

MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG)
TO THE MYELOMA FOUNDATION
OF AUSTRALIA (MFA)



Clinical Practice Guideline **MULTIPLE MYELOMA**

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1 INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells characterised by an abnormal serum and /or urine immunoglobulin or free immunoglobulin light chain as a result of clonal expansion of plasma cells. It is often accompanied by complications of enhanced bone loss associated with diffuse osteopenia or focal lytic lesions, renal failure, hypercalcaemia, immune suppression and anaemia. Approximately 1500 new cases are diagnosed in Australia each year[1]; it is a disease of the elderly with median age at diagnosis of 65-70 years, however, younger patients with MM are also seen. Although MM remains an incurable disease, survival for patients with MM has improved to a median of 5 to 7 years[1, 2]. This is due to the introduction of first, high dose therapy (HDT) and autologous stem cell transplant (ASCT) in the late 1990s, followed by first and second generation immunomodulatory drugs (IMiDs: thalidomide, lenalidomide (Revlimid™) and pomalidomide (Pomalyst™) and first generation proteasome inhibitors (PI; the first in class PI bortezomib (Velcade™). Since 2015, a number of novel agents have been approved by the FDA (Food Drug Administration) for the treatment of MM. These include the second generation PIs (including carfilzomib [Kyprolis™] and ixazomib, the monoclonal antibodies (mAb) daratumumab and elotuzumab, and the histone deacetylase inhibitor (HDACi) panabinstat. As of March 2017, of the second generation PIs, only carfilzomib has been registered by the Australian Therapeutic Goods Administration (TGA) and neither mAb has been registered.. Therapeutics for MM will continue to expand with further novel agents under investigation including other PIs (oprozomib and mirazomib) and HDACi (eg. ricolinostat) and newer classes of therapeutics including small molecules (eg. Bcl-2 or MCL1 inhibitors) novel immune approaches including Bispecific T-cell Engagers (BiTEs), chimeric antigen T cell receptors (CAR-T) and immune check point inhibitors.

Indeed, the landscape of treatment for MM is becoming more complicated as treatment options become increasingly diverse. Nonetheless, there is a general global consensus on fundamental treatment principles even though local/regional treatment guidelines may vary depending on the availability of newer therapeutic agents.

The following guideline for the effective treatment of MM pertains to the Australian setting, and is a consensus established by the Australian Medical Scientific Advisory Group (MSAG) to the Myeloma Australia, which consists of a panel of haematologists across Australia. Levels of evidence and grades of recommendations in this guideline are as outlined in table 1

Table 1: Level of evidence and grades of recommendations.

| LEVELS OF EVIDENCE | |
|---------------------------|---|
| 1A | Evidence from meta-analysis of randomised control trials. |
| 1B | Evidence from at least one randomised controlled trial. |
| 2A | Evidence from at least one well-designed non-randomised trial, including phase II trials and case-control studies. |
| 2B | Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies. |
| 3 | Evidence from well-designed non-experimental descriptive studies. |
| 4 | Evidence obtained from expert committee reports or opinions and/or of respected authorities. |
| GRADES OF RECOMMENDATIONS | |
| A | Recommendation based on at least randomised controlled trial of good quality addressing specific recommendation (evidence level 1A and 1B). |
| B | Recommendation based on well-conducted studies but no randomised controlled trial on topic of recommendation. (Evidence level 2A, 2B, and 3). |
| C | Recommendation based on expert opinions or reports (Evidence level 4). |

2 DIAGNOSTIC CRITERIA

The diagnosis of MM is usually confirmed by demonstrating the presence of a paraprotein in serum and/or urine with an increased number of bone marrow plasma cells. Recently there has been a revision to the IMWG (International Myeloma Working Group) criteria for the diagnosis of symptomatic MM[3]. The updated criteria now include validated biomarkers of malignancy in addition to existing requirements for myeloma defining events, as defined by the acronym CRAB (hypercalcaemia, renal failure, anaemia, and bone lesions). There are three stages of disease: An initial premalignant stage termed monoclonal gammopathy of uncertain significance (MGUS), followed by smouldering (or asymptomatic) MM and symptomatic MM. Multiple myeloma is almost always preceded by MGUS[3]. Table 2 and 3 outline the updated criteria for the diagnosis of MGUS, smouldering and symptomatic MM.

Table 2: Diagnostic criteria according to the International Myeloma Working Group 2014[4].

| MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS) | SMOULDERING MYELOMA | SYMPTOMATIC MYELOMA |
|---|---|---|
| <ul style="list-style-type: none"> - Serum paraprotein <30g/l or Abnormal FLC ratio (<0.26 or >1.65) in the absence of Ig heavy chain expression on immunofixation with increased level of the appropriate involved light chain (increased K FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26) - Bone marrow clonal plasma cells <10% in the aspirate, and low level of plasma cell infiltration in the trephine. - No myeloma defining events or biomarkers of malignancy (table 3). - No evidence of other B-cell lymphoproliferative disease (LPD) or light chain associated amyloidosis or other light chain, heavy chain or immunoglobulin associated tissue damage. | <ul style="list-style-type: none"> - Serum paraprotein \geq30g/l or urinary monoclonal protein \geq500 mg per 24 hours and/or bone marrow clonal plasma cells 10-60%. - Absence of myeloma defining events and biomarkers of malignancy (table 3) - No evidence of amyloidosis | <p>Clonal bone marrow plasma cells \geq10% or biopsy-proven bony or extramedullary plasmacytoma* and presence of either:</p> <p>Myeloma defining events (table 3).</p> <p>Or</p> <p>Biomarkers of Malignancy (table 3)</p> |

Table 3: Myeloma defining events and biomarkers of malignancy.

| MYELOMA DEFINING EVENTS | |
|--|--|
| C - Increased calcium level | Corrected serum Calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l |
| R - Renal insufficiency | Creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL) |
| A - Anaemia | Hb <100g/L or 20g/L below the lower limit of normal. |
| B - Bone lesions | One or more osteolytic lesions on skeletal radiography, CT, or PET-CT |
| BIOMARKERS OF MALIGNANCY | |
| Clonal bone marrow plasma cell percentage* ≥60% | |
| Involved: uninvolved serum free light chain ratio **≥100 | |
| >1 focal lesion on MRI studies*** | |

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence.

** These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

*** Each focal lesion must be 5 mm or more in size.

2.1 THE ROLE OF PROGNOSTIC MARKERS

The natural history of MM can vary markedly between patients; survival can range from several months, to many years. Prognostic factors at diagnosis serve as a basis on which comparison of treatment outcomes can be made between clinical trials, and may influence design of clinical trials, in view of the efficacy of agents such as bortezomib in high-risk patients[5].

Currently, the most widely adopted prognostic model is the international prognostic index (IPI; table 4) [6]. This model is based on serum levels of β_2 microglobulin (β_2 M) and albumin, and separates MM patients into three prognostic groups irrespective of treatment modality [table 4]. However, there are other major independent prognostic factors that also predict outcome[7]. Table 5 outlines the prognostic factors associated with poorer prognosis in patients with MM. By definition, patients with high-risk MM are considered those with an OS of 2 years or less despite treatment with IMiDs and proteasome inhibitors[7]. The most robust factors that are consistently associated with such poor survival are higher ISS stage and the cytogenetic abnormalities 17p deletion and t(4;14). Recently, this has led to a proposed revised(R)-ISS risk stratification system that incorporates ISS stage, LDH and high-risk iFISH (del17p and t(4;14))[8]. The R-ISS risk stratification system (table 5) was recently shown to clearly identify 3 different MM prognostic groups in patients who were treated in the era of IMiDs and proteasome inhibitors. If this is confirmed by prospective evaluation, it will likely supersede the current ISS staging system.

Table 4: International Prognostic index [6].

| INTERNATIONAL PROGNOSTIC INDEX (ISS) | | | |
|--|--|------------|-----------|
| Stage | Criteria | Median OS* | |
| I | Serum β_2 M <3.5mg/l and serum Albumin >35g/l | 62m | |
| II | Neither I nor III | 45m | |
| III | Serum β_2 M>5.5mg/l | 29m | |
| REVISED (R)- ISS RISK STRATIFICATION MODEL | | | |
| Stage | Criteria | Median OS* | 5 Year OS |
| R-ISS I | - ISS I (Serum β_2 M <3.5mg/l and serum Albumin >35g/l) AND - Normal LDH AND - No high risk iFISH profile (defined as del17p and/or t(4;14) and/or t(14;16)) | NR | 81% |
| R-ISS II | Patients failing to meet criteria for R-ISS I or III. | 83m | 62% |
| R-ISS III | ISS III (Serum β_2 microglobulin >5.5mg/L) AND High risk iFISH OR High LDH | 43m | 39% |

* Note the OS quoted for ISS and R-ISS are derived in different eras and are therefore not comparable between the two prognostic systems.

Table 5: Factors associated with poorer prognosis in multiple myeloma.

| HIGH RISK FACTORS | The following tests for high-risk disease are routinely available in Australia and are recommended. |
|---|---|
| <p>ISS (international stage system) III (Serum β_2 microglobulin >5.5mg/L)</p> <p>Conventional Cytogenetics</p> <ul style="list-style-type: none"> - Del17p - Hypodiploidy - Deletion of chromosome 13* <p>Fluorescent in situ hybridisation (FISH)</p> <ul style="list-style-type: none"> - t(4;14) - t(14;16) - Del17p - 1q21 amplification <p>Plasma cell labelling index $\leq 3\%$ High lactate dehydrogenase (LDH)</p> | <p>β_2 microglobulin Albumin</p> <p>Conventional Cytogenetics **</p> <p>Fluorescent in situ hybridisation (FISH) **</p> <ul style="list-style-type: none"> - t(4;14) - t(14;16) - Del 17p - 1q21 amplification. <p>Plasma cell labelling index (by flow cytometry) *** LDH</p> |

* t(4;14) and del(17p) are often associated with del(13q) and it appears that most of the negative impact of del(13q) is related to t(4;14) or del(17p).

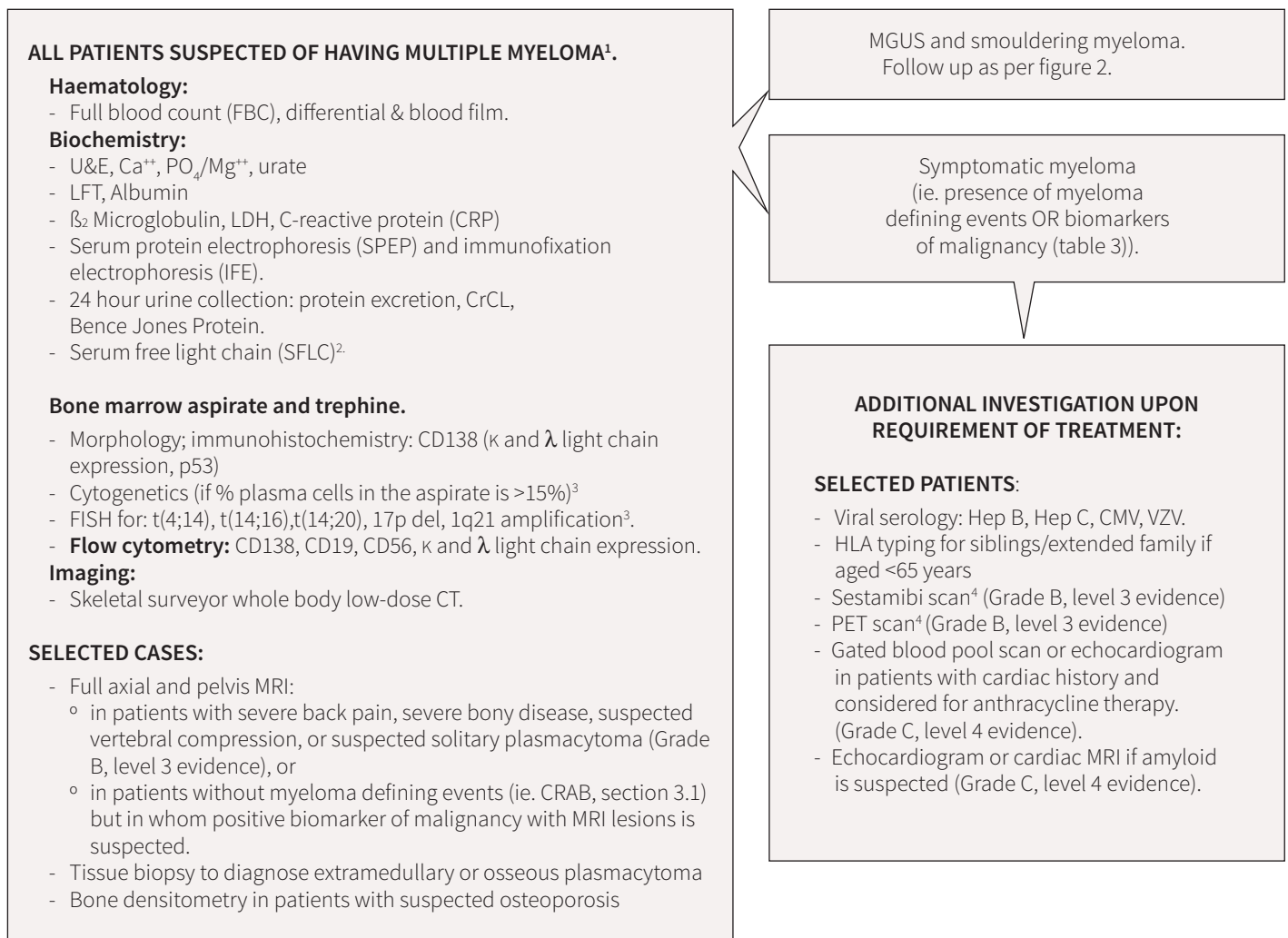
** Cytogenetics and FISH should only be requested in patients in whom the identification of high risk would impact management. Cytogenetics is often only possible in patients with >15% plasma cells in the aspirate as the yield of metaphases is low with a lesser plasma cell burden.

*** Available at Royal Prince Alfred Hospital, NSW, Australia; The bone marrow plasma cell labelling index by flow cytometry. Pope et al. Cytometry 1999, 15;38(6):286-92.

2.2 INITIAL DIAGNOSTIC WORK-UP

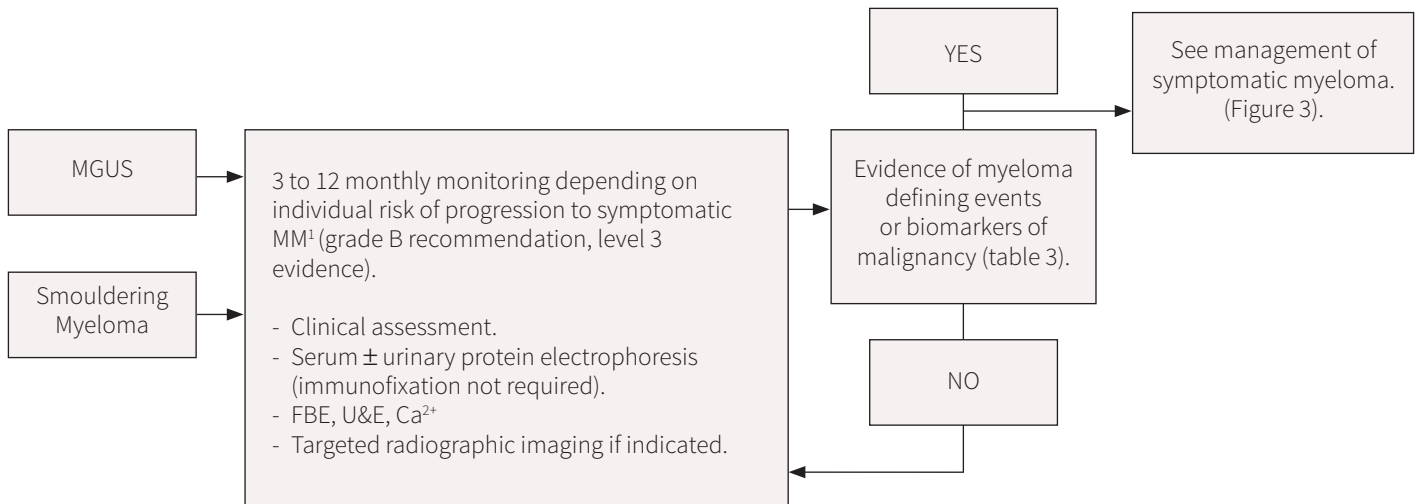
The initial diagnostic work-up process (Figure 1) aims to establish the diagnosis, the stage of disease, and prognostic markers, which may influence subsequent treatment. The following recommendations are grade C and based on level 4-evidence unless otherwise stated.

Figure 1: Initial diagnostic work up



1. The extent of initial diagnostic work up for patients with MGUS is more limited compared to patients suspected of having multiple myeloma, and is dependent on the level of paraprotein and individual risk assessment for progression towards multiple myeloma. Please refer to the recent international myeloma working group (IMWG) consensus [9].
2. The serum immunoglobulin-free light chain (SFLC) assay is recommended by the IMWG as part of screening in combination with SPE and IF, which altogether yields high sensitivity, and may be used in place of 24 hour urine BJP [10].
3. Cytogenetics is often only possible in patients with >15% plasma cells in the aspirate as the yield of metaphases is low with a lesser plasma cell burden.
4. Sestamibi or PET can be useful additional diagnostic tools for detection of otherwise occult myelomatous sites in early stage MM. Overall sensitivity for MIBI is ~92% and specificity is 96% [11]. MIBI is more sensitive in detecting soft and skeletal lesions compared to conventional radiography. In MGUS patients, MIBI is always negative [11-13]. Sensitivity of PET in detecting myelomatous involvement is ~85% and specificity is ~92% [13]. PET is more sensitive than conventional radiography in detecting osseous MM involvement. Compared to MRI, PET failed to show abnormal areas of bone marrow involvement in up to 30% of patients detected by MRI. However, PET can sometimes detect abnormalities, which are out of field of view of MRI. The specific role of PET is still unclear, and it is not currently recommended as standard of care.

Figure 2: Management of MGUS and Smouldering Myeloma.

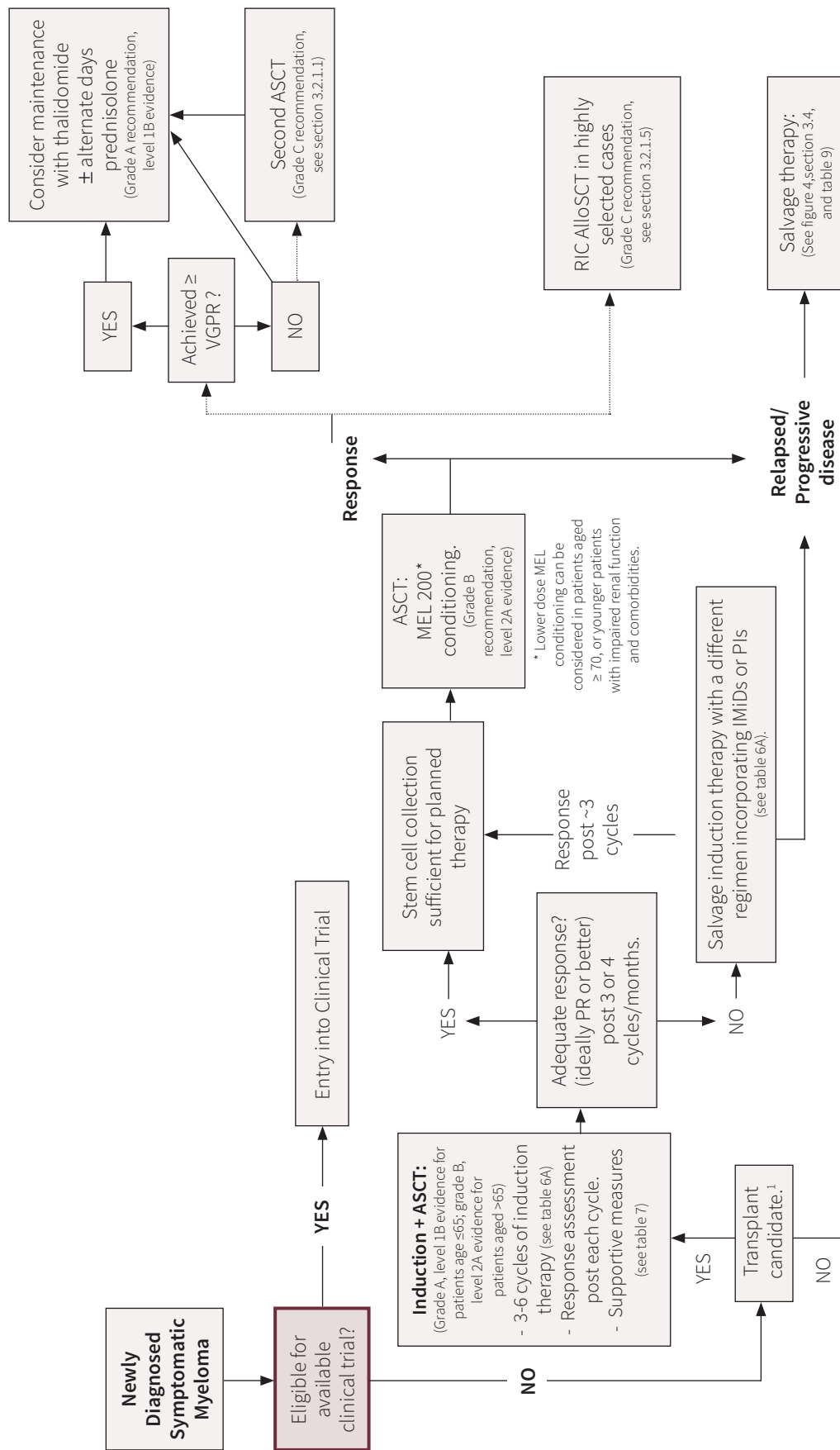


¹For MGUS:

- When serum paraprotein level is $\leq 15\text{g/l}$ and stable, IgG type, and normal SFLC kappa: lambda ratio, SPEP can be repeated annually.
- When paraprotein value is $>15\text{g/l}$ or there is an abnormal SFLC kappa: lambda ratio, a bone marrow aspirate and trephine is considered if paraprotein is rising to assess for evidence of MM. If these results are satisfactory, patients can be followed at 6 monthly intervals for 1 year, then yearly provided the treating physician is contacted upon any clinical changes [13].

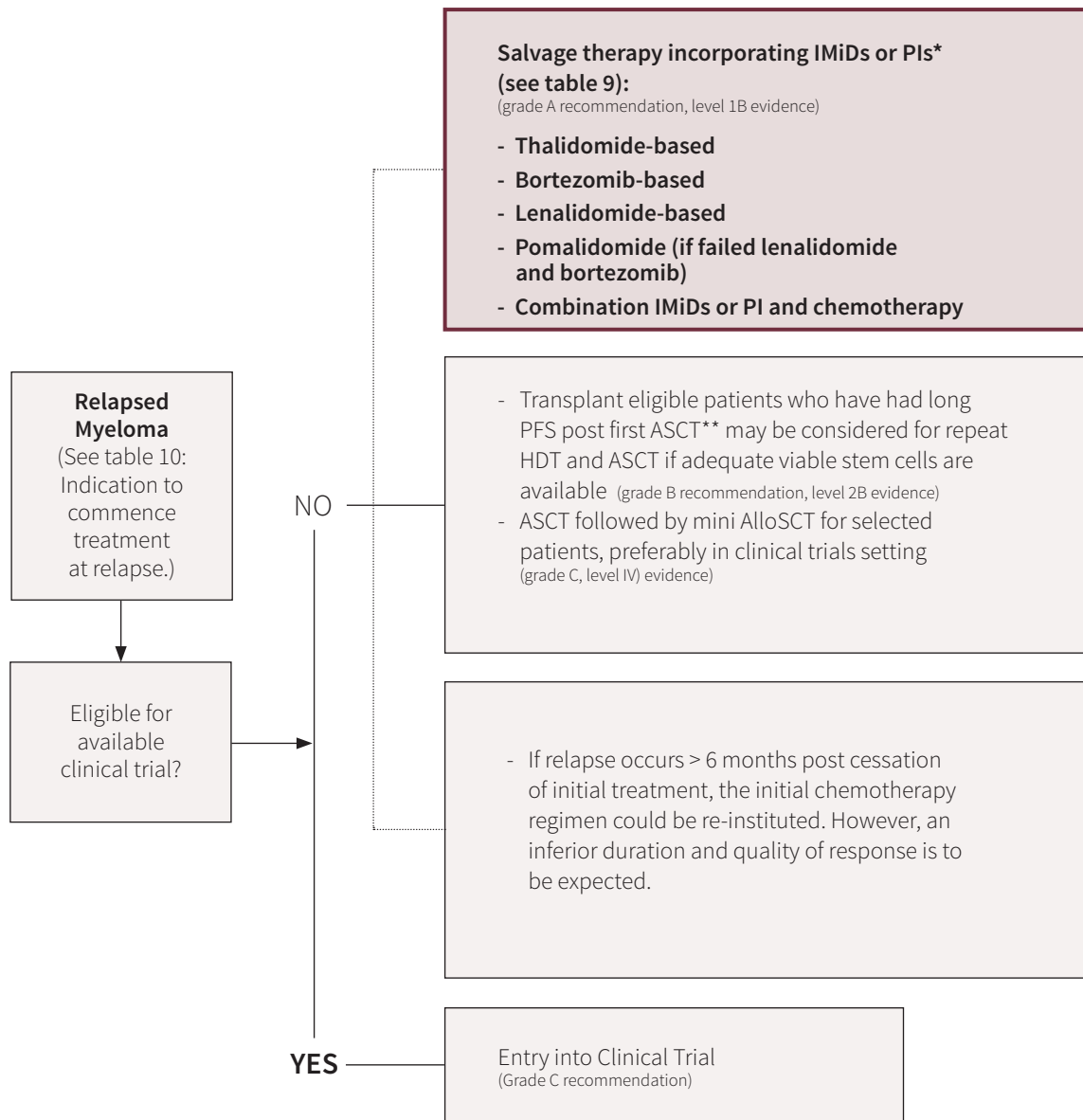
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Figure 3: Management of Newly Diagnosed Symptomatic Myeloma (see section 3)



1. Suitable candidates for autologous stem cell transplants are generally patients who are aged <70 years with good performance status and no significant co-morbidities. Individual assessment of biological fitness for HDT and ASCT by the treating physician is advised.
2. Patients who are not immediate transplant candidates but in whom AuSCT may still be a viable option at relapse should avoid the alkylating agent melphalan so as not to compromise potential stem cell harvest. Induction regimens without melphalan are outlined in table 6A.
3. Thalidomide-based induction should only be used in patients in whom there is a contraindication to lenalidomide or bortezomib-based treatment.

Figure 4: Management of relapsed Myeloma.



* Note: A number of novel agents have been approved by the FDA (Food Drug Administration) for the treatment of RRMM (see section) but are currently not reimbursed by the Australian PBS for the treatment of MM. These include second generation proteasome inhibitors carfilzomib and ixazomib, mAbs including daratumumab and elotuzumab, and the HDACi panabinstat. Please refer to section 4.0.

** Data from the British Blood and Bone Marrow Transplant Registry suggested that a PFS of at least 9 months to the first ASCT is associated with improved survival outcome to a second ASCT in relapsed MM (Cook et al. Biol Blood Marrow Transplant 2011). In the era of novel therapies, most myeloma experts in Australia would consider a second ASCT for salvage therapy upon at least 12-18 months to the first ASCT.

Table 6A: Induction treatment regimens for upfront treatment of myeloma prior to autologous stem cell transplantation

This table summarizes the commonly used induction regimens and is not intended to be exhaustive. Please refer to recommendations regarding induction therapy

| REGIMEN | SCHEDULE | RESPONSES AND COMMENTS | |
|-------------------------------------|--|---|--|
| BORTEZOMIB-BASED | | | |
| CyBorD/BCD [52, 153, 154] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 Cyclophosphamide 300mg/m ² po D1,8,15,22 (or cyclophosphamide 900mg/m ² IV D1) Dexamethasone 20mg po on day of and day after bortezomib. Cycles repeated every 21 days x for 3-4 cycles prior to ASCT | ORR 88%, ≥VGPR 61% post induction | This is the most commonly used induction regimen for TE patients in Australia, according to the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) Subcutaneous bortezomib is non inferior to bortezomib with respect to efficacy but has improved toxicity profile [88] |
| | Or Bortezomib 1.5mg/m ² IV (or SC) D1,8,15,22 Cyclophosphamide 300mg/m ² po D1,8,15,22 Dexamethasone 20mg po on day of and day after bortezomib. Cycles repeated every 28 days x for 3-4 cycles prior to ASCT | ORR 93%, ≥VGPR 60% post induction | |
| BD [48, 88] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 Dexamethasone 20mg on day of and day after bortezomib Cycles repeated every 21 days for 3-4 cycles prior to ASCT | CR/nCR 22% post induction. CR/nCR 38% post ASCT | |
| PAD [41, 53, 155] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 , Doxorubicin 20/m ² IV D1 and 4 or Doxorubicin 9mg/m ² IV D1,2,3,4 (daily bolus or continuous infusion), Dexamethasone 20mg po daily, D1,2,4,5,8,9,11,12. Cycles repeated every 3 weeks for 3-4 cycles prior to ASCT | ORR 95%; 65% ≥VGPR, 24% CR. Assessment following ± ASCT: ORR 95%, 81% ≥VGPR, 43% CR. | |
| IMMUNOMODULATORY DRUGS-BASED | | | |
| CTD [50, 156] | Thalidomide 100mg po daily. Cyclophosphamide 500mg po/IV weekly. Dexamethasone 40mg po daily 1-4, 12-15, or Dexamethasone 40mg weekly. Cycles repeated every 28 days for 3-4 cycles prior to ASCT | ORR 89% | |
| TAD[51] | Thalidomide 200mg po daily Doxorubicin 9mg/m ² IV rapid infusion, D1-4 Dexamethasone 40mg po, days 1-4, 9-12, and 17-20 Cycles repeated every 28 days for 3-4 cycles prior to ASCT. | ORR with TAD 72% vs. 54% with VAD, p<0.001. CR+VGPR higher post ASCT in TAD arm (49% vs. 32%, p<0.001) | |
| TD [47, 157, 158] | Thalidomide 200mg po daily Dexamethasone 40mg po daily D1-4. Cycles repeated every 4 weeks for 3-4 cycles prior to ASCT | Pre-transplant ORR varies from 64%-76%. [47] When Thalidomide is used for TE patients, a triplet combination (eg. CTD) is preferable to TD as the response to the latter is not much better than that seen with conventional chemotherapy. | |

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| | | | |
|---------------------------------|--|---|---|
| Ld [159] | Lenalidomide 25mg po daily d1-21 every 28 days D Dexamethasone 40mg po weekly. Cycles repeated every 28 days for 3-4 cycles prior to ASCT, otherwise, until disease progression. | CR/VGPR 42% post induction. | In Australia, Lenalidomide is currently not reimbursed by the PBS for the initial induction in patients in TE patients with MM. |
| LCD [54, 128] | Lenalidomide 25mg po daily d1-21 every 28 days Cyclophosphamide 300mg/m ² po daily D1,8,15 Dexamethasone 40mg po daily, D1,8,15, and 22 Cycles repeated every 28 days for 3-4 cycles prior to ASCT, | VGPR 38%, CR 2% post induction | |
| COMBINATION PI AND IMiDS | | | |
| BTD[55] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 Thalidomide 200mg po d1-21 Dexamethasone 40mg po on day of and day after bortezomib Cycles repeated every 21 days for 3-4 cycles prior to ASCT, | CR/nCR 31% post induction; CR was 57% post ASCT | In Australia combination bortezomib and thalidomide/lenalidomide cannot be used in combination on the PBS. |
| (BTDC) [160] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11, Dexamethasone 40mg po D1-4, 9-12 Thalidomide 100mg po daily Cyclophosphamide 400mg/m ² IV D1, 8. Cycles repeated every 21 days for 3 cycles prior to ASCT, or additional 4 cycles for patient who became ineligible for ASCT. | Post induction: ORR 96%; CR/nCR 44% post ASCT : ORR 100%; CR/nCR 78% | |
| LBD[161] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11, Lenalidomide 25mg po D1 to 14 Dexamethasone 40mg po, days 1,8,15 Cycles repeated every 21 days for 4 cycles prior to ASCT for those patients who achieved ≥PR, or additional 4 cycles otherwise prior to maintenance. | ORR 100% ≥VGPR 74% | |
| CHEMOTHERAPY-BASED | | | |
| CID [162] | Cyclophosphamide 100mg/m ² po D1,2,3,4 Idarubicin 10mg/m ² po D1,2 Dexamethasone 40mg po daily, D 1-4,8-11,15-18 for cycle 1; days 1-4 for cycles 2-4. Cycles repeated 21 days for 3-4 cycles prior to ASCT. | ORR 66% (CR 9%) post-CID, ORR 80% (34% CR) post ASCT. | |
| PCAB [163] | Doxorubicin 30mg/m ² IV D1, Carmustine 30mg/m ² IV D1, Cyclophosphamide 600mg/m ² IV D1, Prednisolone 60mg/m ² po D1-5, Pegfilgrastim 6mg sc D2. Cycles repeated every 4 weeks up to 12 cycles. | ORR 48% (41% PR, 7% CR) | |

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Table 6B: Commonly used initial induction regimen for patients not eligible for ASCT.

| SCHEDULE | SCHEDULE | RESPONSES AND COMMENTS | |
|---------------------------|--|--|---|
| LENALIDOMIDE-BASED | | | |
| Ld[90, 91] | Lenalidomide 25mg po daily, days 1-21. Dexamethasone 40mg (20mg for patients age >75 years) po daily, days 1,8,15,22 Cycles repeated every 4 weeks. Treatment until disease progression. | ORR 75% (CR15%) | Ld is reimbursed by the Australian PBS for the upfront treatment of MM. Continuous Ld is superior to fixed duration (18m) Ld with respect to PFS, time to next therapy, and is superior to MPT in PFS and OS |
| LCd[128] | Lenalidomide 25mg po daily, days 1-21. Dexamethasone 40mg (20mg for patients age >75 years) po daily, days 1,8,15,22 Cyclophosphamide 300mg/m ² days 1,8,15 | ORR 85% ≥ VGPR 47% | MPL is less well tolerated in patients over the age of 75. Note, PBS-reimbursed lenalidomide can only be used in combination with dexamethasone (Ld) |
| MPL-(L)[164] | Melphalan 0.18mg/kg po D1-4 Prednisone 2mg/kg po D1-4 Lenalidomide 10mg po daily Cycles repeated every 4 weeks x 9 ± lenalidomide continued until relapse. | ORR 77%, CR 16% Med TTP 24.7m 2 yr OS 86.2% | |
| BORTEZOMIB-BASED | | | |
| BMP[87, 89, 118]* | Bortezomib ^{**} : 1.3 mg/m ² IV (SC preferable) days 1, 4, 8, 11, 22, 25, 29, and 32 (cycles one to four) and days 1, 8, 22, and 29 (cycles five to nine) every 6 weeks for nine cycles Melphalan: 9mg/m ² orally D1-4 every 6 weeks for nine cycles Prednisone: 60mg/m ² orally D 1-4 every 6 weeks for nine cycles. <i>** Note: weekly bortezomib improve tolerability in transplant ineligible patients without compromising efficacy. We recommend either: Bortezomib 1.3mg/m² IV (or SC) D 1,8,15,22 every 5 weeks for nine cycles [87, 89] or alternatively Bortezomib 1.3mg/m² or 1.5mg/m² IV (or SC) weekly.[165].</i> <i>**Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved toxicity profile[85].</i> | CR 24-30% Med PFS 22-27m 2 yr OS 85-87%. | Bortezomib is reimbursed by the Australian PBS for the upfront treatment of MM in Australia with or without alkylating agents. Triplet combination (bortezomib + alkylating agent + dexamethasone) is more efficacious compared to doublet combination (bortezomib + dexamethasone. Cyclophosphamide is often preferred over melphalan due to equivalent efficacy but better tolerability. |
| BCD[52]* | Bortezomib: 1.5mg/m ² IV (SC preferable) D1,8,15,22 every 4 weeks for 4 to 12 cycles Cyclophosphamide: 300mg/m ² orally D1,8,15,22 every 4 weeks for 4 to 12 cycles. Dexamethasone: 40mg orally D1,8,15,22 every 4 weeks for 4 to 12 cycles. | ORR 82% CR 12% | Doublet combination may be more tolerable and is acceptable for the elderly frail patient. |
| Bd[88]* | Bortezomib ^{**} : 1.3 mg/m ² IV (SC preferable) D1, 4, 8, and 11 IV every 3 weeks for six cycles Dexamethasone ^{***} : 40mg orally on day of and day post bortezomib. <i>** Note: weekly bortezomib improve tolerability in transplant ineligible patients without compromising efficacy. We recommend either: Bortezomib 1.3mg/m² IV (or SC) D 1,8,15,22 every 5 weeks for nine cycles [87, 89] or alternatively Bortezomib 1.3mg/m² or 1.5mg/m² IV (or SC) weekly.[165].</i> <i>**Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved toxicity profile[85].</i> <i>***Low dose dexamethasone, 40mg weekly (or 20mg weekly for patients aged >75 years) have been shown to be more tolerable and has largely replaced the schedule of dexamethasone 40mg on day of and day post bortezomib.</i> | ORR 88% (CR 6%) | |

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| THALIDOMIDE-BASED | | | |
|--|--|--|---|
| MPT[80] | Melphalan: 0.25mg/kg orally D1-4 every 6 weeks for 12 cycles OR 4mg/m ² orally D1-7 every 4 weeks for 6 cycles. Prednisone: 2mg/kg orally D1-4 every 6 weeks for 12 cycles OR 40mg/m ² po D1-7 every 4 weeks for 6 cycles. Thalidomide: 200mg/day for 12 cycles (6-week cycles) or 100mg orally until disease progression. | CR 13-16% Med PFS 20.3m Med OS 39.3m | Thalidomide is reimbursed by the Australian PBS for the upfront treatment of MM in Australia. Thalidomide –based regimens remain one of the effective treatment options for induction therapy in transplant ineligible patients, however, treatment is hampered by toxicities including venous thromboembolism and peripheral neuropathy such most patient will tolerate a maximum of 12 months of treatment. Doublet thalidomide and dexamethasone is not superior to MP owing to greater toxicities, particularly in patients age above 75 years, and is therefore not commonly used. |
| CTDa[81] | Cyclophosphamide: 500 mg orally weekly for 6 to 9 cycles every 3 weeks. Thalidomide: 100 mg/day orally for 6 to 9 cycles every 3 weeks. Dexamethasone: 20 mg orally on days 1-4 and 15-18 for six to nine cycles every 3 weeks. | CR 13% Med PFS 13m Med OS 33m | |
| COMBINATION BORTEZOMIB AND THALIDOMIDE OR LENALIDOMIDE | | | |
| BTP[87] | Bortezomib: 1.3 mg/m ² given IV (or SC) D 1, 4, 8, 11, 22, 25, 29, and 32 (cycle one), every 6 weeks, and 1.3 mg/m ² on days 1, 8,15, and 22 every 5 weeks (cycles two to six). Thalidomide: 100 mg/day orally daily every cycle for six cycles. Prednisone: 60 mg/m ² given orally on days 1-4 every cycle for six cycles | CR 28% Med PFS 31m 3 yr OS 70% | |
| BMPT[89] | Bortezomib: 1.3 mg/m ² IV (or SC) days 1, 8, 22, 29, every 6 weeks for nine cycles Melphalan: 9 mg/m ² orally on days 1-4 every 6 weeks for nine cycles Prednisone: 60 mg/m ² orally on days 1-4 every 6 weeks for nine cycles. Thalidomide: 50 mg/day orally daily every 6 weeks for nine cycles. | CR 38% Med PFS 33m 3 yr OS 86% | |
| BLd[86] | Bortezomib: 1.3 mg/m ² IV (or SC) D 1, 4, 8, and 11 every 3 weeks for eight cycles. Lenalidomide: 25 mg orally on days 1-14 every 3 weeks for eight cycles. Dexamethasone: 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 every 3 weeks for eight cycles. | CR 37% PFS at 18m 75% OS at 18m 97% | While combination IMiDs and PIs are very effective and can obviate the need for additional chemotherapy agent, such combinations are not reimbursed by the Australian PBS for the treatment of MM. Quadruplet-combinations are not superior to triplet-combinations with respect to survival outcome, but is more toxic. |
| BLCd | Bortezomib: 1.3 mg/m ² IV (or SC) D 1, 4, 8, and 11 every 3 weeks for maximum eight cycles. Lenalidomide: 15 mg orally on days 1-14 every 3 weeks for maximum eight cycles. Cyclophosphamide 500mg/m ² orally on days 1,8 every 3 weeks for maximum eight cycles. Dexamethasone: 40mg orally days 1,8,15, every 3 weeks for maximum eight cycles. | CR 25% 1 yr PFS 86% | |

Table 7: Supportive measures.

| | |
|---------------------------|--|
| Localised bony lesions | <ul style="list-style-type: none"> • Most bone lesions can be treated with chemotherapy and analgesics without the use of radiation therapy. Localised radiation is beneficial in patients with bony pain who have a well-defined focal process. • Patients with lytic lesions in long bones, with threat of fractures should be referred to orthopaedics for prophylactic internal fixation. • Patients with spinal compression fractures and disabling pain may benefit from balloon kyphoplasty[15]; the benefit of vertebroplasty is unclear. • Patients with evidence of spinal cord compression on MRI require surgical intervention, or urgent radiotherapy in combination with corticosteroids if spinal cord compression is due to soft tissue mass arising from vertebrae. • Bisphosphonates: please refer to the Australian guideline for bisphosphonates in the treatment of multiple myeloma[16]. |
| Venothromboembolism (VTE) | <ul style="list-style-type: none"> • The incidence of VTE is ~1% annually in the general population and is increased by up to 10-30 fold in the presence of malignancy. In MM, this is further increased by the use of thalidomide and lenalidomide. Thalidomide alone does not increase the risk of VTE (incidence ~3-4%), but the risk increases to 14-26% in combination with dexamethasone, and up to approximately 30% when used in combination with chemotherapy, especially anthracyclines. The risk is higher in newly diagnosed patients, and within the first 3 months of therapy. <i>Lenalidomide, like thalidomide, does not appear to significantly increase the risk of VTE as a single agent.</i> In combination with dexamethasone or chemotherapy however, VTE risk increases in the order of ~ 14-16%. • VTE prophylaxis is recommended for patients treated with thalidomide or lenalidomide in combination with high-dose corticosteroids and/or chemotherapy. The choices include aspirin, LMWH (equivalent of enoxaparin 40mg daily) or full dose warfarin (target INR 2-3). The choice is dependent on individual assessment of prothrombotic risks[17] |
| rEpo | <ul style="list-style-type: none"> • Recombinant erythropoietin (rEpo) is currently not approved on PBS for use in MM but may be considered in selected patients especially those with renal failure (indication for which it is approved under S100). |
| IV Ig | <p>Selected patients with recurrent infections (≥ 2 chest infections per year) and hypogammaglobulinaemia are eligible for IVIg.</p> <ul style="list-style-type: none"> • Dose: 0.4g/kg every 4 weeks as per CLL. • Please refer to www.nba.gov.au for criteria for the clinical use of intravenous immunoglobulin in Australia. |
| Infection Prophylaxis. | <p>Pharmaceutical prophylaxis against infection should follow local institutional guideline.</p> <ul style="list-style-type: none"> • Valaciclovir, acyclovir or famciclovir prophylaxis against Varicella Zoster reactivation in patients receiving proteasome inhibitors, especially when used in combination with dexamethasone. • Trimethoprim-Sulfamethoxazole prophylaxis against Pneumocystis Jiroveci in patients who are on high dose corticosteroids that is equivalent to at least 20mg of prednisolone daily for at least 4 weeks. Dapsone, Pentamidine or Atovaquone are possible second line prophylactic agents if Trimethoprim-Sulfamethoxazole is contraindicated. • Patients should be vaccinated against hepatitis B, pneumococcus, influenza and other pathogens deemed necessary because of epidemiologic prevalence. Live vaccines should be avoided. Non-immune close contacts of patients should also be vaccinated[18]. |
| Other prophylaxis | <ul style="list-style-type: none"> • Proton pump inhibitor or histamine H2-receptor antagonist is recommended in patients receiving ongoing corticosteroids. |

3 MANAGEMENT OF MULTIPLE MYELOMA – AN OVERVIEW

Despite much improved survival outcome for patients with multiple myeloma (MM) over the years, MM remains an incurable disease. The expansion of effective treatments has converted a disease with median overall survival (OS) of 3 years, to now a chronic disease capable of long-term control, often for 7 years or more. While we continue to strive towards to ultimate goal of “cure” for the future, currently, the treatment goals in the management of MM are to control the disease, maximise quality of life and prolong survival.

3.1. THE DECISION TO COMMENCE MYELOMA THERAPY

A key step in managing MM is to determine which patients require therapy, and the following applies to both transplant-eligible and -ineligible patients. This decision is generally determined by the presence of myeloma defining events, manifested by either hypercalcemia, renal impairment, anaemia or bone disease (so-called CRAB criteria) or positive biomarkers of malignancy (table 3) that predicts an 80% of developing end organ damage within 2 years [3]

The average risk of progression from monoclonal gammopathy of uncertain significance (MGUS) to symptomatic myeloma is approximately 1% per year[18]. For SMM, the median time to progression is between 12 to 32 months[19]. Monitoring of MGUS and SMM should be indefinite; the frequency may vary depending on the individual’s risk of progression.

Early intervention in patients with MGUS and SMM is of no proven clinical benefit. However, the role of early treatment in the subset of patients with “high risk” smouldering myeloma (HR-SMM) is still being evaluated. Complicating interpretation of studies of HR-SMM is the lack of a unified definition of this condition. The Mayo Clinic ($\geq 10\%$ bone marrow plasma cells plus paraprotein of $\geq 30\text{g/L}$)[19] and Spanish ($\geq 95\%$ plasma cells demonstrated to be clonal on flow cytometry and immunoparesis) criteria have both been used in prospective trials, however there is only a 30% concordance rate between them[20]. One small randomised trial of patients meeting either the Mayo Clinic or Spanish criteria has shown improvement in PFS and OS with early lenalidomide-dexamethasone treatment[21]. However, the OS of the untreated group was unusually low in this study, and confirmatory studies are required. Figure 2 and Box 1 outlines the recommended follow up algorithm for patients with MGUS and SMM.

Box 1: Recommendation for monitoring of MGUS and Asymptomatic MM:

Monitoring of MGUS and asymptomatic MM should be indefinite; the frequency may vary depending on the individual’s risk of progression (Grade C recommendation, level 4 evidence).

Three to 12 monthly visits are sufficient, depending on the individual risk assessment for progression towards symptomatic MM. (Grade C recommendation, level 4 evidence).

Monitoring should include a clinical assessment, full blood evaluation, renal function, electrolytes including calcium levels, serum \pm urinary para-protein, and targeted radiographic imaging when indicated. (Grade C recommendation, level 4 evidence).

Early treatment of patients with “high-risk” multiple myeloma (as defined by either the Spanish or Mayo criteria, see text) is still considered investigational and should be only undertaken in a clinical trials setting.

Patients without evidence of myeloma defining events (CRAB criteria, table 3) but with positive markers of malignancy (table 3) are now classified as having multiple myeloma according to the updated IMWG diagnostic criteria and should be treated as such.

3.2 UPFRONT TREATMENT OF MULTIPLE MYELOMA – AN OVERVIEW:

Currently, the standard initial treatment for patients with symptomatic MM depends on their eligibility for high dose therapy (HDT) and autologous stem cell transplant (ASCT), that is in turn dependent on the patient's age, comorbidities and functional status. Whether or not ASCT is incorporated as part of initial treatment, the aim is to induce a maximal depth of response, especially complete response (CR), without unacceptable toxicities. CR is associated with prolongation of PFS and OS [22, 23] in both the ASCT [24-26] and non-ASCT setting [23, 27, 28], and in both young and elderly patients. However, the prognostic impact of CRs on survival may be less important in patients in whom symptomatic myeloma had progressed from a previous prolonged period of MGUS or smouldering myeloma [29]. Conversely, the prognostic impact of CR on survival outcome was more evident in patients with high-risk versus standard risk MM as defined by gene-expression profiling [30]. Currently, CR is considered an objective of initial treatment, provided there is no unacceptable toxicity. Amongst patients with CR, MRD (minimal residual disease) negativity as defined by multi-parameter flow cytometry, polymerase chain reaction or next generation sequencing, has been shown to correlate strongly with OS. MRD negativity is increasingly accepted as a surrogate correlate for improved OS [31]. At present, methods for assessment of MRD are not consistent across laboratories and generally only available in tertiary treatment centres in Australia. MRD is not generally used to influence treatment decisions and is therefore mainly used in the clinical trial setting.

3.2.1 Patients eligible for ASCT:

The superiority of ASCT (when used as part of initial therapy) over a non-transplant approach has now been confirmed in the era of IMiDs and proteasome inhibitors in two randomised phase III trials, the GIMEMA MM-RV-209 [32] and EMN MM-RV-441 trial [33]. In both trials, patients age <65 years were given lenalidomide-dexamethasone induction prior to stem cell collection, then randomised to either ASCT or a further 6 cycles of MPL (Melphalan, Prednisone, Lenalidomide; GIMEMA trial) or CLD (cyclophosphamide, lenalidomide, dexamethasone; EMN trial). Both studies have demonstrated superiority of the ASCT approach as part of initial treatment with respect to PFS and OS. Similar results were seen in the ongoing phase III IFM 2009 study evaluating lenalidomide bortezomib dexamethasone induction with or without upfront ASCT, then lenalidomide maintenance. Marked improvement in PFS was seen with the upfront ASCT approach (HR 0.69, $p < 0.001$). Importantly, an impressive superiority in the rate of MRD negativity was seen with the ASCT approach (80% (ASCT arm) vs. 65%, $p = 0.001$), which in turn is generally correlated with improved OS [31].

The traditional notion that patients aged above 65 years are ineligible for ASCT is no longer appropriate as it is clear that older patients who are biologically fit do benefit from intensive treatment [34]. In assessing eligibility for ASCT (generally in patients aged up to 70 years), individual assessment that takes into consideration the patient's age, comorbidities, frailty (variously defined as poor endurance, weakness and low physical activity) and disability (dependency in activities of daily living (ADL) due to physical or mental impairment) [35] is required (please refer to the section on patients ineligible for ASCT). Clinical tools such as the haematopoietic stem cell transplant co-morbidity index (HCT-CI) may be useful to assess suitability for ASCT [36].

3.2.1.1 Tandem vs. single ASCT:

Prior to the era of IMiDs, PIs, and other novel therapeutic agents, tandem ASCT (in which the second ASCT is planned to occur 3 to 6 months after the first) was found to benefit mainly patients who have not achieved at least VGPR to the initial transplant [37, 38]. However, in the era of IMiDs and PIs and other effective novel agents, the role of tandem ASCT has been less clear.

In a meta-analysis of 6 randomised-control trials of 1803 patients, comparing tandem versus single ASCT for upfront treatment of MM, Kumar et al [39] reported that whilst there was a superior overall response rate (ORR) with tandem ASCT (risk ratio 0.79), there was a significant increase in transplant related mortality (TRM) (risk ratio 1.71). Overall, tandem ASCT did not result in improved OS or EFS compared to single ASCT. However, the trials that were included in this meta-analysis were heterogeneous, mainly due to the inclusion of a trial which compared single transplant plus thalidomide maintenance therapy to tandem transplant, that favoured single transplant [40]. This trial has been subsequently retracted, resulting in a statistically significant change in the hazard ratio for EFS favouring tandem transplant, but not OS in this meta-analysis.

In the HOVON-65/GMMG-HD4 trial that compared VAD (vincristine, doxorubicin, dexamethasone) vs. PAD (bortezomib, doxorubicin, dexamethasone) followed by ASCT then maintenance with thalidomide (VAD arm) or bortezomib (PAD arm), tandem ASCT emerged on multivariate analysis as a significant factor for improved OS ($p = 0.03$) [41].

In an integrated analysis of data from phase III European studies in which patients were prospectively assigned to receive either single or double (tandem) ASCT, double ASCT resulted in superior PFS (med 38 vs. 50 months, $p < 0.001$) and OS (5 year estimates: 63% vs. 75%, $p = 0.002$), particularly for patients with high-risk cytogenetics [42].

Conversely, the preliminary analysis of the ongoing BMT CTN 0702 – StaMINA Trial, a second ASCT had no impact on PFS and OS compared to single ASCT when effective induction (combination IMiD and PI) and lenalidomide maintenance was incorporated (see section on consolidation)[43].

Tandem ASCT with its associated acute toxicity may therefore be a reasonable strategy, perhaps in selected patients who have had a suboptimal response to first transplant, and particular patients with high-risk MM[42]. Otherwise, it seems apparent that consolidation or maintenance therapies with newer agents, and effective salvage therapies in the current era, may well mitigate any OS advantage of tandem ASCT over single ASCT.

Our recommendations for transplant eligible patients is as outlined in Box 2.

Box 2: Recommendation for transplant eligible patients:

High dose therapy (HDT) and autologous stem cell transplant (ASCT) remains the standard upfront treatment for patients aged ≤65 years, and patients between 65-70 years with good performance status and organ reserve (Grade A recommendation, level 1B evidence for patients age ≤65; grade B recommendation, level 2A evidence for patients aged >65)

Tandem ASCT is not routinely recommended. (Grade A recommendation, level 1B evidence).

3.2.1.2 Induction therapy prior to AuSCT

The ideal induction regimen for transplant-eligible patients should rapidly reduce tumour burden and reverse disease related complications, to allow patients to proceed promptly to transplant without antecedent toxicities. Deeper pre-transplant responses is associated with better post transplant outcome[44].

Proteasome inhibition results in multiple anti-MM effects including 1) inhibition of clearance of misfolded proteins, 2) blockade of the transcription factor nuclear-factor kappa B (NFkB) that in turn results in reduced cytokines that promote MM-cell growth, and 3) accumulation of tumour suppressor proteins[45]. The first in class PI, bortezomib, is available in Australia on PBS and is widely used in the treatment of MM.

Immunomodulatory drugs (IMiDs) are so called due to their ability to increase T-cell costimulation and enhance NK cell activity, in addition to other antimyeloma activities including induction of apoptosis and antiangiogenesis[46]. Recent studies have shown that IMiDs exert their actions via binding to cereblon in plasma cells and T cells, a protein that forms part of the E3 ubiquitin ligase complex. This interference of ubiquitin ligase function in turn result in alteration in key proteins (200+) such as Ikaros and Aiolos which alter downstream gene promotion of survival in plasma cells and immune regulatory genes in T cells[45].

Induction-regimens that incorporate IMiDs and/or proteasome inhibitors (table 6A) are superior to chemotherapy-only regimens, particularly in poor-risk patients such as those with poor cytogenetics or other adverse prognostic features[47-49].

Two-drug combinations where dexamethasone is combined with thalidomide (TD), lenalidomide (Ld) or bortezomib (BD) are superior to VAD[47-49]. Of note, Ld or BD achieves CR/VGPR rates of 20-40% prior to ASCT, which is superior to the TD combination that induces CR/VGPR rates of approximately 10-16%[47]. Three-drug combinations appear to further improve efficacy with respect to depth of initial response; the addition of a chemotherapy agent, either cyclophosphamide or doxorubicin to thalidomide (CTD, TAD)[50, 51], bortezomib (CyBorD, PAD) [52, 53], or lenalidomide (LCD)[54] induces CR/VGPR rates between 37-65%. Similar impressive efficacy is seen with three-drug regimens that combine IMiDs and proteasome inhibitors[55, 56]. In contrast, no further advantage was seen with a four-drug combination, which instead results in greater toxicity[56]. It should be noted that combinations of IMiDs and proteasome inhibitors are not currently reimbursed by the PBS in Australia.

There have been no clinical trials that directly compare bortezomib-based regimens to IMiD-based regimens for induction prior to ASCT. One meta-analysis showed that bortezomib-based regimens (BD or BTd) were superior to non-bortezomib based regimens with respect to PFS and OS[57], but this was not surprising given that the non-bortezomib comparator was VAD or TD, both of which are known to induce only modest responses. Nonetheless, bortezomib certainly induces rapid and quality responses, and given that it can partially mitigate the impact of adverse cytogenetics, bortezomib-based regimens are often used preferentially as first-line induction in transplant eligible

patients. A weekly schedule of bortezomib 1.5mg/m² appears to result in reduced toxicity without compromising efficacy compared to the traditional schedule of bortezomib 1.3mg/m² days 1,4,8,11 every 21 days[52]. Similarly, it appears that weekly subcutaneous bortezomib is better tolerated than IV without compromising efficacy in transplant eligible patients, based on preliminary results of a phase II study[58]. Recommendations for induction therapy prior to ASCT are summarised in Box 3.

Box 3: Recommendation for induction therapy prior to ASCT:

Transplant-eligible patients should be treated with 3-6 cycles of induction prior to ASCT (grade A recommendation, level 1B evidence).

The incorporation of proteasome inhibitors and/or immunomodulatory drugs as part of front line induction therapy (table 1) improves quality of responses and is considered standard of care. Currently, only bortezomib or thalidomide but not lenalidomide are available on the Australian PBS for induction therapy for transplant eligible patients with newly diagnosed MM. Note that the Australian PBS does not allow the concurrent use of bortezomib and thalidomide or lenalidomide.

Three-drug combinations appear more efficacious than two-drug combinations (grade B recommendation, level 2A evidence). Four-drug combinations are more toxic without added efficacy, and are not recommended (grade A recommendation, level 1B evidence)

The choice of induction therapy (table 6A) is dependent on local availability/access to novel therapeutic agents, and should take into consideration the patient's prognostic indices and comorbidities, for example:

- *For patients categorised as having high risk MM (table 5) or with renal impairment, the use of bortezomib early in the disease course should be considered (grade A recommendation, level 1B evidence).*
- *For patients with pre-existing neuropathy, thalidomide or bortezomib should be used with caution with appropriate dose attenuation upon worsening of neuropathic symptoms. A weekly schedule of bortezomib 1.5mg/m² and subcutaneous route of administration appear to significantly reduce neurotoxicity compared to the traditional bortezomib schedule of 1.3mg/m² IV on days 1,4,8,11 every 21 days.*
- *For patients with severe renal impairment, lenalidomide-based regimens are not the induction of choice due to renal clearance of lenalidomide.*
- *For patients with previous history or at high-risk of thromboembolic complications, thalidomide and lenalidomide, although not absolutely contraindicated, should be avoided if other effective induction options are available.*

3.2.1.3 Stem cell mobilisation

The most common regimen used to mobilise peripheral blood stem cells (PBSC) for MM patients is recombinant human granulocyte colony stimulating factor (rhG-CSF), such as filgrastim™, 10mcg/kg, or high dose cyclophosphamide with rhG-CSF. The addition of high dose cyclophosphamide for mobilisation does not necessarily improve depth of response over induction therapy, and does not improve CR rates or time to progression (TTP) in patients undergoing ASCT[59]. However, using cyclophosphamide for mobilisation has the advantage of increasing the CD34+ cell yield. A higher dose of cyclophosphamide (3-4g/m²) will give a better CD34+ yield, but may also cause more toxicity requiring hospital admissions compared to cyclophosphamide 2g/m²[60].

More recently, plerixafor (Mozobil®), a chemokine receptor-4 antagonist, has been shown to be a potent stem cell mobiliser. Its use in combination with rhG-CSF significantly improves stem cell mobilization compared to rhG-CSF alone[61]. Due to high cost, plerixafor is generally reserved for patients who fail to mobilize adequately as either a rescue strategy or during a second mobilization attempt, under the PBS re-imburement criteria in Australia (pbs.gov.au).

Bortezomib and thalidomide does not appear to impair stem cell mobilization [62] in patients who have received fewer than 4 induction treatment-cycles. In these cases, rhG-CSF alone is often adequate for the initial attempt at stem cell mobilization although many centres continue to use rhG-CSF in addition to high-dose cyclophosphamide as part of institutional protocol. In fact, recent reports have indicated that thalidomide and oral cyclophosphamide, two agents that have not been shown to impact stem cell mobilization individually, may

induce a higher rate of stem cell mobilization failure when used in combination[63]. Lenalidomide has been reported to reduce the number of CD34+ cells collected. Mobilization using rhG-CSF alone after lenalidomide-based induction therapy may be inferior to combination therapy using rhG-CSF and high-dose cyclophosphamide[64], and the latter should be considered for stem cell mobilization, especially in patients who have received more than 4 cycles of lenalidomide-based induction therapy. Recommendations for stem cell mobilisation are summarised in box 4.

Box 4: Recommendation for stem cell mobilisation:

Stem cell mobilization regimen should follow institution protocol.

Stem cells can be mobilized with rhG-CSF alone or rhG-CSF(10mcg/kg) in combination with high-dose cyclophosphamide (2 to 4g/m²).

The use of high-dose cyclophosphamide has the advantage of increasing CD34+ yield, but is also associated with more toxicity.

rhG-CSF alone may be adequate for the initial attempt of stem cell mobilization after thalidomide or bortezomib-based induction therapy. However, combination rhG-CSF and high dose cyclophosphamide may be required after lenalidomide-based induction therapy, and it is recommended that stem cell mobilisation is attempted before patients have received more than 4 treatment cycles (Grade B recommendation, level 2B evidence).

Plerixafor in combination with rhG-CSF significantly improves stem cell mobilization and is reserved for patients who fail to mobilize adequately on cyclophosphamide plus rh-GCSF, or rhG-CSF alone (Grade B recommendation, level 2B evidence).

3.2.1.4 Monitoring of patients after ASCT

The average time to progression for patients after HDT and ASCT is in the order of 2-4 years for younger patients, and shorter for older patients. The final magnitude of response post ASCT should be assessed after 2-3 months. Patients should be followed up with clinical and laboratory assessments, looking for evidence of relapse/progression. Testing should include serum or urinary paraprotein and SFLC levels (especially in patients with unmeasurable paraprotein in blood or urine), FBC, serum calcium levels, and renal function. In assessing response, it is important not to misinterpret the emergence of oligoclonal bands as relapse disease or clonal evolution. Oligoclonal response after primary therapy is a well recognised event, and can appear as multiple oligoclonal bands in serum and/or urine immunofixation; it is thought to be related to immune reconstitution and is associated with favourable outcome[65]. Initial follow up for patients is usually monthly until stable, then 3 monthly or less frequent subsequently if there appears to be disease stability. Please refer to Durie et al. 2006 [66], for uniform response criteria to assess response and relapse after treatment. Recommendation regarding follow up post ASCT are summarised in box 5.

Box 5: Recommendations regarding follow up post ASCT:

Post HDT+ASCT, patients should be followed up monthly until stable, then 3 monthly or less frequent if there appears to be disease stability (grade C recommendation, level 4 evidence)

Follow up assessment should include:

- *Clinical assessment.*
- *Serum ± urinary protein electrophoresis (immunofixation not required)*
- *Serum free light chains.*
- *FBE, U&E, Ca²⁺*
- *Targeted radiographic imaging if indicated.*

3.2.1.5 Allogeneic Stem Cell Transplant

“Graft versus myeloma (GVM)” effect does exist in the setting of allogeneic stem cell transplantation (alloSCT) [67]. However, while this may give rise to some long-term durable remissions [68], myeloablative alloSCT is associated with a high TRM of up to 50%. Reduced intensity conditioning (RIC) alloSCT lowers TRM to approximately 10-15% at 1 year, whilst maintaining the GVM effect, however chronic graft-versus-host disease remains a major problem in many survivors. A number of prospective trials have been published. The IFM99-03 study [69], included only patients with high risk (del13q + B2M>3mg/ml), and patients with available sibling donors underwent MEL200 ASCT followed by RIC AlloSCT with anti-thymocyte globulin, busulphan and fludarabine conditioning. Patients without a donor had a second ASCT in the companion IFM99-04 study. At the time of initial reporting median EFS and OS were similar in the two studies, EFS 35 months vs 32 month, $p=ns$, and OS 47 months vs 35 months, $p=ns$, in ASCT + RIC alloSCT vs. tandem ASCT respectively. However after longer follow up, OS was found to be significantly inferior in patients assigned to RICalloSCT [70]. An Italian randomized study, also comparing tandem ASCT vs. ASCT followed by RIC alloSCT (non-myeloablative total body irradiation conditioning), and not requiring poor prognostic features for selection demonstrated a superior long-term outcome in those who had available sibling donors (OS: 80 vs. 54 months, $p=0.01$; EFS: 35 vs.29 months. $P=0.02$) [71]. In the Spanish PETHEMA trial [72], comparisons were made between a second ASCT vs. RIC (Melphalan and fludarabine) alloSCT in a group of patients who achieved < VGPR to their first ASCT. A higher rate of CR in favour of RIC alloSCT was seen (40% vs. 11%, $p=0.001$) and a plateau in PFS was also seen in this group. However, due to a higher TRM and GVHD, no statistical difference in EFS and OS was observed. Similarly, interim results from the BMT-CTN (Blood and Marrow Transplant Clinical Trials Network) 0102 Trial showed equivalent 3-year PFS and OS for tandem auto-auto vs. auto-allo stem cell transplant both high-risk [73], and standard-risk [74] MM patients. Two Gy total body irradiation was used as the non-myeloablative conditioning regimen in the allo-SCT arm. There was a suggestion of lower late PFS and time to progression/relapse in the auto-allo SCT arm in the high-risk group ($p=0.09$), however, no added benefit from auto-alloSCT was seen in the standard-risk group over tandem ASCT due to increased TRM. At present, a number of studies are ongoing to investigate the role of AlloSCT with novel immunological approaches. However, given the lack of consistent survival benefit to date, the use of AlloSCT should still be restricted to clinical trials, with the exception of selected cases of very high risk MM (please see section 3.4: patients with high risk MM)[75]. Recommendations regarding AlloSCT are summarised in box 6.

Box 6: Recommendation regarding AlloSCT:

Currently, alloSCT is still considered investigational and should ideally be performed in the setting of a clinical trial (Grade C recommendation).

Young patients with very high-risk disease (please refer to section 3.4) who are deemed suitable for alloSCT should be referred early to the transplant physician at the outset of treatment (Grade C recommendation).

3.2.2 Patients not eligible for ASCT

3.2.2.1 Pre-treatment consideration: fit versus frail elderly patients

Aging is associated with comorbidities and reduced organ function that may reduce tolerance to therapy. Chronological and biological age can differ greatly in the elderly patient population, and the pitfalls of choosing therapy based purely on chronological age are now recognised. Whilst the goal of achieving complete remission (CR) is important irrespective of age[76], substantial treatment-related toxicities can mitigate benefits of CR in frail elderly patients. In the group of frail elderly patients, opting for disease control to optimize quality of life (QoL) may be preferable.

Based on age, comorbidities, frailty (variably defined as poor endurance, weakness and low physical activity) and disability (dependency in activities of daily living (ADL) due to physical or mental impairment)[35], elderly patients can be divided according to three broad subgroups: very fit, fit and unfit. Broadly speaking, very fit patients are patients with excellent performance status, no significant co-morbidities (in particular cardiac, pulmonary, renal, hepatic or gastrointestinal), disabilities or frailty. Fit patients are patients with comorbidities or factors that may preclude ASCT, but have reasonable performance status and no significant disabilities. Unfit patients are those of older age (typically but not always patients age above 75 years) with significant co-morbidities, limitations in physical activity and/or dependency in ADLs due to physical or cognitive impairment[77].

The traditional notion that patients aged above 65 years are ineligible for transplant is no longer appropriate. For patients aged between 65-75 who are 'very fit', induction therapy incorporating IMiDs or proteasome inhibitors followed by HDT+ASCT and subsequent maintenance can induce profoundly deep responses[78, 79] (Please refer to section on transplant eligible patients). Reduced-dose conditioning (melphalan 100-140mg/m²)[78, 79] is tolerable and has been shown to induce a median PFS of 4 years in this group of patients[78].

“Fit” elderly patients with reasonable performance status but with co-morbidities or other factors that preclude HDT+ASCT should undergo full dose treatment with regimens containing an IMiD or a proteasome inhibitor, while 'unfit' patients should be considered candidates for such therapies albeit with reduced dose-intensity (please see box 7).

Box 7: Recommendations for the assessment of suitability of elderly patients for the intensity of therapy:

- *Based on age, comorbidities, frailty and disability, elderly patients should be classified as either, very fit, fit or unfit to guide treatment choice.*
- *Very fit patients aged between 65-75 can be considered for full dose induction therapy incorporating IMiDs or proteasome inhibitors (see table 6A) followed by HDT+ASCT. Reduced dose conditioning (melphalan 100-140mg/m²) can be considered (Grade B recommendation, level 2A evidence)*
- *Fit elderly patients who are deemed ineligible for HDT+ASCT should undergo full dose induction therapy incorporating IMiDs or proteasome inhibitors (see table 6B) (Grade A recommendation, Level 1A evidence)*
- *Reduced-intensity treatment is suggested for those more frail 'unfit' elderly patients (see table 8) (Grade B recommendation, Level 2A evidence)*
- *Patients who are considered ineligible for any treatment should be referred early to a palliative care unit.*

3.2.2.2 Initial treatment for transplant ineligible patients

Thalidomide-based regimens:

In Australia, thalidomide is reimbursed on the PBS for the treatment of MM. It is often used in a triplet combination, with an alkylating agent (either cyclophosphamide or melphalan) and corticosteroid (either dexamethasone or prednisolone); see table 6B. For transplant ineligible patients, the addition of thalidomide to melphalan and prednisolone (MPT) improves PFS and OS compared to MP by 5.4 and 6.6 months, respectively, according to a meta-analysis of 1682 patients from the 6 randomized clinical trials that compared MP to MPT[80]. However, the addition of thalidomide comes at a price of higher toxicity, mainly, myelosuppression, venous thromboembolism (VTE), and peripheral neuropathy. The use of cyclophosphamide as an alternative alkylating-agent to melphalan, in combination with thalidomide and dexamethasone (CTD) is equally efficacious as induction therapy[81](table 6B). As doublet therapy, the efficacy of thalidomide and dexamethasone (Td) is not superior to MP, resulting in similar PFS (16.7 vs. 20.7m, p=0.1). Indeed, OS is shorter with Td compared to MP due to greater toxicities particularly in patients aged ≥75 years with poor performance status[82]. Thus, when thalidomide is used, it is often used in triplet combination (eg. CTD or MPT) rather than doublet combination (Td). In the First (MM020) study (see below) MPT was demonstrated to be inferior to Ld and so should be only used if lenalidomide or bortezomib combinations are contraindicated.

Bortezomib-based regimen

In Australia, bortezomib (Velcade®) is reimbursed on the PBS for the initial treatment of MM and at relapse subject to other eligibility criteria (please refer to <http://www.medicareaustralia.gov.au>). For transplant ineligible patients, the addition of bortezomib (Velcade®) to MP (BMP) results in an improved survival (56.4 (BMP) vs. 43.1 months (MP)) as demonstrated by the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) trial which compared BMP to MP[83].

Currently, both MPT and BMP are considered 'standards-of-care' in Australia for transplant ineligible patients (table 6B). The weekly schedule of bortezomib has been shown to be more tolerable and resulted in a similar cumulative dose delivered compared to the traditional schedule of bortezomib on days 1,4,8,11 every 21 days[84]. For transplant ineligible patients, the weekly schedule of bortezomib is now considered standard of care (table 6B). Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved safety profile[85]. The use of cyclophosphamide in place of melphalan is of comparable efficacy[52]. The combination of an IMiD and bortezomib is attractive but this does not appear superior to a simple (and cheaper) alkylating agent combination[86, 87]. Moreover, such an IMiD + bortezomib combination is not approved by PBS for the treatment of MM in Australia. BTP is particularly toxic with respect to cardiac adverse events[87].

In unfit elderly patients in whom an alkylating agent may not be suitable, a doublet combination of bortezomib and dexamethasone is efficacious with RR and CR of up to 70% and 25%, respectively[88]. Conversely, a 4-drug regimen combining bortezomib, lenalidomide, cyclophosphamide and dexamethasone (BLCD) have been shown to be more toxic without added efficacy[56, 89].

Lenalidomide-based regimens

Based on the pivotal phase III FIRST (Frontline Investigation of Revlimid and dexamethasone versus Standard Thalidomide) clinical study, combination lenalidomide and dexamethasone (Ld) has emerged as one of the most effective induction regimen for transplant ineligible patients in first line treatment[90]. Final analysis demonstrated superiority of continuous Ld (i.e. Ld until disease progression) over MPT with respect to PFS (4 year PFS 32.6 vs. 16.6 months (MPT), $p < 0.00001$) and OS (predicted 4 year OS: 59% vs. 51% (MPT), $p = 0.0023$)[91]. Of note, continuous Ld significantly improve PFS over fixed duration (18 months) Ld. Four year PFS was 32.6 months with continuous Ld vs. 14.3 months with fixed duration Ld. However, OS was similar (predicted 4 year OS: 59m (cont. Ld) vs. 58m (18m Ld), respectively). This may be partly explained by the fact that a significant proportion of patients in the fixed duration Ld arm were retreated with Ld again upon first relapse. Importantly, the time to next treatment was approximately 8 months (~30 months for patients who have achieved at least VGPR) longer in the continuous Ld group compared to 18m Ld group. Effectively, what this means is that while the OS may be the same between the two groups at 4 years, patients in the 18m Ld arm required another line of treatment to stay alive. At present, continuous Ld is considered as one standard of care for initial induction therapy in transplant ineligible patients.

As of February 2017, lenalidomide is reimbursed in Australia for the initial treatment of transplant ineligible patients with MM.

As triplet combination, the addition of lenalidomide (Revlimid®) to MP (MPL) is less well tolerated in elderly patients mainly due to myelosuppression, especially those over the age of 75 years. This perhaps accounts for the absence of a PFS improvement despite higher ORR when compared to MP (27). As was seen in the FIRST study, the use of continuous lenalidomide (i.e. the addition of lenalidomide maintenance to MPL (MPL-L)) resulted in a profound improvement in PFS by 18 months compared to MP. Again, this was noted only for patients aged less than 75 years[92]. Overall, the addition of an alkylating agent (cyclophosphamide or melphalan) to Ld has not been found to improve ORR, PFS or OS in first line treatment of transplant ineligible patients[93]; when combined with Ld, melphalan is more myelotoxic compared to cyclophosphamide.

Unlike thalidomide and bortezomib, the risk of neurological toxicity with lenalidomide is significantly lower. Myelosuppression is common, especially in patients with impaired renal function. Like thalidomide, VTE prophylaxis is recommended (see supportive measures, table 7). Lenalidomide-associated secondary primary malignancies (SPM) have been a concern since increased rates of SPM were noticed in 3 major studies that assessed lenalidomide maintenance[92]. In a recent meta-analysis of 7 phase III lenalidomide clinical trials of over 3200 patients, the 5-year cumulative incidences of all SPM was 6.9% compared to 4.8% in patients who did or did not receive lenalidomide, respectively (HR 1.55, $p = 0.037$). The risk of haematological SPM appears highest when lenalidomide is combined with oral melphalan (HR 4.86, $p < 0.0001$ compared to melphalan alone), whilst combination lenalidomide-dexamethasone with or without cyclophosphamide did not increase haematological SPM[94]. Table 6B outlines the more common induction treatment regimens for transplant ineligible patients. Recommendations for initial induction therapy for transplant ineligible patients are summarised in box 8.

Box 8. Recommendations for initial induction therapy for transplant ineligible patients.

- *The current accepted standard of care for the initial treatment of transplant ineligible patients with multiple myeloma include:*
 - o *Continuous lenalidomide and dexamethasone (Ld) (Level 1B evidence, grade A recommendation).*
 - o *Bortezomib, melphalan and prednisolone (BMP) (level 1A evidence, grade A recommendation).*
 - *Cyclophosphamide could be substituted for melphalan (CyBorD regimen)*
 - *For unfit elderly patients (section 3.3.1), bortezomib and dexamethasone (Bd) as doublet should be considered (level 1B, grade B recommendation)*
- *Thalidomide, melphalan and prednisolone (MPT) has now been shown to be inferior to Ld (Level 1B evidence) and should only be used if only used if lenalidomide or bortezomib combinations are contraindicated (Grade A recommendation).*
- *Cyclophosphamide is therapeutically equivalent compared with melphalan and may be more tolerable; it is often preferentially used in place of melphalan in IMiDs or proteasome inhibitor containing regimens (eg. CTD or BCD), (level 1B, grade B recommendation), see table 6B table 6B.*
- *For bortezomib, a weekly and subcutaneous schedule is recommended.*

3.2.2.3 Dose attenuation in unfit elderly patients

Treatment-related toxicities and early treatment discontinuation have each been shown to be associated with shorter survival in elderly patients with MM[95], highlighting the need for treatment dose-attenuation particularly in the unfit elderly patient (table 8).

For bortezomib, the weekly schedule (as opposed to days 1,4,8,11 every 21 days) significantly reduces the rate of grade ≥ 3 peripheral neuropathy from 28% to 8% without impact on efficacy[84]. In addition, one randomized trial in patients with relapsed and/or refractory myeloma(RRMM)has shown that the subcutaneous route of administration was associated with reduced peripheral neuropathy without compromising efficacy[85]. In patients aged above 75 years, low-dose thalidomide (50-100mg) is more tolerable than doses of 200mg or more. Similarly, lower-dose oral melphalan (0.18-0.2mg as opposed to 0.25mg per kg) is safer in this age group such that the best MPT result in patients aged above 75 years was achieved with reduced-dose thalidomide and melphalan[96].

Traditional high-dose dexamethasone (40mg days 1-4, 9-12, 17-22) is associated with significant toxicities in elderly patients, and this has been shown to decrease OS compared to lower dose dexamethasone (40mg weekly)[49]. For patients older than 75 years or who are frail, a lower starting dose of dexamethasone, 20mg weekly, could be considered[77].

Standard-dose lenalidomide (25mg) is generally well tolerated in elderly patients. However, dose reduction is recommended in patients with impaired renal function. Finally, lenalidomide at 10mg, when combined with melphalan and prednisone (MPR) did not improve PFS, as compared with MP, in patients age ≥ 75 years, but dose reductions were required more frequently than for younger patients [92].

Table 8: Recommended dose attenuation in unfit elderly patients.

| | 65-75 years (standard dose) | >75 years or unfit 65-75years (reduced dose) |
|--|---|---|
| Dexamethasone weekly | 40mg | 20mg |
| Melphalan days 1-4 | 0.25mg/kg | 0.12-0.18mg/kg |
| Cyclophosphamide weekly | 300mg/m ² | 150mg/ m ² |
| Thalidomide (per day) | 100mg | 50-100mg |
| Bortezomib | 1.3mg/m ² weekly Consider subcutaneous route. | 1.3mg/m ² weekly Prompt dose-reduction to 1.0mg/m ² weekly upon side effects. Consider subcutaneous route. |
| Lenalidomide (with dexamethasone) days 1-21 every 28 days | 25mg | 25mg* |

* Elderly patients are more susceptible to lenalidomide-induced myelosuppression due to impaired renal function. Suggest close monitoring at the commencement of treatment and prompt dose reduction in the event of toxicity. A lower starting dose is required for all patients with CrCL \leq 60ml/min.

3.2.3 Patients with high risk MM

Several factors are known to confer a poorer prognosis in patients with MM (table 5). These include older age [97], higher ISS stage, high LDH, high plasma cell labelling index and the cytogenetic abnormalities: t(4;14), t(4;16) and 17p deletion (as identified by FISH) [98-100], 13q deletion (identified by standard cytogenetic), as well as hypodiploidy and complex (combination of \geq 3) cytogenetic abnormalities. Amplification of chromosome 1q21 (by FISH) has also been shown to be associated with both shorter time to disease progression and poorer prognosis[101, 102].

In the assessment of primary genetic abnormalities, FISH remains the standard technique, whereas molecular approaches such as gene expression profiling or SNP (single nucleotide polymorphism) mapping arrays are only used in the context of clinical studies.[103]

In the era of IMiDs and PIs, patients with high-risk MM are defined as those with an expected OS of <3 years for transplant eligible or <2 years for transplant ineligible. For transplant eligible patients, those with an expected OS <2 years are classified as “ultra high risk”[6, 103]. The most robust factors that are consistently associated with such poor survival are higher ISS stage and the cytogenetic abnormalities 17p deletion and t(4;14). The revised(R)-ISS risk stratification system now incorporates ISS stage, LDH and high-risk iFISH (del17p and t(4;14)),(table 4). In the era of IMiDs and PIs, the R-ISS can clearly identify 3 different MM prognostic groups in patients and now supersedes the previous ISS staging system[6, 104].

With respect to treatment, thalidomide does not overcome HR cytogenetic abnormalities. Several reports have confirmed that bortezomib improves PFS and OS in the presence of poor risk cytogenetics (13q deletion, t(4;14), amp1q21, and perhaps even 17p deletion) [4, 41, 102, 105, 106] although it does not overcome the entire adverse impact of these mutations, especially when t(4;14) and del17p are combined[42].

There are limited data for lenalidomide in patients with high-risk cytogenetics. For transplant eligible patients, lenalidomide maintenance post ASCT appears to improve PFS but not OS for t(4;14) and del17p lesions [32, 107-109]. For transplant ineligible patients, results from the major phase III studies of lenalidomide (MM015[92] and FIRST[90]) showed no strong evidence that continuous lenalidomide can curb the impact of high risk cytogenetics. Limited data exist for pomalidomide[110]. There are some data supporting the combined use of bortezomib and lenalidomide in patients with high-risk cytogenetics[56, 111], however, most of these data are from small non-randomized studies and further confirmation is required. Of note, the combined use of IMiDs and PI is not reimbursed by the PBS in Australia.

Tandem ASCT may have a role in patients with poor prognostic features, as was suggested in an integrated analysis of phase III European studies, in which patients were prospectively assigned to receive either single or tandem ASCT. Tandem ASCT resulted in OS benefit compared

to single ASCT, that was particularly evident in patients with high-risk cytogenetics and who failed to achieve CR post bortezomib-based induction (5-year OS estimate 70% vs. 17% with single ASCT, $p < 0.001$) [42].

The role of AlloSCT in patients with high-risk MM remains uncertain as the data are scarce. In one retrospective study of 143 patients, the PFS and OS of patients with high risk cytogenetics (del13q, t(4;14) and del17p) was similar to those without these high risk lesions. In another prospective study of 101 patient in the RRMM setting, alloSCT appear to overcome the negative prognostic impact of t(4;14) but not del17p, with respect to PFS and OS. Nonetheless, numbers were small in this study. Due to the heterogeneity of these trials, no firm conclusion can yet be made and AlloSCT remains an area of active investigation. Importantly, optimal results from either tandem ASCT or alloSCT are seen in early phase of the disease, hence early referral to a transplant physician is important.

Recommendations for patients with high risk MM are summarised in box 9.

Box 9: Recommendations for patients with high risk MM:

Although there are a number of prognostication models, in the clinic, the R-ISS (table 4) is an accepted risk stratification approach to identify patient with high-risk MM. Patients with R-ISS 3 are considered high risk with a median OS <2 years in the era of IMiDs and PIs.

The optimal management for patients with high-risk multiple myeloma remains unclear in the absence of definitive trial data

- *Consider using bortezomib-based regimen as part of induction treatment (grade A recommendation, level 1B evidence)*
 - o *Note: combination IMiDs and PIs appear effective for patients with high-risk MM (grade 2B evidence), but concurrent use of IMiDs and PIs are not reimbursed in Australia by the PBS.*
- *Consider tandem autologous stem cell transplant for patients who have not achieved a CR to bortezomib-based induction (grade B recommendation, level 2A evidence)*
- *Consider early referral for allogeneic stem cell transplant consideration for selected patients with HLA-matched sibling. However, the role of allogeneic stem cell transplant, even in the high risk setting is still unclear and requires discussions with both the transplant and treating haematologist early in the disease course (grade C recommendation, level 4 evidence)*

3.3 CONSOLIDATION/MAINTENANCE THERAPY

3.3.1 Consolidation/maintenance therapy post ASCT

Consolidation following ASCT refers to a short treatment-course that improves depth of response [55]. To date, there have been insufficient data to determine whether consolidation improves long-term survival; studies of consolidation post ASCT demonstrate improvement in depths of responses and PFS but none of which have shown OS benefit [55, 111]. More recently, the phase III BMT CTN StaMINA study looked specifically at the role of consolidation. Patients aged <71 years (n=758) were randomised after induction, 1:1:1 to either single ASCT, or consolidation with either a second (tandem) ASCT or 4 cycles of RVD (lenalidomide, bortezomib, dexamethasone), prior to maintenance lenalidomide therapy. The addition of consolidation, whether it be a second ASCT or 4 cycles of RVD was not found to be superior to no consolidation with respect to PFS or OS. Thus, if one gives effective induction and lenalidomide maintenance post ASCT, then there is little incremental benefit with consolidation. This conclusion may not be extrapolated to the Australian setting where IMiDs and PIs cannot be used in combination in induction (as was the case for the majority of patients in the StaMINA study), and lenalidomide is not available for maintenance post ASCT. The Australian VCAT study (Bortezomib Consolidation (With Thalidomide and Prednisolone) Vs Thalidomide and Prednisolone Alone in Previously Untreated Subjects With Multiple Myeloma After VCD Induction and ASCT) may be more relevant to the Australian setting, and may elucidate the role of consolidation therapies in our group of patients in due course.

Maintenance therapy with thalidomide post ASCT has proven to prolong both PFS and OS [112]. Treatment is generally tolerated for a median of approximately 12 months. Toxicity, in particular peripheral neuropathy, is the main reason for early thalidomide discontinuation.

Lenalidomide maintenance post ASCT has been assessed in two phase-III studies. A reduced risk of disease progression by 50-52% ($p < 0.001$) [107, 113] was seen, and one study showed OS benefit [113]. A subsequent meta analysis of data from both these studies and a subset of patients from the GIMEMA-RV 209 study demonstrated superior OS from lenalidomide maintenance post ASCT compared to placebo (HR 0.74, $p = 0.001$) (ref: attal et al. J Clin Oncol 34, 2016 (suppl; abstr 8001). Grade ≥ 3 neutropenia was the most frequent adverse-event. A higher incidence of secondary malignancies was noted in the lenalidomide arm in both studies [7.8-8.5% lenalidomide vs. approximately 3% placebo]. With respect to lenalidomide-associated second primary malignancies, a recent meta-analysis has shown that the risk pertains to secondary haematological malignancies and is closely related to the use of oral melphalan [94]. The current general consensus is that the benefits of lenalidomide treatment with lenalidomide until disease progression appear to outweigh the risks, although longer-term follow up is required.

In Australia, lenalidomide is not reimbursed by the PBS for maintenance therapy post ASCT. Although less optimal, thalidomide is used in place of lenalidomide for a maximal duration of 12 months to avoid cumulative risk of neurotoxicity. It is assumed that bortezomib, like thalidomide or lenalidomide, likely improves depth of response when used as consolidation or maintenance. However, the design of available studies, which incorporated different induction and consolidation arms make it difficult to elucidate the impact of bortezomib maintenance on survival [41]. As such, no firm conclusions regarding bortezomib maintenance can be made. Please see box 10.

Box 10: Recommendations regarding maintenance therapy post ASCT:

Consolidation therapy is not routinely recommended in Australia as there is not yet firm evidence to show that consolidation therapy improves long-term survival, especially when effective induction (incorporating either IMiDs and/or PIs) before and maintenance post ASCT is given (grade B recommendation, level 2A evidence).

Maintenance therapy with thalidomide 100mg daily with or without corticosteroids is recommended in patients following first line treatment with HDT and ASCT (Grade A recommendation, level 1A evidence).

Thalidomide \pm Prednisolone maintenance post ASCT should continue for approximately 12 months. The benefit of maintenance beyond 12 months remains to be proven (Grade A recommendation, level 1A evidence).

Lenalidomide maintenance post ASCT is well tolerated, improves PFS and OS (Grade A recommendation, level 1A evidence). At present, lenalidomide is not registered for this indication and hence we cannot currently routinely recommend lenalidomide maintenance.

The dose schedule and role of maintenance bortezomib is still unclear, and bortezomib is not registered for this use. Bortezomib maintenance is not recommended. (Grade C recommendation, level 4 evidence)

3.3.2 Maintenance therapy in patients not eligible for ASCT

In transplant ineligible patients, emerging evidence exists for the benefit of ongoing therapy with IMiDs in respect to PFS but not always OS. In the MRC Myeloma IX trial [112], thalidomide maintenance in both transplant and non-transplant patients improved PFS ($p < 0.001$) but not OS. However, a meta-analysis that included studies in both transplant and non-transplant setting showed a late OS benefit of thalidomide maintenance [112]. Neurotoxicity poses the main toxicity for prolonged thalidomide such that maintenance thalidomide is usually not tolerated beyond 12 months.

Lenalidomide maintenance appears more tolerable compared to thalidomide and can be given until disease progression. Two pivotal randomized phase III trial have demonstrated the benefit of continuous lenalidomide in transplant ineligible patients. In a pre-specified landmark analysis of the MM015 trial that compared MP vs. MPL vs. MPL with lenalidomide maintenance (MPL-L), lenalidomide maintenance improved PFS by 17 months, but as yet not survival [92]. In the final analysis of the FIRST trial, continuous Ld until disease progression improved both PFS and OS compared to a fixed duration MPT (HR 0.69, $p < 0.00001$ and HR 0.78, $p = 0.0023$, respectively). Ld until disease progression was superior to fixed duration Ld with respect to PFS (HR 0.7) but not OS [91]. For patients who start with bortezomib-based induction, currently there is no data on lenalidomide maintenance post induction therapy. For patients who start with thalidomide-based

induction therapy, a subset analysis of the ongoing phase III Myeloma XI study is assessing the impact of lenalidomide maintenance versus placebo, however, data are not yet sufficiently mature to make firm conclusions.

With respect to bortezomib maintenance for transplant ineligible patients, two randomized studies have been reported. However, these trials were not designed to assess the isolated impact of bortezomib maintenance. The GIMEMA study compared BMPT followed by BT maintenance to BMP alone. BT maintenance improved CR rate slightly from 58% (post BMPT induction) to 62%; 3-year PFS was higher in the BMPT-BT arm (56 vs. 41%, $p=0.008$). Five year OS was superior in the BMPT-BT arm compared to BMP (59 vs. 46%, $p=0.04$)[89]. The PETHEMA study compared BMP to BTP induction followed by BT or BP maintenance. Maintenance therapy overall improved CR rate from 24 to an astounding 42%[87] but no difference with respect to PFS or OS was seen between BP or BT maintenance. Recommendations on maintenance therapy in patients who are not transplant eligible are summarised in box 11.

Box 11: Recommendations on maintenance therapy in patients with MM who are not transplant eligible:

- *The benefit of maintenance therapy with respect to PFS and possibly OS for transplant ineligible patients is most evident for lenalidomide and dexamethasone combination.*
 - *For transplant ineligible patients initially treated with Ld, we recommend that this be continued until disease progression (grade A recommendation, level 1B evidence)*
 - *For transplant ineligible patients initially treated with thalidomide or bortezomib-based induction regimen, there are currently no firm data published to support the initiation of maintenance lenalidomide post induction therapy to improve OS.*
- *In Australia, lenalidomide is not registered or reimbursed by the PBS for maintenance therapy post thalidomide or bortezomib-based induction.*
- *Thalidomide maintenance improves PFS but OS impact in the non-transplant setting is unclear (Grade A recommendation, level 1B evidence). Long-term thalidomide use is limited by peripheral neuropathy.*
- *The benefit of bortezomib maintenance therapy is unclear. Bortezomib is currently not TGA-registered in Australia for this indication (Grade A recommendation, level 1B evidence)*

3.4 TREATMENT OF RELAPSED MULTIPLE MYELOMA

The management of patients with relapsed/refractory MM (RRMM) requires careful evaluation, taking into account prior treatments and associated toxicities, duration of response to prior treatment, and the patient's current clinical status and tempo of relapse. Relapsed MM refers to disease that has recurred after an initial response, and is objectively defined as per IMWG criteria[114]. The aim of treatment is not only to prolong survival, but to also treat or prevent development of myeloma related end organ damage.

Many but not all patients will require immediate treatment at first detection of relapse. For patients with relapse with worsening or new CRAB symptoms, immediate treatment is mandatory. In the absence of worsening or new CRAB symptoms, immediate treatment may also be warranted in patients with rapidly progressive paraprotein level or SFLC (table 10), to prevent the onset of irreversible end organ damage. Otherwise, for patients with slow indolent biochemical relapse without any overt worsening or new CRAB symptoms, careful monitoring until significant progression occurs is acceptable.

Currently, there is no single standard treatment for patients with relapsed myeloma. The choice of salvage regimen takes into account patient factors (age and frailty), disease factors (tempo of relapse, risk-group stratification), and prior treatment-related factors (response or refractoriness to prior type of treatment.)

Table 9: Salvage treatment regimens for relapsed/refractory MM*

This table lists the commonly used salvage regimens in Australia for patients with relapsed and/or refractory multiple myeloma and is by no means exhaustive.

| REGIMEN | | EFFICACY | COMMENTS |
|--------------------------|--|--|---|
| THALIDOIMDE BASED | | | |
| TD [166] | Thalidomide 200mg po.daily Dexamethasone 40mgpo. D1-4 Cycles repeated every 4 weeks until disease progression. | Phase II trial. ORR ~50-60% CR ~6% | DVT developed in 8% of patients (without prophylaxis) Gde ≥3 Sensory neuropathy up to 30%. |
| CTD [50, 156]2, 3] | Thalidomide 100mg po. Daily Cyclophosphamide 500mg po.weekly Dexamethasone 40mgpo. D1-4, 12-15 or 40mg po. weekly. Cycles repeated every 4 weeks until best response. | Phase II trial. ORR 79% CR 17% | Minimal infective complications. Moderate emesis, fatigue, myelosuppression. |
| ThaDD [167] | Thal 100mgpo. daily Dexamethasone 40mgpo. D1-4, 9-12, Peg liposomal doxorubicin 40mg/m ² IV D1 Cycles repeated every 28 days for up to 6 cycles, followed by thalidomide and dexamethasone (40mg D1-4 every 28 days) maintenance until disease progression. | Phase II trial. N=47 ORR 92%, CR/nCR 30% | High rates of hematologic toxicity. |
| DTPACE [5] | Dexamethasone 40mgpo. D1-4 Thalidomide 400mg po.daily Cisplatin 10mg/m ² daily IVcontinuous infusion D1-4. Cyclophosphamide 400mg/m ² daily IVcontinuous infusion D1-4. Etoposide 40mg/m ² daily IVcontinuous infusion D1-4. Doxorubicin 10mg/m ² daily IVcontinuous infusion D1-4. Cycles repeated every 4 weeks for 3-6 cycles | Phase II trial. ORR post 2 cycles 48%. CR/nCR 16% | DVT developed in 16% of patients. |
| DCEP-T [168] | Dexamethasone 40mg po. D1-4 Thalidomide 400mg po.daily Cisplatin 15mg/m ² daily IVcontinuous infusion D1-4. Cyclophosphamide 400mg/m ² daily IVcontinuous infusion D1-4. Etoposide 40mg/m ² daily IVcontinuous infusion D1-4. Cycles repeated every 4 weeks for 3-6 cycles. | Phase II trial. ORR after 3 cycles 36% compared to 18% with DCEP alone. | DVT developed in 2.5% of patients. |

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| LENALIDOMIDE-BASED | | | |
|-----------------------------------|---|--|--|
| Len-dex [125, 126, 159] | <p>Lenalidomide 25mgpo. D1-21q28 Dexamethasone 40mg po. D1-4,9-12,17-20 (C1-4), 40mg po. D1-4 (C5 onwards)</p> <p>Consider using low dose dexamethasone (40mg [20mg for patients age >75 years] per week) in view of the ECOG trial showing higher toxicity with standard dose dex[159]</p> <p>Cycles repeated every 28 days until disease progression.</p> | <p>Phase III trial (MM009/010) RR 60% CR~14-16%</p> | <p>Gde≥3 neutropenia 30-40% Gde≥3 thrombocytopenia 11% DVT 11-15% (no thromboprophylaxis) Gde≥3 fatigue 6%</p> |
| RCD [54] | <p>Lenalidomide 25mg po. D1-21. Cyclophosphamide 500mg po.weekly Dexamethasone 40mg po.D1-4 and D12-15.</p> <p>Cycles repeated every 28 days for a maximum of 9 cycles. Ongoing maintenance with single agent lenalidomide may be considered.</p> <p>Consider using low dose dex (40mg per week [20mg for patients age >75 years]) in view of the ECOG trial showing higher toxicity with standard dose dex[159]</p> | <p>Phase II trial. ORR 65%. CR 5% (one patient in 20)</p> | <p>Median time to best response is prompt (31 days).</p> <p>After 3 cycles, 48% of patients required dose reduction or withdrawal of cyclophosphamide, and 24% of patients required dose reduction of lenalidomide.</p> <p>G-CSF required in 57% of patients to maintain neutrophil count >1.</p> |
| RAD [169] | <p>Lenalidomide 25mgpo. D1-21 Adriamycin 9mg/m² IV D1-4 Dexamethasone 40mgpo. D1-4 and D17-20</p> <p>Cycles repeated every 28 days for 6 cycles.</p> <p>Consider using low dose dex (40mg per week (20mg in patients age >75 years)</p> | <p>Phase I/II ORR 73% CR+VGPR 74%</p> | <p>Grade 3 and 4 neutropenia 48% Grade 3 and 4 thrombocytopenia 38. Severe infections 10.5%. Thromboembolic events 4.5%.</p> |
| POMALIDOMIDE-BASED | | | |
| Pom-dex | <p>Pomalidoimde 4mg po. D1-21 Dexamethasone 40mg po D1,8,15,22</p> <p>Cycles repeated every 28 days until disease progression.</p> | <p>Phase III ORR 31% Med PFS 4m (patients who have failed at least 2 previous treatment including bortezomib and lenalidomide)</p> | <p>Grade 3 and 4 anaemia 33% Grade 3 and 4 neutropenia 48% Grade 3 and 4 thrombocytopenia 22%</p> |

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MULTIPLE MYELOMA

| BORTEZOMIB-BASED | | | |
|--|--|--|--|
| Note: Bortezomib, when given subcutaneously and/or as a weekly schedule have been shown to reduce neuropathy. | | | |
| Bortezomib and Dexamethasone [133] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 every 21 day for cycles 1-8 D1,8,15,22 every 35 day for cycles 9-12 Dex 20mg po. on day of and day after bortezomib. | Phase III trial. (SUMMIT/APEX) RR ~38% CR ~6% | Gde≥3 fatigue 5% Gde≥3 peripheral neuropathy 8% Gde≥3 thrombocytopenia 30% Gde≥3 anaemia 10% Gde≥3 neutropenia 14% |
| CyBorD/ VCD [52, 135] | Cyclophosphamide 300mg/m ² po. weekly. Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 every 21 days, for cycles 1-8 D1,8,15,22 every 35 days, for cycles 9-14 Dex 20mg on the day of and day after bortezomib Alternate dosing regimen of CyBorD as per table 6 can also be used. | Phase II trial RR (CR+PR) 82%, CR 16% | Gde≥3 AE = leukopenia, thrombocytopenia infection, herpes zoster |
| PAD [136, 170] [171] | Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 , Doxorubicin 20mg/m ² IV D1 and 4 Dexamethasone 40mg po. D1,2,4,5,8,9,11,12. Cycles repeated every 28 days x 6. | Phase II trial. ORR 67%, CR/VGPR 25% (no difference in efficacy between doxorubicin vs liposomal doxorubicin.) | Gde≥3 thrombocytopenia 23% Gde≥3 neutropenia 20%. Gde≥3 anaemia 11% Gde≥3 peripheral neuropathy 10% |
| Bortezomib + Melphalan [172] | Bortezomib 1mg/m ² IV (or SC) D1,4,8,11 Melphalan 0.1mg/kg po. D1-4 Cycles repeated every 28 days for a maximum of 9 cycles. | Phase I/II trial. N=35 ORR (PR+CR)= 47% CR/nCR=14% | Main gde≥3 toxicities = myelosuppression. |
| Bortezomib + Bendamustine + Dexamethasone [141] | Bendamustine 70mg/m ² IV D 1,4 Bortezomib 1.3mg/m ² IV (or SC) D1,4,8,11 Dexamethasone 20mg po D1,2,4,5,8,9,11,12 Cycles repeated every 21 days for 8 cycles. | Phase II trial ORR 60.8% VGPR/CR 35.5% PFS 9.7 mnths | Gde≥3 thrombocytopenia 38% Gde≥3 neutropenia 17%. Gde≥3 anaemia 18% Gde≥3 peripheral neuropathy 6% Note: bendamustine is not TGA approved or reimbursed by the PBS for the treatment of myeloma |
| CHEMOTHERAPY | | | |
| Non-myeloablative-melphalan [173] | Melphalan 25mg/m ² IV | -- | Myelosuppression. |
| High dose cyclophosphamide [116] | Cyclophosphamide 600mg/m ² IV daily x 4 (total dose 2400mg/m ²) Or Single dose of 2 to 4g/m ² IV could also be used. | Phase II trial, N=56, ORR 43%, PFS 3m, OS 9m. | Myelosuppression. Haemorrhagic cystitis. |
| Bendamustine [174] | Bendamustine 60-100mg/m ² IV D1, 2 of each 28-day cycle. | Phase I –dose escalation, n=31 ORR 55% Med PFS 6.5m | Maximal tolerated dose: 100mg/m ² due to febrile neutropenia. Toxicities are mainly haematological and are mainly mild. Note: bendamustine is not TGA approved or reimbursed by the PBS for the treatment of myeloma |

*Thalidomide is available for treatment of patients with MM through the Pharmaceutical Benefit Scheme Highly Specialised Drug Program. Please visit <http://www.health.vic.gov.au/hstdp>

*Bortezomib, as monotherapy or in combination with a corticosteroid and/or cyclophosphamide, is available through the Pharmaceutical Benefit Scheme for patients with MM who has progressive disease after at least 1 prior therapy, and who has undergone or is ineligible for a primary stem cell transplant. The patient must have experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease. Applications are made through Medicare Australia, please visit <http://www.medicareaustralia.gov.au>

*Lenalidomide as monotherapy or in combination with corticosteroid is available through the Pharmaceutical Benefit Scheme Highly Specialised Drug Program (<http://www.health.vic.gov.au/hstdp>) for patients with MM who has progressive disease after at least 1 prior therapy, and who has undergone or is ineligible for a primary stem cell transplant. The patient must have experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease. Applications are made through Medicare Australia, please visit <http://www.medicareaustralia.gov.au>

* Pomalidomide in combination with dexamethasone is reimbursed on the PBS for the treatment of MM in patients who have failed two or more prior therapies including lenalidomide and bortezomib.

* Bendamustine is not registered by the Therapeutic Goods Administration for the treatment of MM within Australia.

Table 10: Indications to commence treatment for myeloma at relapse [3].

| CLINICAL RELAPSE: |
|--|
| <ul style="list-style-type: none"> • Development of new soft tissue plasmacytomas or bone lesions • Definite increase ($\geq 50\%$) size of existing plasmacytomas or bone lesions. • Hypercalcaemia ($\geq 11.5\text{mg/dl}$; 2.875mmol/l) • Decrease in haemoglobin by $\geq 20\text{g/L}$ or to $< 100\text{g/L}$ due to myeloma. • Rise in serum creatinine by 2mg/dL due to myeloma. |
| SIGNIFICANT BIOCHEMICAL RELAPSE PRIOR TO THE ONSET OF END ORGAN DAMAGE: |
| <ul style="list-style-type: none"> • Doubling of paraprotein in two consecutive measurements less than two months apart or • In two consecutive measurements any of the following increases: <ul style="list-style-type: none"> ◦ The absolute level of paraprotein by $\geq 10\text{g/L}$ or ◦ The increase of urinary M protein (BJP) by $\geq 0.5\text{g}$ per 24 hours or ◦ Increase of involved FLC level by $\geq 200\text{mg/L}$ (with abnormal K:L ratio) or 25% increase (whichever is greater). |

In Australia, the main treatment options for relapsed/resistant disease are IMiDs (thalidomide, lenalidomide and pomalidomide), first generation PI, bortezomib, alkylating agents, anthracyclines, and corticosteroids, administered alone or in various combinations, with selected patients undergoing HDT with ASCT. These various agents can be used in different combinations and sequences. No best sequence has been defined (Figure 4; table 9). However, the generally accepted principles are as follows:

1. Switch drug class, especially if remission to prior drugs was short or patient had concerning associated toxicity or
2. Retreatment with a prior line of treatment is feasible if a long 1st remission (eg. treatment free interval > 1 year), was achieved with no concerning toxicity. However, an inferior duration and quality of response is to be expected.
3. HDT and ASCT can be considered in patients who have had a deep (at least PR) and durable response to this treatment modality in the past [115]. Data from the British Blood and Bone Marrow Transplant Registry suggested that a PFS of at least 9 months to the first ASCT is associated with improved survival outcome to a second ASCT in relapsed MM [115]. In the era of novel therapies, most myeloma experts in Australia would consider a second ASCT for salvage therapy upon the achievement of at least 12-18 months PFS to the first ASCT.

4. In patients with a slow tempo of disease relapse, single-agent novel therapy with or without dexamethasone, or indeed ongoing observation in the absence of end-organ damage may be appropriate, especially if they cannot tolerate more intensive treatment.
5. In contrast, in patients with rapidly progressive, intensive regimens combining an IMiD or PI with one or more chemotherapy (table 9) can be considered if the patient has good performance status and organ function.
6. Finally, when all newer agents and different treatment combinations have been exhausted, conventional doses of cyclophosphamide[116], non-myeloablative doses of melphalan[117], or low-modest doses of corticosteroids remain viable options, as is palliation in patients who cannot tolerate any further therapy. Please see box 12.

In addition to these general principles, the choice of salvage also depends on pre-existing co-morbidities. In patients with pre-existing neuropathy, exacerbation may occur with bortezomib or thalidomide. For patients with a previous history of VTE, or who are at high-risk of VTE events, thalidomide and lenalidomide, although not absolutely contraindicated, should be avoided if other effective induction options are available. VTE risks are highest when these immunomodulatory drugs are used with high-dose dexamethasone or anthracycline chemotherapy. Prophylactic or therapeutic-dose anticoagulation should therefore be instituted as appropriate. Lenalidomide cleared by the kidneys, and generally, is not the treatment of first choice in patients with moderate to severe renal impairment although judicious dose adjustment will overcome this issue. Thalidomide, or bortezomib are usually preferred in such patients[118].

Thalidomide monotherapy can induce a RR in relapsed MM in approximately 25% to 30%; responses are durable with median EFS of 6-12 months and median OS of 14 months.[119, 120] Thalidomide and dexamethasone is associated with a superior RR of approximately 50-55% in the relapse/refractory setting [121, 122]. The addition of an alkylating agent (e.g. cyclophosphamide or melphalan) increases RR to 75-80% [123, 124]. Thus the use of thalidomide remains an option for patients with RRMM, especially if patients are thalidomide-naïve, when oral treatment is needed or when patients are not otherwise eligible for Bortezomib, lenalidomide or pomalidomide.

Lenalidomide monotherapy induces an ORR of 22-25% in relapsed/refractory MM. Len-dex combination increases the RR to approximately 60%. Two pivotal phase III randomised, double-blind, placebo controlled trials conducted in parallel (US MM-009 and European MM-010) [125, 126] compared dex 40mg/d (d1-4, 9-12,17-20) with or without len (25mg/d d1-21) every 28 days shows superiority in the len-dex arm. RR and CR rates were 61% and 27% in the MM-009, and 58% and 14% in MM-010 trial, respectively. Importantly, lower dose dexamethasone (40mg weekly as opposed to the traditional pulsed dexamethasone) should be used in combination with lenalidomide (Ld) as per the ECOG E4A03 trial [127]. Ld is especially effective for lenalidomide naïve patients, however, retreatment can also be effective for patients who have had prior lenalidomide but have not progressed on or within 60 days of cessation of lenalidomide[128]. For patients who are vulnerable based on renal impairment, baseline cytopenia or elderly age, lower dose lenalidomide (15mg) at the outset decreases toxicity and appear not to compromise efficacy based on results from the Australian RevLite study[129]. Cyclophosphamide can be added to doublet Ld as a triplet salvage regimen.

Pomalidomide, a second generation IMiD have shown efficacy in patients with RRMM, even in patients with disease refractory to both lenalidomide and bortezomib. In a randomised phase III trial (MM003)[110], combination pomalidomide and low-dose dexamethasone (pom-dex) resulted in superior PFS (4 vs. 1.9m, $p<0.001$) and OS (12.1 vs. 8.1m, $p<0.001$) compared to dexamethasone. This result is clinically significant given that 50% patients in the latter group had already crossed over to the pomalidomide-arm at the time of analysis. Importantly, patients who were double refractory to lenalidomide and bortezomib gained similar survival benefit from pom-dex[110]. The optimal starting pomalidomide dose is 4mg daily days 1-21 every 28 days in combination with dexamethasone 40mg weekly (20mg in patients age >70 years)[130]. In Australia, pomalidomide in combination with dexamethasone, is TGA approved and reimbursed by the PBS for the treatment of MM in patients who have failed two or more prior therapies including lenalidomide and bortezomib.

Like lenalidomide, the main side effects of pomalidomide are fatigue and haematological toxicities, while neuropathic toxicities are low. Venous thromboembolic complications are also low, especially when prophylactic measures are used.

Bortezomib monotherapy induces an ORR of approximately 35-40% in relapsed, refractory MM, with an average duration of response of 1 year [131-133]. Dexamethasone ought to be added to bortezomib upfront, which improves ORR by a further 20% according to the Australian BOMER study which compared up-front BD to a matched cohort of patient on the APEX study[134]. Increased efficacy is seen with triplet combinations of Bd with either cyclophosphamide or anthracycline[135, 136] (table 9)

The combination of IMiDs and Pis is very effective for the treatment of RRMM (table 9), however, such combination is not reimbursed by the PBS for the treatment of MM in Australia.

In general, incorporation of IMiDs or PIs at first relapse appear to produce superior outcome compared to their use as later lines of salvage-treatment[137, 138]. Alkylating agents such as cyclophosphamide and melphalan have traditionally been the chemotherapy-backbone on which to add IMiDs and proteasome inhibitors.

Bendamustine is another alkylating agent that has a place in the treatment of RRMM. It has a unique biochemical structure that confers both alkylating agent and nucleoside analogue activity, that result in both induction of apoptosis and inhibition of mitotic check points, as opposed to induction of necrosis alone as seen with other alkylators[139]. In phase I and II trials, bendamustine was efficacious as monotherapy, and in combination with thalidomide, lenalidomide or bortezomib[140]. Combination bendamustine, bortezomib and dexamethasone was recently shown to induce an ORR of 68% (CR/VGPR 35.5%) and PFS of 9.7 months in a group of patients with a median 2 prior lines of treatment[141]Currently, bendamustine is not TGA approved or reimbursed by the PBS for the treatment of myeloma.

Box 12: Recommendation for the treatment of relapsed multiple myeloma:

There is no one standard treatment for patients with relapsed myeloma. Management should be individualised taking into account of prior therapy and associated toxicity, duration of response to prior therapy, tempo of disease progression, and current physical status (Grade C recommendation).

- *Common salvage options are outlined in table 9.*
- *Indications to commence treatment at relapse are outlined in table 10*

If relapse occurs >12 months following cessation of the last treatment regimen, the same regimen can be re-considered, however, an inferior duration and quality of response is to be expected (Grade C recommendation)

Second ASCT can be considered in a select group of patients who have achieved at least a PR and durable remission(eg. >9 months) to the first ASCT (Grade B recommendation, level 2A evidence).

When all novel agents and different treatment combinations have been exhausted, conventional moderate doses of cyclophosphamide, bendamustine, non-myeloablative doses of melphalan, or low-modest doses of corticosteroids remain viable options, as is palliation in patients who cannot tolerate any further therapy (Grade C recommendation).

4 NEW AGENTS NOT CURRENTLY REIMBURSED BY THE AUSTRALIAN PBS AND OTHER EMERGING NOVEL THERAPEUTICS

We are now moving beyond the era of first generation immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), with a number of efficacious new drugs and drug groups that have emerged over recent years. In 2015, five new drugs were approved for the treatment of RRMM by the FDA (Food Drug Administration). These include the second generation PIs carfilzomib and ixazomib, the monoclonal antibodies (mAb) daratumumab and elotuzumab, and the histone deacetylase inhibitor (HDACi) panobinostat. These agents are currently not reimbursed by the PBS for the treatment of MM in Australia. Carfilzomib is TGA registered for this indication but is not current reimbursed by the PBS.

Other promising novel therapeutics that are in early phase of development include novel immune therapies of chimeric antigen receptors (CAR-T) and bispecific T cell engagers (BiTEs), as well as small molecules including including the BH3-mimetic venetoclax.

Newer generation proteasome inhibitors (PI):

Second generation proteasome inhibitors include carfilzomib, ixazomib, marizomib and oprozomib. Both carfilzomib and ixazomib are FDA-approved for the treatment of RRMM in combination with lenalidomide. Results from the pivotal phase III ASPIRE study showed superiority of triplet carfilzomib (C), lenalidomide and dexamethasone (CRd) over Rd with respect to PFS (HR 0.69, $p=0.0001$) and a trend towards improved OS with CRd (HR 0.79, $p=0.04$)[142] As doublet, Cd is superior to Bd for patients with RRMM with respect to PFS (HR 0.53, $p<0.0001$) as was seen in the phase III (ENDEVOR) study[143]. In first line treatment however, triplet combination CMP was not superior to the current standard of care VMP in the phase III CLARION study. Carfilzomib is given IV at a schedule of D1,2,8,9,15,16 in a 28-day cycle. It is not associated with risk of peripheral neuropathy. The main side effects include hypertension, thrombocytopenia, lethargy and diarrhoea that are generally manageable. Cardiac-related events including cardiac failure, dyspnoea, and arrhythmias were identified in early studies and further evaluation to assess their association with carfilzomib are required.

Ixazomib is an oral second generation PI that is given weekly for 3 weeks in a 4-week cycle. Triplet combination of ixazomib and Ld (ILd) is superior to Ld doublet in the treatment of RRMM with respect to PFS (HR 0.74, $p=0.01$) based on the phase II TOURMALINE-1 study. It is a very well tolerated drug, and like carfilzomib is minimally associated with peripheral neuropathy. Because of this and the convenience of oral therapy, ixazomib is being studied for maintenance therapy in ongoing trials.

Other second generation PIs include oprozomib (ONX-0912; previously pR047) and marizomib (NPI-0052)[45]. Oprozomib show promising efficacy in phase I/II clinical trials with minimal neuropathic side effects but with some degree of gastrointestinal intolerance. Marizomib is given as an intravenous infusion. Results from early phase clinical trials demonstrated efficacy in heavily pretreated patients with minimal neuropathy.

Monoclonal antibodies (mAb):

Daratumumab (Humax™-38; Jansen) is a humanised mAb against CD38 that induces myeloma cell killing via three mechanisms including induction of NK-cell mediated ADCC, complement dependent cytotoxicity and direct apoptosis by crosslinking and/or allosteric inhibition on CD38 enzymatic activity. As monotherapy, daratumumab induced an impressive ORR 31% (\geq VGPR 13%) and PFS 19.9 months in a group of heavily pretreated patients who were mostly (86%) refractory to both IMiDs and PI[144]. When added to the backbone of Ld (phase III POLLUX study)[145] or Bd (phase III CASTOR study)[146], daratumumab was found to improve rate and depths of response for RRMM, in particular impressive rates of MRD (10-5) negativity in the order of 14-23%, and PFS (HR 0.37 ($p<0.0001$) for POLLUX study and 0.39 ($p<0.0001$) for CASTOR study, respectively). Daratumumab monotherapy is FDA approved for patients with RRMM who have received at least 3 prior lines of therapy including a PI and IMiD, or who are double refractory to PI and IMiDs. Daratumumab in combination with either Ld or Bd is also FDA-approved for patients who have had 1 to 3 prior lines of treatment.

SAR650984 (Isatuximab™, Sanofi) is another mAb against CD38, that has similar profile to daratumumab. Phase I/II trials are underway, evaluating the combination of SAR650984, lenalidomide and dexamethasone. Latest preliminary results showed a robust response (ORR 64.5%; \geq VGPR 32%) in a group of patients with a median of 6 prior line of treatment, 85% of whom were relapsed or refractory to at least one prior IMiD-based therapy. With only a short follow up of 9 months. PFS was already impressive at 6 months[147].

Elotuzumab is a humanized mAb to SLAMF7 (also known as CS1; signaling lymphocytic activation molecule 7), a glycoprotein that is highly specific to plasma cells although it may also be expressed on NK cells. As elotuzumab's main mechanism of action is via NK-cell mediated ADCC (antibody dependent cytotoxicity), its efficacy as monotherapy in MM is only modest due to defective NK cell function in patients with MM. However, when combined with lenalidomide, that is known to enhance NK cell function, the combination elotuzumab-lenalidomide and dexamethasone (ELd) in the phase III ELOQUENT-2 study [148] resulted an ORR of 79%, and is superior to Ld with respect to PFS (HR 0.7, $p < 0.001$) and on long term follow up, also OS (HR 0.77, $p = 0.026$). Based on this data, ELd has also received FDA approval for treatment of RRMM in patients who have received 1 to 3 prior therapies.

Other mAb that are in early phase clinical trials have shown only modest efficacy in the treatment of MM. Some of these include lorvotuzumab (anti-CD56 mAb), nBT062 (anti-CD138 mAb), dacetuzumab and lucatumumab (anti-CD40 mAb), and siltuximab (anti-IL6 mAb).

Histone deacetylase inhibitors (HDACi):

This group of drugs work via epigenetic activity targeting histones, but they also acetylate non-histone proteins relevant to tumour progression [149]. Several HDACi have been tested in MM such as panobinostat (Farydak™), vorinostat and romidepsin. As monotherapy, the efficacy against MM is only modest. However there appears to be synergism when combined with bortezomib as was demonstrated in the PANORAMA 1 trial [150]. Here, combination panobinostat-bortezomib-dexamethasone was superior to bortezomib-dexamethasone alone with respect to CR/near CR rate ($p = 0.00006$) and PFS by 4 months ($p < 0.001$) in a group of patients with RRMM. These preliminary results confirm the synergism between panobinostat and bortezomib that was seen in the PANORAMA 2 study, where this combination was able to recapture the response in 34% of patients who were refractory to bortezomib-based therapy [151]. The same could not be said for vorinostat. Although the addition of bortezomib to vorinostat (without dexamethasone) resulted in improved ORR, this translated to minimal improvement in PFS and no OS advantage [149]. Currently panobinostat in combination with Bd is FDA approved for the treatment of RRMM in patients who have had at least 2 prior therapies. Ricolinostat is another HDACi (specifically HDAC-6 inhibitor) that appears to be promising in early phase clinical studies in combination with IMiDs and studies are ongoing [152].

5 CONCLUDING REMARKS

The treatment for multiple myeloma has become more complex as the therapeutic landscape expands. What is considered as standard therapy will continue to change as trial data mature with respect to newer-therapeutic agents. It is important to note that the standard of care in Australia may differ from that in the US and Europe, and is based on what is reimbursed by the Australian PBS, which in turn, is subjected to rigorous evidence-based and cost analysis assessment. At present, MM remains an incurable disease. It is anticipated that survival for patients with MM will continue to improve as more effective novel agents are approved and made available for use in the clinic.

The above treatment guideline from the Australian Myeloma Scientific Advisory Group (MSAG) to Myeloma Australia are based on current published data, local clinical experience and PBS-approved therapies. We believe that a National consensus of treatment algorithm for MM will not only improve patterns of care nationally, but will also establish a foundation for future clinical studies that are locally-relevant.

6 REFERENCES

1. Australian Institute of Health and Welfare (AIHW) 2016. *ACIM (Australia Cancer Incidence and Mortality Book, AIHW: Canberra.*
2. Turesson, I., et al., *Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic.* Mayo Clin Proc, 2010. **85**(3): p. 225-30.
3. Rajkumar, S.V., et al., *International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma.* Lancet Oncol, 2014. **15**(12): p. e538-e548.
4. Jagannath, S., et al., *Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials.* Leukemia, 2007. **21**(1): p. 151-7.
5. Greipp, P.R., et al., *Development of an international prognostic index (IPI) for myeloma: report of the international myeloma working group.* Hematol J, 2003. **4**: p. S42.
6. Chng, W.J., et al., *IMWG consensus on risk stratification in multiple myeloma.* Leukemia, 2014. **28**(2): p. 269-77.
7. Palumbo, A., et al., *Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group.* J Clin Oncol, 2015. **33**(26): p. 2863-9.
8. Kyle, R.A., et al., *Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management.* Leukemia, 2010. **24**(6): p. 1121-7.
9. Dispenzieri, A., et al., *International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders.* Leukemia, 2009. **23**(2): p. 215-24.
10. Villa, G., et al., *Staging and therapy monitoring of multiple myeloma by 99mTc-sestamibi scintigraphy: a five year single center experience.* J Exp Clin Cancer Res, 2005. **24**(3): p. 355-61.
11. Giovanella, L., et al., *99mTc-sestamibi imaging and bone marrow karyotyping in the assessment of multiple myeloma and MGUS.* Nucl Med Commun, 2008. **29**(6): p. 535-41.
12. Bredella, M.A., et al., *Value of FDG PET in the assessment of patients with multiple myeloma.* AJR Am J Roentgenol, 2005. **184**(4): p. 1199-204.
13. Kyle, R.A. and S.V. Rajkumar, *Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: emphasis on risk factors for progression.* Br J Haematol, 2007. **139**(5): p. 730-43.
14. Berenson, J., et al., *Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial.* Lancet Oncol, 2011. **12**(3): p. 225-35.
15. Dickinson, M., et al., *Osteonecrosis of the jaw complicating bisphosphonate treatment for bone disease in multiple myeloma: an overview with recommendations for prevention and treatment.* Intern Med J, 2009. **39**(5): p. 304-16.
16. Palumbo, A., et al., *Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma.* Leukemia, 2008. **22**(2): p. 414-23.
17. *Consensus guidelines for Infection Prophylaxis Including Vaccination in Multiple Myeloma.* 13th International Myeloma Work Shop, Paris, France., 2011 May 3rd-6th.
18. Kyle, R.A., et al., *A long-term study of prognosis in monoclonal gammopathy of undetermined significance.* N Engl J Med, 2002. **346**(8): p. 564-9.
19. Kyle, R.A., et al., *Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma.* N Engl J Med, 2007. **356**(25): p. 2582-90.
20. Cherry, B.M., et al., *Modeling progression risk for smoldering multiple myeloma: results from a prospective clinical study.* Leuk Lymphoma, 2013. **54**(10): p. 2215-8.
21. Mateos, M.V., et al., *Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma.* N Engl J Med, 2013. **369**(5): p. 438-47.
22. Chanan-Khan, A.A. and S. Giralt, *Importance of Achieving a Complete Response in Multiple Myeloma, and the Impact of Novel Agents.* J Clin Oncol.
23. Gay, F., et al., *Complete response correlates with long-term progression-free and overall survivals in elderly myeloma treated with novel agents: analysis of 1175 patients.* Blood, 2011.
24. Attal, M., et al., *A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome.* N Engl J Med, 1996. **335**(2): p. 91-7.

25. Barlogie, B., et al., *Total therapy 2 without thalidomide in comparison with total therapy 1: role of intensified induction and posttransplantation consolidation therapies*. *Blood*, 2006. **107**(7): p. 2633-8.
26. Alvares, C.L., et al., *Long-term outcomes of previously untreated myeloma patients: responses to induction chemotherapy and high-dose melphalan incorporated within a risk stratification model can help to direct the use of novel treatments*. *Br J Haematol*, 2005. **129**(5): p. 607-14.
27. Kyle, R.A., et al., *Complete response in multiple myeloma: clinical trial E9486, an Eastern Cooperative Oncology Group study not involving stem cell transplantation*. *Cancer*, 2006. **106**(9): p. 1958-66.
28. Palumbo, A., et al., *Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial*. *Blood*, 2008. **112**(8): p. 3107-14.
29. Pineda-Roman, M., et al., *Complete response in myeloma extends survival without, but not with history of prior monoclonal gammopathy of undetermined significance or smouldering disease*. *Br J Haematol*, 2007. **136**(3): p. 393-9.
30. Haessler, J., et al., *Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling*. *Clin Cancer Res*, 2007. **13**(23): p. 7073-9.
31. Paiva, B., J.J. van Dongen, and A. Orfao, *New criteria for response assessment: role of minimal residual disease in multiple myeloma*. *Blood*, 2015. **125**(20): p. 3059-68.
32. Palumbo, A., et al., *Autologous transplantation and maintenance therapy in multiple myeloma*. *N Engl J Med*, 2014. **371**(10): p. 895-905.
33. Gay, F., et al., *Autologous Transplantation Versus Cyclophosphamide-Lenalidomide-Prednisone Followed By Lenalidomide-Prednisone Versus Lenalidomide Maintenance in Multiple Myeloma: Long-Term Results of a Phase III Trial (Abstract)*. *Blood*, 2015. **126**(392).
34. Muchtar, E., et al., *Autologous stem cell transplant for multiple myeloma patients 70 years or older*. *Bone Marrow Transplant*, 2016. **51**(11): p. 1449-1455.
35. Charlson, M., et al., *Validation of a combined comorbidity index*. *J Clin Epidemiol*, 1994. **47**(11): p. 1245-51.
36. Saad, A., et al., *Hematopoietic cell transplant comorbidity index is predictive of survival after autologous hematopoietic cell transplantation in multiple myeloma*. *Biol Blood Marrow Transplant*, 2014. **20**(3): p. 402-408 e1.
37. Attal, M., et al., *Single versus double autologous stem-cell transplantation for multiple myeloma*. *N Engl J Med*, 2003. **349**(26): p. 2495-502.
38. Cavo, M., et al., *Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study*. *J Clin Oncol*, 2007. **25**(17): p. 2434-41.
39. Kumar, A., et al., *Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis*. *J Natl Cancer Inst*, 2009. **101**(2): p. 100-6.
40. Giralt, S., et al., *Re: Tandem vs single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis*. *J Natl Cancer Inst*, 2009. **101**(13): p. 964; author reply 966-7.
41. Sonneveld, P., et al., *Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/ GMMG-HD4 Trial*. *J Clin Oncol*, 2012. **30**(24): p. 2946-55.
42. Cavo, M., et al., *Double Vs Single Autologous Stem Cell Transplantation After Bortezomib-Based Induction Regimens For Multiple Myeloma: An Integrated Analysis Of Patient-Level Data From Phase European III Studies (Abstract)*. *Blood*, 2013. **122**: p. Abstract 767.
43. Stadtmauer, E., et al., *Comparison of Autologous Hematopoietic Cell Transplant (autoHCT), Bortezomib, Lenalidomide (Len) and Dexamethasone (RVD) Consolidation with Len Maintenance (ACM), Tandem Autohct with Len Maintenance (TAM) and Autohct with Len Maintenance (AM) for up-Front Treatment of Patients with Multiple Myeloma (MM): Primary Results from the Randomized Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – StaMINA Trial) (Late Breaking Abstract)*. 58th Annual meeting & Exposition of American Society Hematology (ASH), San Diego, CA Dec 3-6., 2016.
44. O'Shea, D., et al., *Predictive factors for survival in myeloma patients who undergo autologous stem cell transplantation: a single-centre experience in 211 patients*. *Bone Marrow Transplant*, 2006. **37**(8): p. 731-7.
45. Ocio, E.M., et al., *New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG)*. *Leukemia*, 2014. **28**(3): p. 525-42.
46. Quach, H., et al., *Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma*. *Leukemia*, 2010. **24**(1): p. 22-32.
47. Cavo, M., et al., *Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma*. *Blood*, 2005. **106**(1): p. 35-9.

48. Harousseau, J.L., et al., *Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial*. J Clin Oncol, 2010. **28**(30): p. 4621-9.
49. Rajkumar, S.V., et al., *Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial*. Lancet Oncol, 2010. **11**(1): p. 29-37.
50. Kyriakou, C., et al., *Low-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma*. Br J Haematol, 2005. **129**(6): p. 763-70.
51. Lokhorst, H.M., et al., *A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma*. Blood, 2010. **115**(6): p. 1113-20.
52. Reeder, C.B., et al., *Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma*. Blood, 2010. **115**(16): p. 3416-7.
53. Popat, R., et al., *Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up*. Br J Haematol, 2008. **141**(4): p. 512-6.
54. Morgan, G.J., et al., *Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients*. Br J Haematol, 2007. **137**(3): p. 268-9.
55. Cavo, M., et al., *Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study*. Lancet, 2010. **376**(9758): p. 2075-85.
56. Kumar, S., et al., *Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma*. Blood, 2012. **119**(19): p. 4375-82.
57. Sonneveld, P., et al., *Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials*. J Clin Oncol, 2013. **31**(26): p. 3279-87.
58. Simpson, D., et al., *Weekly Subcutaneous Bortezomib Is Well Tolerated and Effective As Initial Therapy Of Symptomatic Myeloma (Abstract)*. Blood, 2013. **122**: p. 3229.
59. Dingli, D., et al., *Cyclophosphamide mobilization does not improve outcome in patients receiving stem cell transplantation for multiple myeloma*. Clin Lymphoma Myeloma, 2006. **6**(5): p. 384-8.
60. Hiwase, D.K., et al., *Intermediate-dose CY and G-CSF more efficiently mobilize adequate numbers of PBSC for tandem autologous PBSC transplantation compared with low-dose CY in patients with multiple myeloma*. Cytotherapy, 2007. **9**(6): p. 539-47.
61. DiPersio, J.F., et al., *Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma*. J Clin Oncol, 2009. **27**(28): p. 4767-73.
62. Kumar, S., et al., *Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens*. Blood, 2009. **114**(9): p. 1729-35.
63. Auner, H.W., et al., *High rate of stem cell mobilization failure after thalidomide and oral cyclophosphamide induction therapy for multiple myeloma*. Bone Marrow Transplant, 2011. **46**(3): p. 364-7.
64. Mark, T., et al., *Stem cell mobilization with cyclophosphamide overcomes the suppressive effect of lenalidomide therapy on stem cell collection in multiple myeloma*. Biol Blood Marrow Transplant, 2008. **14**(7): p. 795-8.
65. Fernandez de Larrea, C., et al., *Emergence of oligoclonal bands in patients with multiple myeloma in complete remission after induction chemotherapy: association with the use of novel agents*. Haematologica, 2011. **96**(1): p. 171-3.
66. Durie, B.G., et al., *International uniform response criteria for multiple myeloma*. Leukemia, 2006. **20**(12): p. 2220.
67. Tricot, G., et al., *Graft-versus-myeloma effect: proof of principle*. Blood, 1996. **87**(3): p. 1196-8.
68. Corradini, P., et al., *Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells*. J Clin Oncol, 1999. **17**(1): p. 208-15.
69. Garban, F., et al., *Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma*. Blood, 2006. **107**(9): p. 3474-80.

70. Moreau, P., *Autologous or reduced-intensity conditioning allotransplantation for de novo multiple myeloma*. Bone Marrow Transplant, 2009. **43**(7): p. 591-2.
71. Bruno, B., et al., *A comparison of allografting with autografting for newly diagnosed myeloma*. N Engl J Med, 2007. **356**(11): p. 1110-20.
72. Rosinol, L., et al., *A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma*. Blood, 2008. **112**(9): p. 3591-3.
73. Stadtmauer, E.A., et al., *Tandem Autologous Stem Cell Transplant (auto-auto) with or without Maintenance Therapy Versus Single Autologous Transplant Followed by HLA-Matched Sibling Non-Myeloablative Allogeneic Stem Cell Transplant (auto-allo) for Patients with high Risk Multiple Myeloma: Results From the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 0102 Trial [abstract]*. Blood, 2010. **116**: p. 526.
74. Krishnan, A., et al., *Tandem Autologous Hematopoietic Stem Cell Transplants (AuHCT) with or without Maintenance Therapy (auto-auto) Versus Single AuHCT Followed by HLA Matched Sibling Non-Myeloablative Allogeneic HCT (Auto-Allo) for Patients with Standard Risk (SR) Multiple Myeloma (MM): Results From the Blood and Marrow Transplant Clinical Trials network (BMT-CTN) 0102 Trial [abstract]*. Blood, 2010. **116**: p. 41.
75. Dhakal, B., D.H. Vesole, and P.N. Hari, *Allogeneic stem cell transplantation for multiple myeloma: is there a future?* Bone Marrow Transplant, 2016. **51**(4): p. 492-500.
76. Gay, F., et al., *Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients*. Blood, 2011. **117**(11): p. 3025-31.
77. Palumbo, A., et al., *Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN)*. Blood, 2011. **118**(17): p. 4519-29.
78. Palumbo, A., et al., *Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation-maintenance in untreated multiple myeloma patients*. J Clin Oncol, 2010. **28**(5): p. 800-7.
79. Straka, C., et al., *Prospective randomized trial of Len/Dex induction followed by tandem mel140 with autologous blood stem cell transplantation and Len maintenance versus continued therapy with Len/Dex in myeloma patients age 60–75 years: protocol-defined safety analysis after 100 patients [abstract]*. Blood, 2012. **120**(21): p. 2012.
80. Fayers, P.M., et al., *Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials*. Blood, 2011. **118**(5): p. 1239-47.
81. Morgan, G.J., et al., *Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment*. Clin Cancer Res, 2013. **19**(21): p. 6030-8.
82. Ludwig, H., et al., *Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma*. Blood, 2009. **113**(15): p. 3435-42.
83. San Miguel, J.F., et al., *Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma*. J Clin Oncol, 2013. **31**(4): p. 448-55.
84. Bringhen, S., et al., *Efficacy and safety of once-weekly bortezomib in multiple myeloma patients*. Blood, 2010. **116**(23): p. 4745-53.
85. Moreau, P., et al., *Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study*. Lancet Oncol, 2011. **12**(5): p. 431-40.
86. Kumar, S., et al., *Comparable Outcomes With Bortezomib-Cyclophosphamide-Dexamethasone (VCD) and Bortezomib-Lenalidomide-Dexamethasone (VRD) For Initial Treatment Of Newly Diagnosed Multiple Myeloma (MM) [abstract]*. Blood, 2013. **122**: p. 3178.
87. Mateos, M.V., et al., *Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial*. Lancet Oncol, 2010. **11**(10): p. 934-41.
88. Jagannath, S., et al., *Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma*. Br J Haematol, 2005. **129**(6): p. 776-83.
89. Palumbo, A., et al., *Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival*. J Clin Oncol, 2014. **32**(7): p. 634-40.
90. Benboubker, L., et al., *Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma*. N Engl J Med, 2014. **371**(10): p. 906-17.

91. Facon, T., et al., *Final Analysis of Overall Survival from the First Trial (Abstract)*. 58th Annual meeting & Exposition of American Society Hematology (ASH), San Diego, CA Dec 3-6., 2016.
92. Palumbo, A., et al., *Continuous lenalidomide treatment for newly diagnosed multiple myeloma*. N Engl J Med, 2012. **366**(19): p. 1759-69.
93. Magarotto, V., et al., *Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma*. Blood, 2016. **127**(9): p. 1102-8.
94. Palumbo, A., et al., *Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data*. Lancet Oncol, 2014.
95. Bringhen, S., et al., *Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials*. Haematologica, 2013. **98**(6): p. 980-7.
96. Hulin, C., et al., *Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial*. J Clin Oncol, 2009. **27**(22): p. 3664-70.
97. Ludwig, H., et al., *Survival and years of life lost in different age cohorts of patients with multiple myeloma*. J Clin Oncol, 2010. **28**(9): p. 1599-605.
98. Avet-Loiseau, H., et al., *Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome*. Blood, 2007. **109**(8): p. 3489-95.
99. Harsousseau, J.L., et al., *Double-intensive therapy in high-risk multiple myeloma*. Blood, 1992. **79**(11): p. 2827-33.
100. Stewart, A.K., et al., *A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy*. Leukemia, 2007. **21**(3): p. 529-34.
101. Hanamura, I., et al., *Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation*. Blood, 2006. **108**(5): p. 1724-32.
102. Joshua, D., et al., *Response of newly diagnosed myeloma with 1q21 amplification to bortezomib-based PAD induction therapy [abstract]*. J Clin Oncol, 2010. **28**(Suppl 15): p. 8028.
103. Sonneveld, P., et al., *Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group*. Blood, 2016. **127**(24): p. 2955-62.
104. Stefania, O., et al., *Revised-International Staging System (R-ISS): A New and Simple Prognostic Assessment for Multiple Myeloma (abstract)*. 19th Congress of the European Haematology Association., 2014.
105. Sagaster, V., et al., *Bortezomib in relapsed multiple myeloma: response rates and duration of response are independent of a chromosome 13q-deletion*. Leukemia, 2007. **21**(1): p. 164-8.
106. Neben, K., et al., *Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p*. Blood, 2012. **119**(4): p. 940-8.
107. Attal, M., et al., *Lenalidomide maintenance after stem-cell transplantation for multiple myeloma*. N Engl J Med, 2012. **366**(19): p. 1782-91.
108. Kapoor, P., et al., *Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone*. Blood, 2009. **114**(3): p. 518-21.
109. Reece, D., et al., *Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13*. Blood, 2009. **114**(3): p. 522-5.
110. San Miguel, J., et al., *Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial*. Lancet Oncol, 2013. **14**(11): p. 1055-66.
111. Roussel, M., et al., *Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome*. J Clin Oncol, 2014. **32**(25): p. 2712-7.
112. Morgan, G.J., et al., *The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis*. Blood, 2012. **119**(1): p. 7-15.
113. McCarthy, P.L., et al., *Lenalidomide after stem-cell transplantation for multiple myeloma*. N Engl J Med, 2012. **366**(19): p. 1770-81.
114. Rajkumar, S.V., et al., *Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1*. Blood, 2011. **117**(18): p. 4691-5.

115. Cook, G., et al., *Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry*. *Biol Blood Marrow Transplant*, 2011. **17**(11): p. 1638-45.
116. Lenhard, R.E., Jr., et al., *High-dose cyclophosphamide. An effective treatment for advanced refractory multiple myeloma*. *Cancer*, 1984. **53**(7): p. 1456-60.
117. Sonneveld, P., et al., *Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial*. *Haematologica*, 2007. **92**(7): p. 928-35.
118. San Miguel, J.F., et al., *Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma*. *N Engl J Med*, 2008. **359**(9): p. 906-17.
119. Prince, H.M., B. Schenkel, and L. Mileschkin, *An analysis of clinical trials assessing the efficacy and safety of single-agent thalidomide in patients with relapsed or refractory multiple myeloma*. *Leuk Lymphoma*, 2007. **48**(1): p. 46-55.
120. Glasmacher, A. and M. von Lilienfeld-Toal, *The current status of thalidomide in the management of multiple myeloma*. *Acta Haematol*, 2005. **114 Suppl 1**: p. 3-7.
121. Palumbo, A., et al., *Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma*. *Hematol J*, 2004. **5**(4): p. 318-24.
122. Dimopoulos, M.A., et al., *Thalidomide and dexamethasone combination for refractory multiple myeloma*. *Ann Oncol*, 2001. **12**(7): p. 991-5.
123. Dimopoulos, M.A., et al., *Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma*. *Hematol J*, 2004. **5**(2): p. 112-7.
124. Garcia-Sanz, R., et al., *The combination of thalidomide, cyclophosphamide and dexamethasone (ThaCyDex) is feasible and can be an option for relapsed/refractory multiple myeloma*. *Hematol J*, 2002. **3**(1): p. 43-8.
125. Weber, D.M., et al., *Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America*. *N Engl J Med*, 2007. **357**(21): p. 2133-42.
126. Dimopoulos, M., et al., *Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma*. *N Engl J Med*, 2007. **357**(21): p. 2123-32.
127. Rajkumar, S.V., *Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group [abstract]*. *J Clin Oncol*, 2007. **25**(18 Suppl): p. 8025a.
128. Kumar, S.K., et al., *Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial*. *Am J Hematol*, 2011. **86**(8): p. 640-5.
129. Quach, H., et al., *Upfront lower dose lenalidomide is less toxic and does not compromise efficacy for vulnerable patients with relapsed refractory multiple myeloma: final analysis of the phase II RevLite study*. *Br J Haematol*, 2017.
130. Dimopoulos, M.A., et al., *Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma*. *Leukemia*, 2014. **28**(8): p. 1573-85.
131. Richardson, P.G., et al., *A phase 2 study of bortezomib in relapsed, refractory myeloma*. *N Engl J Med*, 2003. **348**(26): p. 2609-17.
132. Jagannath, S., et al., *A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma*. *Br J Haematol*, 2004. **127**(2): p. 165-72.
133. Richardson, P.G., et al., *Bortezomib or high-dose dexamethasone for relapsed multiple myeloma*. *N Engl J Med*, 2005. **352**(24): p. 2487-98.
134. Harrison, S.J., et al., *The addition of dexamethasone to bortezomib for patients with relapsed multiple myeloma improves outcome but ongoing maintenance therapy has minimal benefit*. *Am J Hematol*, 2015.
135. Kropff, M., et al., *Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma*. *Br J Haematol*, 2007. **138**(3): p. 330-7.
136. Palumbo, A., et al., *Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma*. *Ann Oncol*, 2008. **19**(6): p. 1160-5.
137. Stadtmauer, E.A., et al., *Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma*. *Eur J Haematol*, 2009. **82**(6): p. 426-32.
138. Vogl, D.T., et al., *Impact of prior therapies on the relative efficacy of bortezomib compared with dexamethasone in patients with relapsed/refractory multiple myeloma*. *Br J Haematol*, 2009. **147**(4): p. 531-4.
139. Leoni, L.M., et al., *Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents*. *Clin Cancer Res*, 2008. **14**(1): p. 309-17.

140. Gentile, M., et al., *An old drug with a new future: bendamustine in multiple myeloma*. Expert Opin Pharmacother, 2013. **14**(16): p. 2263-80.
141. Ludwig, H., et al., *Bendamustine-bortezomib-dexamethasone is an active and well-tolerated regimen in patients with relapsed or refractory multiple myeloma*. Blood, 2014. **123**(7): p. 985-91.
142. Stewart, A.K., et al., *Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma*. N Engl J Med, 2015. **372**(2): p. 142-52.
143. Dimopoulos, M., et al., *Carfilzomib and Dexamethasone vs Bortezomib and Dexamethasone in Patients With Relapsed Multiple Myeloma: Results From the Phase 3 Study ENDEAVOR (Abstract)*. European Hematology Association, Vienna, Austria, 2015.
144. Usmani, S.Z., et al., *Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma*. Blood, 2016. **128**(1): p. 37-44.
145. Dimopoulos, M.A., et al., *Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma*. N Engl J Med, 2016. **375**(14): p. 1319-1331.
146. Palumbo, A., et al., *Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma*. N Engl J Med, 2016. **375**(8): p. 754-66.
147. Martin, T.G., et al., *A Phase Ib Dose Escalation Trial of SAR650984 (Anti-CD-38 mAb) in Combination with Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma (abstract)*. 56th ASH Annual Meeting and Exposition, San Francisco, CA, 2014.
148. Lonial, S., et al., *Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma*. N Engl J Med, 2015.
149. Ocio, E.M. and J.F. San Miguel, *The DAC system and associations with multiple myeloma*. Invest New Drugs, 2010. **28 Suppl 1**: p. S28-35.
150. Richardson, P., et al., *Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma (abstract)*. J Clin Oncol, 2014. **32**(5s (abstr 8510)).
151. Richardson, P.G., et al., *PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma*. Blood, 2013. **122**(14): p. 2331-7.
152. Siegel, D., et al., *A phase 1b study of durvalumab (MEDI4736) alone or in combination with pomalidomide (POM) with or without low dose-dexamethasone (LoDEX) in patients (pts) with relapsed and refractory multiple myeloma (RRMM)*. J Clin Oncol 2016. **34**(suppl; abstr TPS8072).
153. Reeder, C.B., et al., *Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial*. Leukemia, 2009. **23**(7): p. 1337-41.
154. Einsele, H., et al., *Velcade, Intravenous Cyclophosphamide and Dexamethasone (VCD) Induction for Previously Untreated Multiple Myeloma (German DSMM XIa Trial [abstract])*. Blood, 2009: p. 131a.
155. Oakervee, H.E., et al., *PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma*. Br J Haematol, 2005. **129**(6): p. 755-62.
156. Wu, P., et al., *The combination of cyclophosphamide, thalidomide and dexamethasone is an effective alternative to cyclophosphamide - vincristine - doxorubicin - methylprednisolone as induction chemotherapy prior to autologous transplantation for multiple myeloma: a case-matched analysis*. Leuk Lymphoma, 2006. **47**(11): p. 2335-8.
157. Rajkumar, S.V., et al., *Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group*. J Clin Oncol, 2006. **24**(3): p. 431-6.
158. Rajkumar, S.V., et al., *Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma*. J Clin Oncol, 2002. **20**(21): p. 4319-23.
159. Rajkumar, S.V., et al., *Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial*. Lancet Oncol, 2009.
160. Ludwig, H., et al., *Bortezomib, Thalidomide, and Dexamethasone (VTD) Versus VTD Plus Cyclophosphamide as Induction Therapy in Previously Untreated Multiple Myeloma Patients Eligible for HDT-ASCT: A Randomized Phase 2 Trial [abstract]*. Blood, 2009. **114**: p. 2312.
161. Richardson, P.G., et al., *Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma*. Blood, 2010. **116**(5): p. 679-86.
162. Spencer, A., et al., *Induction with oral chemotherapy (CID) followed by early autologous stem cell transplantation for de novo multiple myeloma patients*. Hematol J, 2004. **5**(3): p. 216-21.

163. Joshua, D.E., et al., *Australian Leukaemia Study Group myeloma II: a randomized trial of intensive combination chemotherapy with or without interferon in patients with myeloma*. Br J Haematol, 1997. **97**(1): p. 38-45.
164. Palumbo, A., et al., *A Phase 3 Study Evaluating the Efficacy and Safety of Lenalidomide Combined with Melphalan and Prednisone in Patients ≥ 65 Years with Newly Diagnosed Multiple Myeloma (NDMM): Continuous Use of Lenalidomide Vs. Fixed-Duration Regimens [abstract]*. Blood, 2010. **116**: p. 662a.
165. Khan, M.L., et al., *A comparison of lenalidomide/dexamethasone versus cyclophosphamide/lenalidomide/dexamethasone versus cyclophosphamide/bortezomib/dexamethasone in newly diagnosed multiple myeloma*. Br J Haematol, 2012. **156**(3): p. 326-33.
166. Anagnostopoulos, A., et al., *Thalidomide and dexamethasone for resistant multiple myeloma*. Br J Haematol, 2003. **121**(5): p. 768-71.
167. Offidani, M., et al., *Thalidomide-dexamethasone plus pegylated liposomal doxorubicin vs. thalidomide-dexamethasone: a case-matched study in advanced multiple myeloma*. Eur J Haematol, 2007. **78**(4): p. 297-302.
168. Zangari, M., et al., *Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy*. Blood, 2002. **100**(4): p. 1168-71.
169. Knop, S., et al., *Lenalidomide, adriamycin, and dexamethasone (RAD) in patients with relapsed and refractory multiple myeloma: a report from the German Myeloma Study Group DSMM (Deutsche Studiengruppe Multiples Myelom)*. Blood, 2009. **113**(18): p. 4137-43.
170. Morris, T.C., et al., *PAD Given at Relapse is More Effective than VAD Given as Induction Therapy -Results of a Phase II Study [abstract]*. Blood, 2007. **110**: p. 2724.
171. Scheid, C., et al., *Influence of Renal Function on Outcome of VAD or Bortezomib, Doxorubicin, Dexamethasone (PAD) Induction Treatment Followed by High-Dose Melphalan (HDM): A Subgroup Analysis From the HONVON-65/GMMG-HD4 Randomized Phase III trial for Newly Diagnosed Multiple Myeloma [abstract]*. Blood, 2010. **116**: p. 2396.
172. Berenson, J.R., et al., *Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma*. J Clin Oncol, 2006. **24**(6): p. 937-44.
173. Petrucci, M.T., et al., *Intermediate-dose (25 mg/m²) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment*. Eur J Haematol, 1989. **42**(3): p. 233-7.
174. Knop, S., et al., *The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy*. Haematologica, 2005. **90**(9): p. 1287-8.