4 cycles.
6. Close monitoring for sensory neuropathy. Grade 2 neuropathy or grade 1 with pain requires dose reduction of bortezomib 1.3 → 1.0 → 0.75 mg/m²
7. If dexamethasone is not added up front and no response is seen after 2 cycles or stable disease after 4 cycles, consider adding dexamethasone 20 mg PO days 1, 2, 4, 5, 8, 9, 11 and 12.
8. High risk of herpes zoster infection. Highly recommend prophylaxis with acyclovir 400mg PO twice daily or valacyclovir 1000 mg PO daily.
9. In patients with renal failure or on hemodialysis, there is no need for bortezomib dose adjustment. In patients on hemodialysis, give bortezomib on the same schedule (days 1,4,8,11) 1 hour from dialysis.
10. Dose adjustment for peripheral neuropathy:

<table>
<thead>
<tr>
<th>Severity of Peripheral Neuropathy Signs/ Symptoms</th>
<th>Modification of Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paresthesia and/or loss of reflexes without pain or loss of function)</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or Grade 2 (interfering with function but not with ADL)</td>
<td>Reduce bortezomib dose to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3 (interfering with ADL)</td>
<td>Withhold bortezomib dose until toxicity resolves then reinitiate at 0.7 m/gm² and administer once per week</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss interfering with function)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

**Lenalidomide ± Dexamethasone**

- 25 mg PO for 21 days in a 28 day cycle + dexamethasone 40 mg PO once weekly until disease progression

**Notes:**

1. Monitor for DVT and pulmonary embolism and prophylaxis with daily aspirin, therapeutic warfarin (INR 2-3) or LMWH. The use of therapeutic dose of warfarin or LMWH is recommended in patients with prior history of DVT or pulmonary embolism.
2. Consider proceeding to stem cell collection within 4 cycles of lenalidomide in patients eligible for stem cell transplantation.
3. Renal failure: dose adjustment for lenalidomide is required in patients with decreased creatinine clearance. The following dosing schema is recommended:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>≥50</th>
<th>30-49</th>
<th>&lt; 30</th>
<th>ESRD on Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>lenalidomide dose (21 days in 28 days cycle)</td>
<td>25 mg PO qday</td>
<td>10 mg³ PO qday</td>
<td>15 mg PO q48 hours</td>
<td>15 mg PO after dialysis</td>
</tr>
</tbody>
</table>

³Dose may be escalated to 15 mg PO daily if patient not responding after two cycles and tolerating treatment.
Melphalan + Prednisone + Thalidomide

**Palumbo regimen:**
- Melphalan 4 mg/m² on days 1–7 q 4 weeks x 6 cycles
- Prednisone 40 mg/m² on days 1–7 q 4 weeks x 6 cycles
- Thalidomide 100 mg /day continuously until relapse or progressive disease

**IFM99-06 regimen:**
- Melphalan 0.25 mg/kg on days 1–4 q 6 weeks x 12 cycles
- Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles
- Thalidomide at the maximum tolerated dose, but < 400 mg/day, x 12 cycles.

**IFM01-01 regimen (patients > 75 years):**
- Melphalan 0.20 mg/kg on days 1–4 q 6 weeks x 12 cycles
- Prednisone 2 mg/kg on days 1–4 q 6 weeks x 12 cycles
- Thalidomide 100 mg PO daily x 12 cycles.

**Notes:**
1. Monitor for DVT and pulmonary embolism and prophylaxis with daily aspirin, therapeutic warfarin (INR 2-3) or LMWH. The use of therapeutic dose of warfarin or LMWH is recommended in patients with prior history of DVT or pulmonary embolism.
2. IFM99-06 and IFM01-01 are the preferred dosing regimen.
3. MPT regimen is myelosuppressive and often requires the use of G-CSF.

Melphalan + Prednisone + Bortezomib (VMP)

**9 cycles of VMP:**
- Cycles 1-4 (6 week cycles):
  - Melphalan 9mg/m² days 1-4
  - Prednisone 60mg/m² days 1-4
  - Bortezomib 1.3mg/m² IV days 1,4,8,11,22,25,29,32
- Cycles 5-9 (6 week cycles):
  - Melphalan 9mg/m² days 1-4
  - Prednisone 60mg/m² days 1-4
  - Bortezomib 1.3mg/m² IV days 1,8,22,29

**Notes:**
1. Please refer to the notes under the bortezomib treatment above.
2. Platelet counts should be ≥ 75 and ANC > 1.0 on day 1 of each cycle.
3. On the following days, platelet counts should be ≥ 30 and ANC > 1.0. For patients with recurrent dose delays secondary to cytopenias, dose reductions of melphalan are required.
Modified VISTA regimen:
- Cycle 1 (6 week cycle):
  - bortezomib 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32
  - melphalan 9 mg/m² on days 1-4
  - prednisone 60 mg/m² on days 1-4
- Cycle 2-5 (5 week cycles):
  - bortezomib 1.3 mg/m² on days 1, 8, 15, and 22
  - melphalan 9 mg/m² on days 1-4
  - prednisone 60 mg/m² on days 1-4
- Maintenance (up to 3 years):
  - bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 every 3 months
  - plus either prednisone (50 mg every other day) or thalidomide (50 mg per day)

VMP-VT regimen:
Cycles 1-4 (42 day cycles):
- Melphalan 9 mg/m² on days 1 to 4
- Prednisone 60 mg/m² on days 1 to 4
- Bortezomib 1.3 mg/m² iv on days 1, 4, 8, 11, 22, 25, 29, and 32
- Thalidomide 50 mg per day continuously.
Cycles 5-9
- Melphalan 9 mg/m² on days 1 to 4
- Prednisone 60 mg/m² on days 1 to 4
- Bortezomib 1.3 mg/m² iv on days 1, 8, 22, and 29
- Thalidomide 50 mg per day continuously.

- After the last VMPT course, patients received maintenance therapy with bortezomib 1.3 mg/m² every 14 days and thalidomide 50 mg per day for 2 years or until progression or relapse.

MPR-R regimen: Nine 28-day cycles of
- Melphalan 0.18 mg/kg days 1 through 4
- Prednisone 2 mg per kilogram days 1 through 4
- Lenalidomide 10 mg on days 1 through 21
- Followed by lenalidomide maintenance (10 mg on days 1 through 21 of each 28-day cycle) until disease progression or the development of unacceptable adverse effects

CYBOR-P: 8 cycles of CYBOR-P, 28 days cycle in relapsed and refractory myeloma:
- Cyclophosphamide 300 mg/m² weekly
- Prednisone 100 mg PO every other day
- Bortezomib 1.5 mg/m² IV or s/c days 1, 8, 15
**CYBOR-D:** Cycles are repeated every 28 days. Each cycle consists of:
- Cyclophosphamide 300mg/m² orally weekly for 4 weeks
- Bortezomib 1.5mg/m² intravenous or subcutaneously weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

A twice weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy.

**VRD:** Cycles are repeated every 28 days. Each cycle consists of:
- Lenalidomide 25mg orally daily for 21 days
- Bortezomib 1.5mg/m² IV or s/c weekly for 4 weeks
- Dexamethasone 40mg orally weekly for 4 weeks.

A 21 day schedule can be used for sicker patients requiring a more rapid initial response to therapy:
- Lenalidomide 25mg orally daily for 14 days
- Bortezomib 1.3mg/m² IV or s/c weekly for 2 weeks
- Dexamethasone 40mg orally twice weekly for 2 weeks
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