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

Clinical Practice Guideline
MULTIPLE MYELOMA

Coordinated on behalf of the MSAG,
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Myeloma Australia

V.3 Updated August 2015

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1 INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy characterised by an abnormal serum and /or urine immunoglobulin intact paraprotein 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 1200 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 [2], however, younger patients with MM are also seen. Although MM remains an incurable disease, survival outcomes have improved significantly. This is owing to the introduction of first, high dose therapy (HDT) and autologous stem cell transplant (AuSCT) in the late 1990s, then newer therapeutic agents including the immunomodulatory group of drugs (IMiDs: thalidomide, lenalidomide (Revlimid™) and pomalidomide (Pomalyst™), the proteasome inhibitors (PI; the first in class PI bortezomib (Velcade™) and emerging second generation PI including carfilzomib, ixazomib (MLN9708) and oprozomib), and newer classes of drugs with very promising activity including the monoclonal antibodies (mAb) such as daratumumab, SAR650984 and elotuzumab [3].

Treatment options for MM are increasingly diverse. There are broad basic treatment principles, however, local treatment guidelines vary depending on the local availability of newer therapeutic agents, and familiarity of the treating physician to these agents. The following guideline for the effective treatment of MM is a consensus established by the Australian Medical Scientific Advisory Group (MSAG) to Myeloma Australia (MA), 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[4]. 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[4]. 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
- 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.	- Serum paraprotein ≥30g/l or urinary monoclonal protein ≥500 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	Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and presence of either: Myeloma defining events (table 3). Or Biomarkers of Malignancy (table 3)

Table 3: Myeloma defining events and biomarkers of malignancy.

MYELOMA DEFINING EVENTS	
- Increased calcium level	Corrected serum Calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
- Renal insufficiency	Creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
- Anaemia	Hb <100g/L or 20g/L below the lower limit of normal.
- 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 ß2microglobulin (ß2M) 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 lead 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 survival (months)**
I	Serum $ß_2$M <3.5mg/l and serum Albumin >35g/l	62
II	Neither I nor III	45
III	Serum $ß_2$M>5.5mg/l	29
REVISED (R)- ISS RISK STRATIFICATION MODEL		
Stage	**Criteria**	**5 Year OS (%)**
R-ISS I	- ISS I (Serum $ß_2$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))	81%
R-ISS II	Patients failing to meet criteria for R-ISS I or III.	62%
R-ISS III	ISS III (Serum $ß_2$ microglobulin >5.5mg/L) *AND* High risk iFISH OR High LDH	39%

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.
ISS (international stage system) III (Serum ß2 microglobulin >5.5mg/L) **Conventional Cytogenetics** - Del17p - Hypodiploidy - Deletion of chromosome 13* **Fluorescent in situ hybridisation (FISH)** - t(4;14) - t(14;16) - Del17p - 1q21 amplification **Plasma cell labelling index ≤3%** **High lactate dehydrogenase (LDH)**	ß2 microglobulin Albumin **Conventional Cytogenetics **** **Fluorescent in situ hybridisation (FISH) **** - t(4;14) - t(14;16) - Del 17p - 1q21 amplification. **Plasma cell labelling index (by flow cytometry) ***** **LDH**

** 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).*

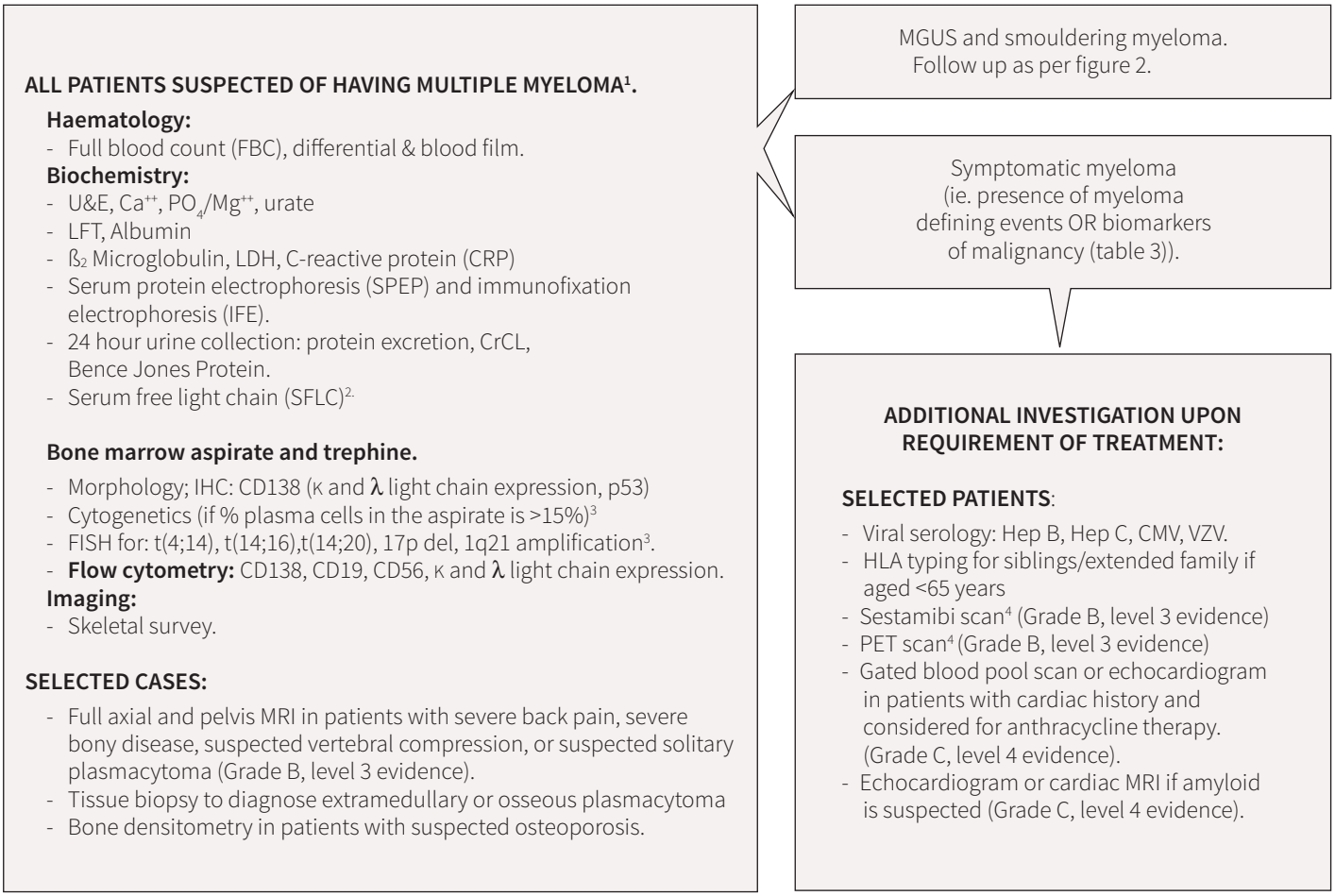
*** Cytogenetics and FISH should only be requested in patients in whom the identification of high risk would impact management. Cytogenetics is often only possible in patients with >15% plasma cells in the aspirate as the yield of metaphases is low with a lesser plasma cell burden.*

**** 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

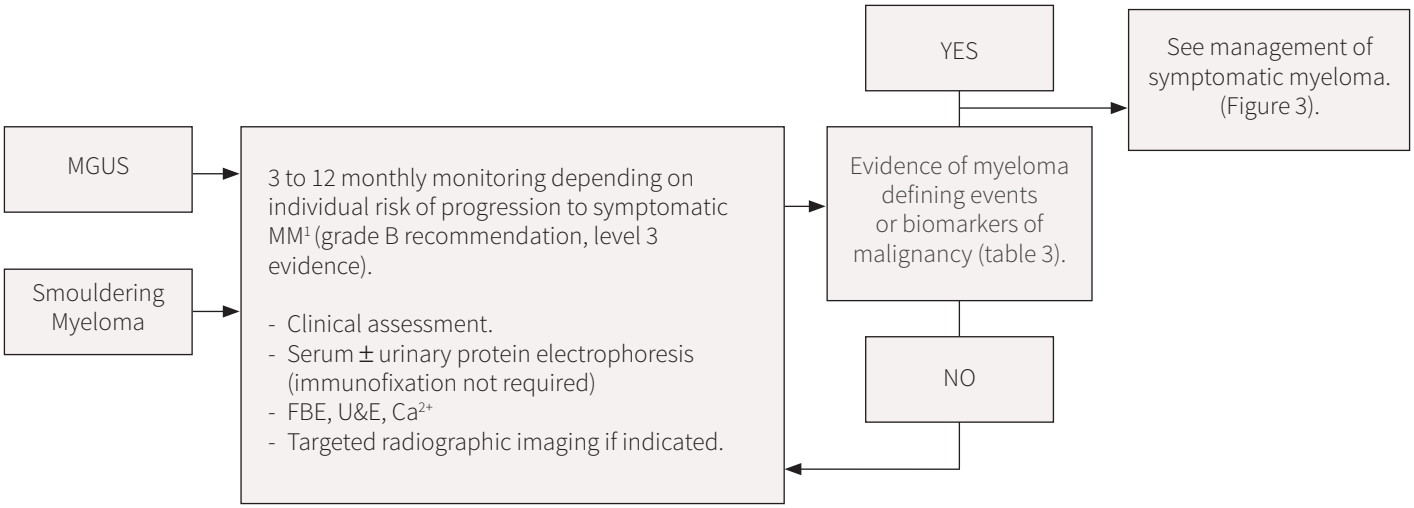
The initial diagnostic work-up process (Figure 1) aims to establish the diagnosis, the stage of disease, and prognostic markers, which may influence subsequent treatment. The following recommendations are grade C and based on level 4-evidence unless otherwise state

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.

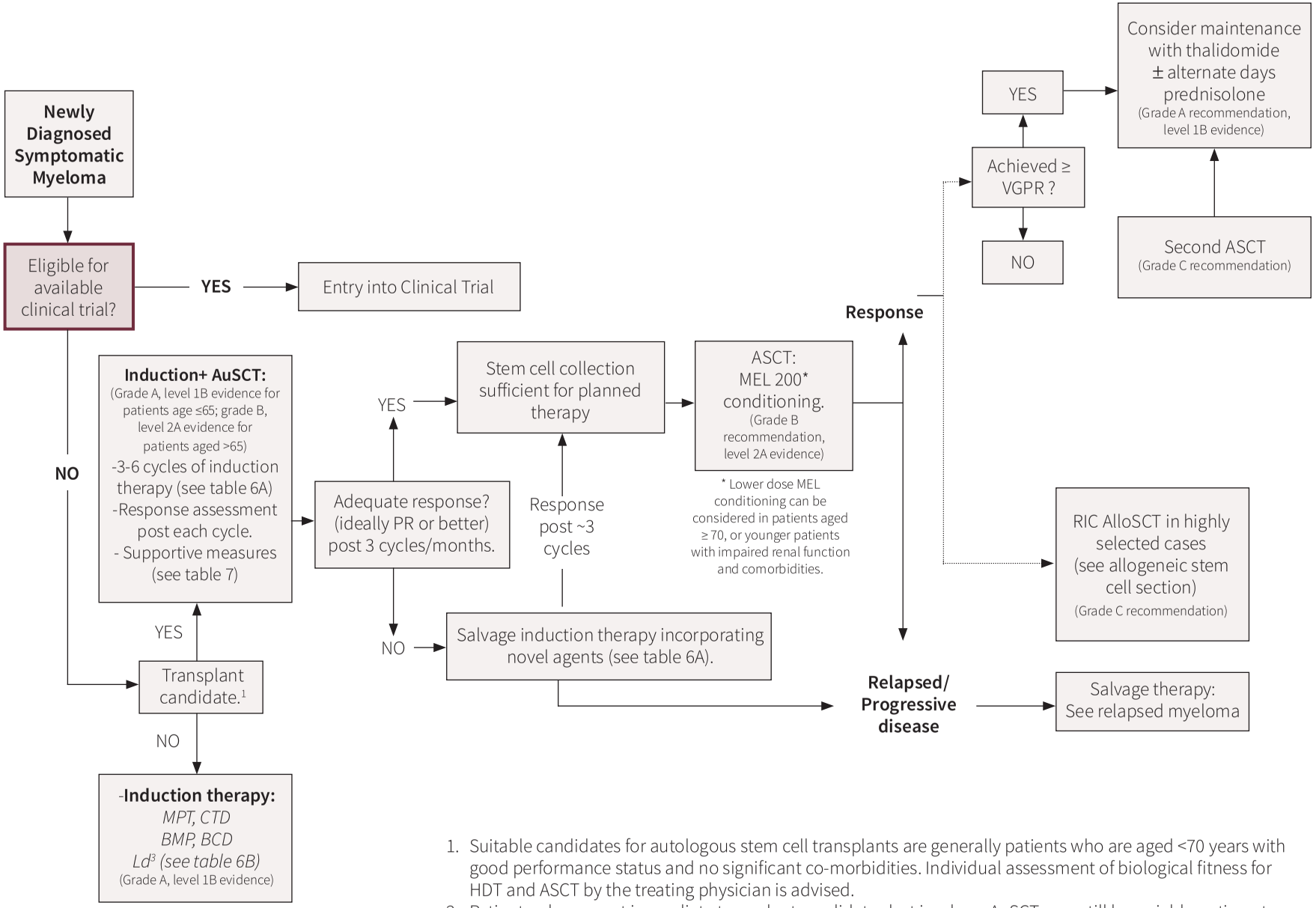
Figure 2: Management of MGUS and Smouldering Myeloma.



[1]For MGUS:

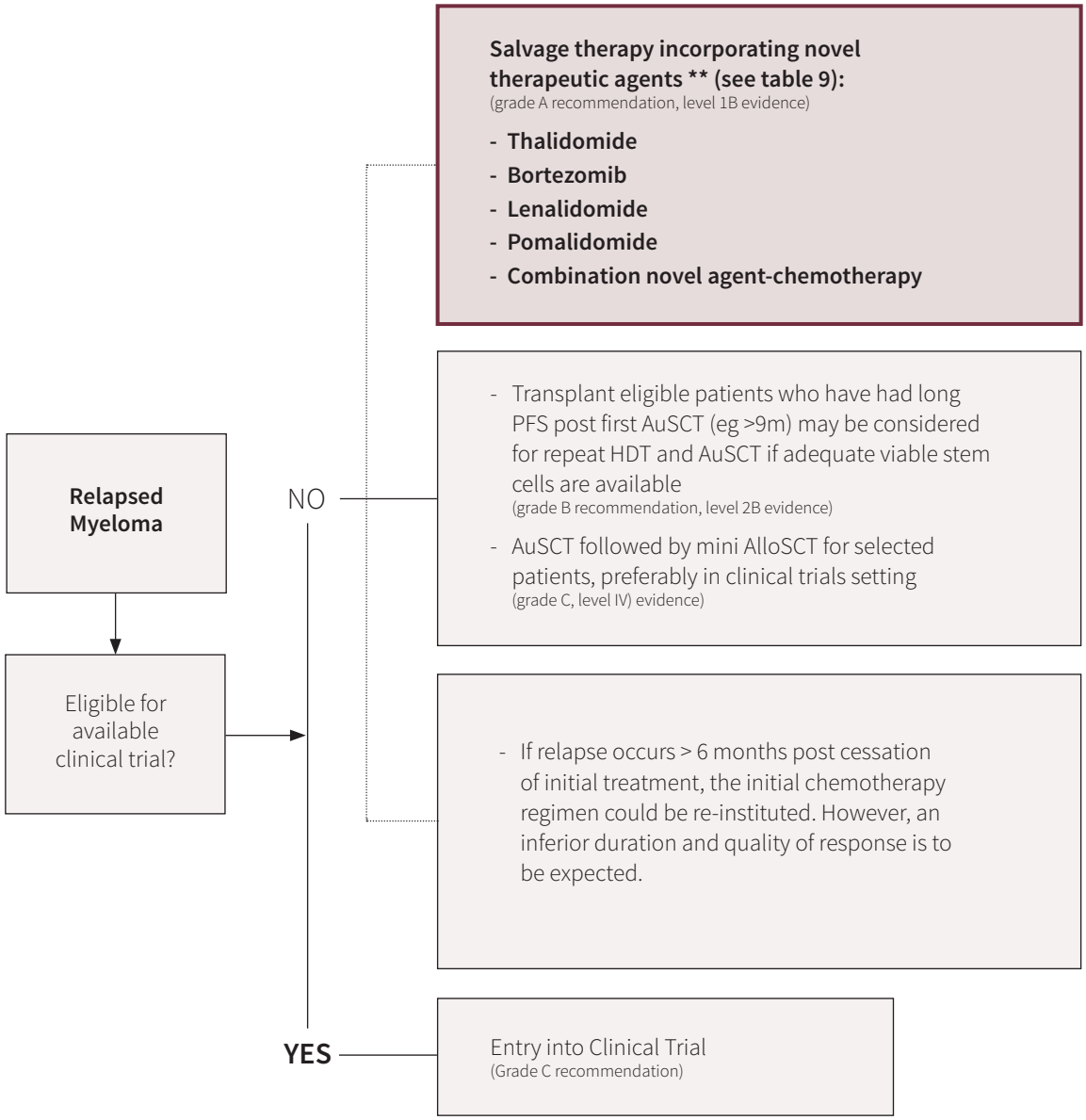
- When serum paraprotein level is ≤15g/l and stable, IgG type, and normal SFLC kappa: lambda ratio, SPEP can be repeated annually.
- When paraprotein value is >15g/l or there is an abnormal SFLC kappa:lambda ratio, a bone marrow aspirate and trephine is considered if paraprotein is rising to assess for 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 [14].

Figure 3: Management of Newly Diagnosed Symptomatic Myeloma.



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. As of August 2015, lenalidomide is not available on PBS for initial treatment of patients with MM.

Figure 4: Management of relapsed Myeloma.



** As of August 2015, pomalidomide is available in Australia through the PBS for patients with RRMM who have failed treatment with bortezomib and lenalidomide. Carfilzomib, a second generation proteasome inhibitor has recently been shown to be effective in patients with RRMM but is not available through PBS in Australia as of August 2015. .Other second generation proteasome inhibitors such as oprozomib and ixazomib are under investigation. The monoclonal antibody class of drugs, elotuzumab, daratumumab and SAR650984 and are extremely promising (see section on promising new agents). These agents are currently not available in Australia on PBS. Bendamustine is not approved in Australia for use in myeloma.

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
CD [64]	Cyclophosphamide 1g/m^2 IV D1 Dexamethasone 40mg D1-4, 9-12. Cycles repeated every 21 days for 2 to 3 cycles prior to ASCT	Post transplant ORR 81% (similar to VAD with ORR of 80%).
CID [65]:	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 AuSCT.
PCAB [66]	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)
TD [25, 67, 68]:	Thalidomide 200mg po daily Dexamethasone 40mg po daily D1-4. Cycles repeat every 4 weeks for 3-4 cycles prior to ASCT	Pre-transplant ORR varies from 64%-76%. ORR 76% with thalidomide-dexamethasone vs. 52% VAD, p<0.001[25]
CTD [5, 69]:	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 [6]	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)
BD [26, 70]:	Bortezomib1.3mg/m^2 IV D1,4,8,11 Dexamethasone 20mg on day of and day after bortezomib Cycles repeat every 21 days for 3-4 cycles prior to ASCT	CR/nCR 22% post induction. CR/nCR 38% post ASCT
PAD [8, 20, 71]:	Bortezomib 1.3mg/m^2 IV 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 AuCT	ORR 95%; 65% ≥VGPR, 24% CR. Assessment following ± ASCT: ORR 95%, 81% ≥VGPR, 43% CR.
CyBorD/BCD [7, 72, 73]	Bortezomib 1.3mg/m^2 IV 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
	Or Bortezomib 1.5mg/m^2 wc 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

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REGIMEN	SCHEDULE	RESPONSES
Ld [74]	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.
LCD [9, 75]	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
BTD [24]:	Bortezomib 1.3mg/m^2 IV 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
(BTDC) [76]	Bortezomib 1.3mg/m^2 IV 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.	ORR 96%; CR/nCR 44% post induction ORR 100%; CR/nCR = 78% post ASCT

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

MPT[13]*	Melphalan: 0.25mg/kg orally D1-4 every 6 weeks for 12 cycles OR 4mg/m2 orally D1-7 every 4 weeks for 6 cycles. Prednisone: 2mg/kg orally D1-4 every 6 weeks for 12 cycles OR 40mg/m2 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
CTDa[14]*	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
BMP[21, 24, 33]*	Bortezomib**: 1.3 mg/m^2 IV 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. *** Note: weekly bortezomib improve tolerability in transplant ineligible patients without compromising efficacy. We recommend either:* *Bortezomib 1.3mg/m^2 IV D 1,8,15,22 every 5 weeks for nine cycles [21, 24] or alternatively Bortezomib 1.3mg/m^2 or 1.5mg/m^2 weekly.[34].* ***Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved toxicity profile[18].*	CR 24-30% Med PFS 22-27m 2-year OS 85-87%.
BCD[19]*	Bortezomib: 1.5mg/m^2 IV 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.	–
Bd[22]*	Bortezomib**: 1.3 mg/m^2 IV D1, 4, 8, and 11 IV every 3 weeks for six cycles Dexamethasone: 40mg orally on day of and day post bortezomib. *** Note: weekly bortezomib improve tolerability in transplant ineligible patients without compromising efficacy. We recommend either:* *Bortezomib 1.3mg/m^2 IV D 1,8,15,22 every 5 weeks for nine cycles [21, 24] or alternatively Bortezomib 1.3mg/m^2 or 1.5mg/m^2 weekly.[34].* ***Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved toxicity profile[18].*	CR 6%; nCR 19%
BTP[21]	Bortezomib: 1.3 mg/m^2 given IV 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 year OS 70%
BMPT[24]	Bortezomib: 1.3 mg/m^2 IV 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 years OS 86%

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BLd [20]	Bortezomib: 1.3 mg/m^2 IV 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%
MPL-(L) [25]	Melphalan: 0.18 mg/kg orally on days 1-4 every 4 weeks for nine cycles. Prednisone: 2 mg/kg orally on days 1-4 every 4 weeks for nine cycles. Lenalidomide: 10mg daily orally on days 1-21 every 4 weeks until disease progression.	MPR-R: CR 16% Med TTP 24.7m 2 yr OS 86.2%
Ld [26, 31]	Lenalidomide: 25 mg daily orally days 1-21 every 4 weeks until disease progression. Dexamethasone: 40 mg orally on days 1, 8, 15, and 22 every 4 weeks until disease progression.	CR 15.1% 3 year PFS 42% 4 year OS 59.4%

* These regimens are considered acceptable initial induction therapy for transplant ineligible patients in Australia.
Please refer to figure 2 and the section of "recommendations for initial induction therapy for transplant ineligible patients".

Table 7: Supportive measures.

Localised bony lesions	• 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)	• 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. *Lenalidomide, like thalidomide, does not appear to significantly increase the risk of VTE as a single agent.* 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	• 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	Selected patients with recurrent infections (≥2 chest infections per year) and hypogammaglobulinaemia are eligible for IVIg. • 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.	Pharmaceutical prophylaxis against infection should follow local institutional guideline. • Valaciclovir, acyclovir or famciclovir prophylaxis against Varicella Zoster reactivation in patients receiving bortezomib, 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	• Proton pump inhibitor or histamine H2-receptor antagonist is recommended in patients receiving ongoing corticosteroids

3 MANAGEMENT OF MULTIPLE MYELOMA – AN OVERVIEW

Despite the much improved survival outcome since the introduction of newer therapeutic agents including the immunomodulatory drugs (IMiDs) and proteasome inhibitors, multiple myeloma (MM) is still an incurable disease. However, the expansion of effective treatment option over the last two decades, has converted what was once 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 [4]

The average risk of progression from monoclonal gammopathy of uncertain significance (MGUS) to symptomatic myeloma is approximately 1% per year[19]. For SMM, the median time to progression is between 12 to 32 months[20]. 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 (≥10% bone marrow plasma cells plus paraprotein of ≥30g/L)[20] and Spanish (≥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[21]. 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[22]. 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 ± 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 critiera, 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 HDT and AuSCT that is in turn dependent on the patient's age, comorbidities and functional status. Whether or not an upfront AuSCT approach is undertaken, 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 [23, 24] in both the AuSCT[25-27] and non-AuSCT setting[24, 28, 29], 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[30]. 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[31]. Currently, CR is considered an objective of initial treatment, provided there is no unacceptable toxicity.

3.2.1 Patients eligible for AuSCT:

Since the late 1980s, ASCT as part of front-line therapy was considered superior to delaying transplantation until first relapse on the basis of improved EFS (39 vs. 13 months) and average time without symptoms, treatment and treatment toxicity (TWISTT: 27.8 vs. 22.3 months) compared to when ASCT was 'delayed' until first relapse[32]. No difference in OS was demonstrated.

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[33] and EMN MM-RV-441[34] trial. 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). Preliminary combined analysis of these two trials showed superiority of ASCT as part of front line treatment compared to when ASCT was delayed until relapse, with respect to PFS1 ($p<0.001$) and 4-year OS (85 vs. 76%, $p=0.027$)[35]. Based on these data, ASCT as part of initial treatment, remains the standard of care for patients with MM who are considered eligible [35].

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. 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)[36] 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 [37].

3.2.1.1 Tandem vs. single AuSCT:

Tandem ASCT, in which the second ASCT is planned to occur 3 to 6 months after the first, was developed in an attempt to increase dose intensity to achieve a deeper and sustained remission. Reported CR rates with single SCT have been approximately 25-35%; that for tandem transplant is approximately 40% with a median EFS and OS of 49 months and 62 months, respectively [38]. 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. When this trial was excluded from the meta-analysis, the heterogeneity disappeared, and there was a statistically significant change in the hazard ratio for EFS but not OS favouring tandem transplant.

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]. More recently, an integrated analysis was performed 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)[42]. Tandem ASCT may therefore be a reasonable strategy, perhaps in selected patients who have had a suboptimal response to first transplant given that subset analysis in previous phase III trials have indicated that tandem transplants seem to primarily benefit patients with less than VGPR after the first transplantation[43, 44]. It must be emphasised 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 (Box 2).

Box 2: Recommendation for transplant eligible patients:

High dose therapy (HDT) and autologous stem cell transplant (AuSCT) 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 AuSCT 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[45].

Induction-regimens that incorporate IMiDs and /or proteasome inhibitors (table 6A) are superior to chemotherapy-only regimens such as the classic infusional vincristine, doxorubicin, dexamethasone (VAD), particularly in poor-risk patients such as those with poor cytogenetics or other adverse prognostic features[46-48] Two-drug combinations where dexamethasone is combined with thalidomide (TD), lenalidomide (Ld) (low dose dexamethasone) or bortezomib (BD) are superior to VAD[46-48]. 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%[46].

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)[49, 50], bortezomib (CyBorD, PAD)[51, 52], or lenalidomide (LCD)[53] induces CR/VGPR rates between 37-65%. Similar impressive efficacy is seen with three-drug regimens that combine IMiDs and proteasome inhibitors[54, 55]. In contrast, no further advantage was seen with a four-drug combination, which instead results in greater toxicity[55]. It should be noted that combinations of IMiDs and proteasome inhibitors are not currently available through PBS re-imbursement 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[56], 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[51]. 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[57]. Recommendations for induction therapy prior to ASCT are summarised in Box 3.

Patients eligible for AuSCT should receive stem cell-sparing induction therapy (i.e. regimens not containing melphalan) for 3-4 cycles prior to stem cell collection. Possible induction regimens are outlined in table 6A. The choice is often dependent on local treatment guidelines and access to newer agents.

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).

VAD is no longer a recommended induction regimen (grade A recommendation, level 1B evidence).

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

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/m^2 and subcutaneous route of administration appear to significantly reduce neurotoxicity compared to the traditional bortezomib schedule of 1.3mg/m^2 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 AuSCT[58]. 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 cylophosphamide 2g/m2 [59].

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 mobilisation compared to rhG-CSF alone[60]. Due to high cost, plerixafor is generally reserved for patients who fail to mobilize adequately as either a rescue strategy or during a second mobilisation attempt under the PBS re-imbursement criteria in Australia.

Bortezomib and thalidomide does not appear to impair stem cell mobilisation [61] 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 mobillization 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 mobilisation individually, may induce a higher rate of stem cell mobilisation failure when used in combination[62]. Lenalidomide has been reported to reduce the number of CD34+ cells collected. Mobilisation using rhG-CSF alone after lenalidomide-based induction therapy may be inferior to combination therapy using rhG-CSF and high-dose cyclophosphamide[63], and the latter should be considered for stem cell mobilisation, 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 mobilisation regimen should follow institution protocol.

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

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 mobilisation after thalidomide or bortezomib- based induction therapy. However, combination rhG-CSF and high dose cylophosphamide may be required after lenalidomide-based induction therapy, and it is recommend 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 mobilisation 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 AuSCT

The average time to progression for patients after HDT and AuSCT is in the order of 2-4 years for younger patients, and shorter for older patients. The final magnitude of response post AuSCT 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 levels (SFLC levels is used in patients with unmeasureable 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[64]. 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 [65], 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+AuSCT, 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, Ca^{2+}*
- *Targeted radiographic imaging if indicated.*

3.2.1.5 Allogeneic Stem Cell Transplant

A "Graft versus myeloma (GVM)" has been shown to exist in the setting of allogeneic stem cell transplantation (alloSCT) [66]. While this may give rise to some long-term durable remissions [67], myeloablative alloSCT is associated with a high TRM of up to 50%. Reduced intensity conditioning (RIC) alloSCT has TRM, to approximately 10-15% at 1 year, whilst maintaining the GVM effect. Three prospective trials have been published. The IFM99-03 study [68], included only patients with high risk (del13q + B2M>3mg/ml), and patients with available sibling donors underwent MEL200 AuSCT followed by RIC AlloSCT with anti-thymocyte globulin, busulphan and fludarabine conditioning. Patients without a donor had a second AuSCT 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 AuSCT + RIC alloSCT vs. tandem AuSCT respectively. However after longer follow up, OS was found to be significantly inferior in patients assigned to RICalloSCT [69]. An Italian randomised study, also comparing tandem AuSCT vs. AuSCT 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) [70]. More recently, in the Spanish PETHEMA trial [71], comparisons were made between a second AuSCT vs. RIC (Melphalan and fludarabine) alloSCT in a group of patients who achieved < VGPR to their first AuSCT. 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 [72], and standard-risk [73] MM patients. Two Gy total body irradiation was used as the non-myeloablative conditioning regimen in the allo-SCT arm. There was a trend to 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 AuSCT due to increased TRM. 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 poor prognostic disease 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 AuSCT

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[74], substantial treatment-related toxicities can mitigate benefits of CR in frail elderly patients. In this group, opting for reasonable disease control to optimize quality of life (QoL) may be preferable.

Based on 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)[36], 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[75].

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[76, 77] (Please refer to section on transplant eligible patients). Reduced-dose conditioning (melphalan 100-140mg/m2)[76, 77] is tolerable and has been shown to induce a median PFS of 4 years in this group of patients[76].

"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 followed by HDT+AuSCT (Please refer to position statement on treatment of patients with multiple myeloma who are eligible for stem cell transplantation). 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+AuSCT should undergo full dose induction therapy incorporating IMiDs or proteasome inhibitors (Grade A recommendation, Level 1A evidence)*
- *Reduced-intensity treatment is suggested for those more frail 'unfit' elderly patients (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:

Conventional-dose oral melphalan and prednisolone (MP) consistently gives a response rate (RR) of approximately 50% and a median survival of 3 years. The addition of thalidomide to MP (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 randomised clinical trials that compared MP to MPT[78]. However, the addition of thalidomide comes at a price of higher toxicity, mainly, myelosupression, 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[79](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[80].

Bortezomib-based regimen.

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[81]. Thus both MPT and BMP are considered 'standards-of-care' 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[82]. For transplant ineligible patients, the weekly schedule of bortezomib is now considered standard of care (table 6A). Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved safety profile[83]. The use of cyclophosphamide in place of melphalan is of comparable efficacy[51](table 1). The combination of an IMiD and bortezomib is attractive but this does not appear superior to a simple (and cheaper) alkylkating agent combination[84, 85]. 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[85].

In unfit elderly patients in whom an alkylating agent may not be suitable, bortezomib and dexamethasone alone is efficacious with RR and CR of up to 70% and 25%, respectively[86]. Conversely, a 4-drug regimen combining bortezomib, lenalidomide, cyclophosphamide and dexamethasone(BLCD) have been shown to be more toxic without added efficacy[55, 87].

Lenalidomide-based regimens

The addition of lenalidomide (Revlimid®) to MP (MPL) is less well tolerated in elderly patients mainly due to myelosupression, 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). 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[88]. In contrast, lenalidomide and low-dose dexamethasone (Ld) is well tolerated, and can induce deep responses. Recent preliminary results of the MM020 trial demonstrated superiority of continuous Ld (given until disease progression) compared to MPT with respect to PFS and OS in a group of transplant ineligible patients. Presuming the final analysis confirms these results, this regimen will likely become a new standard-of-care option[89]. Interestingly, in an interim analysis of one phase III trial, the addition of an alkylating agent (cyclophosphamide or melphalan) to Ld was not found to improve ORR, PFS or OS in first line treatment of transplant ineligible patients. When combined with Ld, melphalan seems to induce more toxicity, mainly myelotoxicity, compared to cyclophosphamide[90]

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[88]. 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[91]. 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.

- *In fit elderly patients, melphalan and prednisolone (MP) with either thalidomide (MPT) or bortezomib (MPB) can be considered standard initial treatment for patients ineligible for HDT+ASCT (Grade A recommendation, Level 1A evidence)*
    - *Both thalidomide and bortezomib are PBS approved for reimbursement for first line treatment of patients with MM in Australia.*
    - *Cyclophosphamide is therapeutically equivalent compared to melphalan and may be more tolerable; it may preferentially be used in place of melphalan in IMiDs or proteasome inhibitor containing regimens (eg. CTD or BCD)*
    - *For bortezomib, a weekly schedule is recommended.*
- *Continuous lenalidomide and dexamethasone has emerged as another potential standard-of-care option for upfront treatment in transplant ineligible patients (Grade A recommendation, level 1B evidence)*
    - *As of August 2015, lenalidomide is neither TGA (Therapeutic Goods Administration) approved or PBS-subsidised for this indication in Australia.*

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[92], 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[82]. In addition, one randomised 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[83]. 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[93].

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)[48]. For patients older than 75 years or who are frail, a lower starting dose of dexamethasone, 20mg weekly, could be considered[75].

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 [88].

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	15mg

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 [94], higher ISS stage, high LDH, high plasma cell labelling index and the cytogenetic abnormalities: 13q deletion (identified by standard cytogenetic), t(4;14), t(4;16) and 17p deletion (as identified by FISH) [95-97]. Amplification of chromosome 1q21 (by FISH) has also been shown to be associated with both shorter time to disease progression and poorer prognosis[98, 99]. 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 lead to a proposed revised(R)-ISS risk stratification system that incorporates ISS stage, LDH and high-risk iFISH (del17p and t(4;14)). The R-ISS risk stratification system (table 4) 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[7, 100].

Several reports have confirmed that bortezomib is effective even in the presence of poor risk cytogenetics (13q deletion, t(4;14), amp1q21, and perhaps even 17p deletion) [5, 41, 99, 101, 102] although it does not overcome the entire adverse impact of these mutations. Preliminary

data suggest that the same may apply to lenalidomide but this considerably more investigation[103]. A possible beneficial role of tandem ASCT in patients with poor prognostic features 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 but is an area of active investigation. Recommendations for patients with high risk MM are summarised in box 9.

Box 9: Recommendations for patients with high risk MM:

The optimal management for patients with high-risk multiple myeloma remains uncertain. There is no proven risk stratification approach:

- *Consider using bortezomib-based regimen as part of induction treatment (grade A recommendation, level 1B 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)*
- *Consider tandem autologous stem cell transplant (grade B recommendation, level 2B 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[54]. At the current time there are insufficient data to determine if consolidation therapy improves long-term outcome in MM. The VCAT (Bortezomib Consolidation after Transplant) study has completed accrual and is maturing and may answer this question in due course.

Maintenance therapy with thalidomide post ASCT has proven to prolong both PFS and OS[104]. 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) [105, 106] was seen, and one study showed a significant reduction in risk of death[106]. Grade 3 neutropenia was the most frequent adverse-events. 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[91]. 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. It is unknown whether maintenance with lenalidomide is equivalent to maintenance with thalidomide in terms of efficacy or toxicity. 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:

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±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 possibly OS (Grade A recommendation, level 1B evidence). At present, lenalidomide is not registered for this indication and hence we cannot currently routinely recommended 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[104], 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[104]. 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 randomised 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 [88]. In contrast, in a preliminary analysis of the MM020 trial, continuous Ld until disease progression improved both duration of response by 13 months and OS ($p=0.017$) compared to a fixed duration of treatment with either Ld or MPT[89].

In transplant ineligible patients, two randomised studies have incorporated bortezomib maintenance. However, these trials were not designed to be able 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%, $p=0.04$)[87]. 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%[85] 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:

- *Routine maintenance therapy for transplant ineligible patients is currently not recommended:*
  - *Lenalidomide +/- dexamethasone appears to be most tolerable and promising as maintenance therapy, at least with respect to PFS benefit and possibly OS benefit. (Grade A recommendation, level 1B evidence). Lenalidomide is currently not TGA-registered in Australia for this indication.*
  - *Thalidomide maintenance therapy 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

Despite improved therapies, MM remains an incurable disease approximately one third of patients not responding to front-line therapy [107-109], and eventual relapse occurring in virtually all patients who obtain an initial response. If the rate of disease progression is slow and there are no clinical indications to recommence treatment patients can continue to be monitored for a while. The same criteria as used for initiating front line treatment can be used to decide the timing of salvage therapy. Currently, there is no one standard treatment for patients with relapsed myeloma. Management should be individualised taking into account of previous therapy, duration of response and physical status.

The main treatment options for relapsed/resistant disease are newer agents (thalidomide, bortezomib, lenalidomide and pomalidomide), alkylating agents, anthracyclines, bendamustine and corticosteroids administered alone or in various combinations, with selected patients undergoing HDT with AuSCT. The various agents can be used in different combinations and sequences. No best sequence has been defined (Figure 3; table 9).

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.[110, 111] Thalidomide and dexamethasone is associated with a superior RR of approximately 50-55% in the relapse/refractory setting [112, 113]. The addition of an alkylating agent (eg.cyclophosphamide or melphalan) increases RR to 75-80% [114, 115].

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) [116, 117] 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, the results of the ECOG E4A03 trial [118] recently demonstrated reduced toxicities and improved survival outcome with the use of lower dose dexamethasone (40mg/weekly), especially in patients aged > 65 years, however, this was in the front line setting.

More recently, 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)[119], 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[119]. 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)[120]. In Australia, as of the 1st of August 2015, pomalidomide in combination with dexamethasone is available on PBS for the treatment of MM in patients who have failed two or more prior therapies including lenalidomide and bortezomib.

Bortezomib monotherapy induces an ORR of approximately 35-40% in relapsed, refractory MM, with an average duration of response of 1 year.[121-123] The addition of dexamethasone induces a further ORR of 18%, in patients not responding to single agent bortezomib in the

SUMMIT and CREST trials. The recently completed Australian BOMER study which compared up-front BD to a matched cohort of patient on the APEX study (which only used dexamethasone in patients not responding to bortezomib alone) demonstrated a 20% improvement in RR and prolonged PFS in those receiving dexamethasone from cycle 1 [124]

Due to the heterogeneity and effectiveness of salvage therapy at subsequent relapses, it is difficult to compare OS outcome between different treatment regimens. However, incorporation of newer agents at first relapse appear to produce superior outcome compared to their use as later lines of salvage-treatment[125, 126]. Often, the choice of which agent to use at relapse not only depends on availability, but also on individual preference (oral vs. intravenous route of administration), and importantly, co-morbidities.

Drug selection may indeed depend on pre-existing 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[108].

In patients with relapsed disease that is rapidly progressive, intensive regimens combining newer agents with chemotherapy can be considered if the patient has good performance status and organ function. Alkylating agents such as cyclophosphamide and melphalan has 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[127]. In phase I and II trials, bendamustine was efficacious as monotherapy, and in combination with thalidomide, lenalidomide or bortezomib[128]. 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[129]

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.

HDT and ASCT can be considered in patients who have had a deep (at least PR) and durable (especially more than 9 months) response to this treatment modality in the past[130]. Similarly, if relapse occurs > 6 months following cessation of the last treatment regimen, the same regimen can again be considered, however, an inferior duration and quality of response is to be expected. Finally, when all newer agents and different treatment combinations have been exhausted, conventional doses of cyclophosphamide[131], non-myeloablative doses of melphalan[132], or low-modest doses of corticosteroids remain viable options, as is palliation in patients who cannot tolerate any further therapy. Please see box 12.

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, duration of response to prior therapy, tempo of disease progression, and current physical status. Common options are outlined in table 9.

The choice of newer agents used at relapse is dependent on local availability, access to delivery of intravenous therapy (i.e. bortezomib) and should take into consideration the side-effect profile in the setting of existing patient comorbidities.

If relapse occurs > 6 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

Second ASCT can be considered in a select group of patients who have achieved at least a PR and durable remission to the first ASCT.

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.

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

REGIMEN		EFFICACY	COMMENTS
THALIDOIMDE BASED			
TD **[1]**	Thalidomide 200mg po. daily Dexamethasone 40mg po. 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 **[2, 3]2, 3]**	Thalidomide 100mg po. Daily Cyclophosphamide 500mg po. weekly Dexamethasone 40mg po. 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 **[4]**	Thal 100mg po. daily Dexamethasone 40mg po. 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 40mg po. D1-4 Thalidomide 400mg po. daily Cisplatin 10mg/m^2 daily IV continuous infusion D1-4. Cyclophosphamide 400mg/m^2 daily IV. continuous infusion D1-4. Etoposide 40mg/m^2 daily IV continuous infusion D1-4. Doxorubicin 10mg/m^2 daily IV continuous 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 **[5]**	Dexamethasone 40mg po. D1-4 Thalidomide 400mg po. daily Cisplatin 15mg/m^2 daily IV continuous infusion D1-4. Cyclophosphamide 400mg/m^2 daily IV continuous infusion D1-4. Etoposide 40mg/m^2 daily IV continuous 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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REGIMEN		EFFICACY	COMMENTS
LENALIDOMIDE-BASED			
Len-dex **[6-8]**	Lenalidomide 25mg po. D1-21q28 Dexamethasone 40mg po. D1-4,9-12,17-20 (C1-4), 40mg po. D1-4 (C5 onwards) Consider using low dose dexamethasone (40mg per week) in view of the ECOG trial showing higher toxicity with standard dose dex [8] Cycles repeated every 28 days until disease progression.	Phase III trial (MM009/010) RR 60% CR~14-16%	Gde ≥3 neutropenia 30-40% Gde ≥3 thrombocytopenia 11% DVT 11-15% (no thrombo-prophylaxis) Gde ≥3 fatigue 6%
RCD **[9]**	Lenalidomide 25mg po. D1-21. Cyclophosphamide 500mg po. weekly Dexamethasone 40mg po. D1-4 and D12-15. Cycles repeated every 28 days for a maximum of 9 cycles. Ongoing maintenance with single agent lenalidomide may be considered. Consider using low dose dex (40mg per week) in view of the ECOG trial showing higher toxicity with standard dose dex [8]	Phase II trial. ORR 65%. CR 5% (one patient in 20)	Median time to best response is prompt (31 days). After 3 cycles, 48% of patients required dose reduction or withdrawal of cyclophosphamide, and 24% of patients required dose reduction of lenalidomide. G-CSF required in 57% of patients to maintain neutrophil count >1.
RAD **[10]**	Lenalidomide 25mg po. D1-21 Adriamycin 9mg/m^2 IV D1-4 Dexamethasone 40mg po. D1-4 and D17-20 Cycles repeated every 28 days for 6 cycles.	Phase I/II ORR 73% CR+VGPR 74%	Grade 3 and 4 neutropenia 48% Grade 3 and 4 thrombocytopenia 38. Severe infections 10.5%. Thromboembolic events 4.5%.
POMALIDOMIDE-BASED			
Pom-dex	Pomalidoimde 4mg po. D1-21 Dexamethasone 40mg po D1,8,15,22 Cycles repeated every 28 days until disease progression.	Phase III ORR 31% Med PFS 4m (patients who have failed at least 2 previous treatment including bortezoimib and lenalidomide)	Grade 3 and 4 anaemia 33% Grade 3 and 4 neutropenia 48% Grade 3 and 4 thrombocytopenia 22%

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REGIMEN		EFFICACY	COMMENTS
BORTEZOMIB-BASED **Note: Bortezomib, when given subcutaneously and/or as a weekly schedule have been shown to reduce neuropathy.**			
Bortezomib and Dexametahsone **[11]**	Bortezomib1.3mg/m^2 IV 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 **[12, 13]**	Cyclophosphamide 300mg/m^2 po. weekly. Bortezomib 1.3mg/m^2 IV 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 [14, 15] [16]	Bortezomib 1.3mg/m^2 IV 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 ≥neutropenia 20%. Gde ≥3 anaemia 11% Gde ≥3 peripheral neuropathy 10%
Bortezomib + Melphalan [17]	Bortezomib 1mg/m^2 IV 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 [18]	Bendamustine 70mg/m^2 IV D 1,4 Bortezomib 1.3mg/ m^2 D1,4,8,11 Dexamethasone 20mg po D1,2,4,5,89,11,12 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 ≥neutropenia 17%. Gde ≥3 anaemia 18% Gde ≥3 peripheral neuropathy 6%
BMPT [19]		Phase I/II trial. n=30 ORR 67%, VGPR 43%	Gde ≥3 AE = infections, fatigue, peripheral neuropathy.

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CHEMOTHERAPY			
Non-myeloablative melphalan [20]	Melphalan 25mg/m^2 IV	–	Myelosupression.
High dose cyclophosphamide [21]	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 [22]	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.

*Thalidomide is available for upfront treatment through the Pharmaceutical Benefit Scheme Highly Specialised Drug Program. Please visit http://www.health.vic.gov.au/hsdp

*Bortezomib, as monotherapy or in combination with a corticosteroid and/or cyclophosphamide, is available through the Pharmaceutical Benefit Scheme for patients with multiple myeloma 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/hsdp) for patients with multiple myeloma 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 available on the PBS for the treatment of MM in patients who have failed two or more prior therapies including lenalidomide and bortezoimb as of August 1, 2015.

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

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4 PROMISING NEW AGENTS

We are now moving beyond the era of first generation immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), with a number of efficacious new drugs that have emerged over the last few years. The group of drugs that are most advanced in clinical trials, if not already in clinical use, are the newer generation proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), monoclonal antibodies (mAb), and panobinostat, a histone deacetylase inhibitor (HDACi). These agents are currently not routinely available for the treatment of MM in Australia.

Newer generation proteasome inhibitors (PI): 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[3]. The first in class PI, bortezomib, is available in Australia on PBS and is widely used in the treatment of MM.

Amongst the newer PIs, carfilzomib is the furthest in clinical development. It is approved by the FDA (Food and Drug Administration) for the treatment of patients with MM who have had at least two prior therapies, including bortezomib and IMiD. As monotherapy, carfilzomib induces an ORR of 52% in patients with RRMM[133], and 20% in patients who are refractory to bortezomib[134]. Unprecedented efficacy is seen when carfilzomib is combined with lenalidomide and dexamethasone (KRd). Results from the ASPIRE trial showed that combination KRd induced a PFS of 26.3m in patients with RRMM, of whom 37% were previously treated with both boretzomib and lenalidomide [135]. Neuropathic toxicities were uncommon. In the recent phase III ENDEAVOR trial, carfilzomib in combination with dexamethasone (Kd) was shown to be superior to combination bortezomib and dexamethasone for patients with RRMM with respect to ORR (77%(Kd) vs. 63%, p<0.0001) and median PFS (18.7 (Kd) vs. 9.4 months, p<0.0001)[136].

Other second generation PIs include Oprozomib (ONX-0912; previously pR047), Ixazomib (MLN 9708), and Marizomib (NPI-0052)[3]. Both oprozomib and ixazomib are orally bioavailable, and both 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.

Newer generation IMiDs: Immunomodulatory drugs 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[137]. 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 uniquitin ligase complex. This interference of ubiquitin ligase function in turn result in alteration in key proteins (200+) such as ikaros which alter downstream gene promotion of survival and immune regulatory genes[3].

Thalidomide and lenalidomide have been approved and widely used for the treatment of MM. More recently, pomalidomide has emerged as a potent second generation IMiD [119] and has been made available through the Australian PBS for the treatment of patients with relapsed myeloma who have failed lenalidomide and bortezomib. Like lenalidomide, the main side effects of pomalidoimde are haematological toxicities, while neuropathic toxicities are low. Venous thromboembolic complications are also low, especially when prophylactic measures are used.

Monoclonal antibodies (mAb): The three mAb that are furthest along in clinical trials for the treatment of MM are Elotuzumab, Daratumumab and SAR650984. 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 resulted an ORR of 92% and unprecedented PFS of 32 months in a group of patients with median 2 prior lines of therapy[138]. Final results of the phase III registration enabling trial comparing elotuzumab-lenalidomide-dexamethasone (ELd) to lenalidomde-dexamethasone (Ld) have recently been published[139]. Median PFS was superior in the ELd arm (19.4m (ELd) vs. 14.9m, p <0.001). Interestingly, it appears that the difference in the PFS between the two arms is maintained well beyond 24 months; longer follow up is required to see whether the two curves in PFS diverges.

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 42% in a dose escalation study, in a group of heavily pretreated patients who had a median of 6 prior line of treatment[140]. In combination with lenalidomide and dexamethasone, preliminary results from a phase II study showed ORR of 100% during the dose escalation phase and 87% during the cohort expansion phase[141]. Phase III trials of daratumumab-lenalidomide-dexamethasone combination are ongoing for both relapsed/refractory and front line setting.

SAR650984 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%; ≥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[142].

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[143]. Several HDACi have been tested in MM such as panabinostat, 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[144]. 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[145]. 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[143].

5 CONCLUDING REMARKS

The treatment for multiple myeloma has changed substantially over the last decade and what is considered as standard therapy will continue to change as trial data matures with respect to newer-therapeutic agents. At present, MM remains an incurable disease. However, treatment options continue to increase, rendering this a treatable chronic condition. The above treatment guidelines from the Australian Myeloma Scientific Advisory Group (MSAG) to the Myeloma Foundation of Australia are based on current published data and clinical experience. We believe a National consensus for a treatment algorithm of MM will not only improve patterns of care, but will establish a foundation for future clinical studies.

The above guideline is based on up-to-date information as of August 2015. Some aspect of this guideline may change in the future depending on emerging data from clinical studies. This guideline is due for review in December 2016.

The authors of this guideline declare no potential conflict of interest. This guideline was unsolicited and was established by members of the MSAG without the assistance of or influence by any other organisational body or pharmaceutical company.

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