MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG)
TO MYELOMA AUSTRALIA (MFA)

Clinical Practice Guideline
MULTIPLE MYELOMA

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Myeloma Australia

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TABLE OF CONTENTS

1 INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells characterised by an abnormal serum and /or urine immunoglobulin or free immunoglobulin light chain as a result of clonal expansion of plasma cells. It is often accompanied by complications of enhanced bone loss associated with diffuse osteopenia or focal lytic lesions, renal failure, hypercalcaemia, immune suppression and anaemia. As of 2017, approximately 2100 new cases are diagnosed in Australia each year, with median age at diagnosis of approximately 70 years [1].

The armamentarium for treatment of patients with MM have continued to expand over recent years on top of the current back bones of first generation proteasome inhibitors (PI; bortezomib (Velcade®) and immunomodulatory drugs (IMiDs: thalidomide (thalomid®), lenalidomide (Revlimid®) and pomalidomide (Pomalyst®) to include second generation PIs (carfilzomib [Kyprolis®] and ixazomib [Ninlaro®]) and monoclonal antibodies (elotuzumab [Empliciti®], daratumumab [darzalex®] and isatuximab), as well as a number of new classes of therapeutics that are under active investigations. These include novel immune approaches including immune drug conjugates, Bispecific T-cell Engagers (BiTEs), chimeric antigen T cell receptors (CAR-T) and immune check point inhibitors, as well as small molecules such as BH3-mimetics (Bcl-2 and MCL1 inhibitors), selective inhibitor of nuclear export (SINE; selinexor), and inhibitors of human translation elongation factor 1α2 (eEF1A2; plitidepsin [Aplidin®]).

Although drug access may vary between different parts of the world, there are global consensus on fundamental treatment principles that guide treatment. The following guideline for the effective treatment of MM focusses on drugs that are either reimbursed or can be accessed through other avenues in Australia. This guideline is a consensus established by the Medical Scientific Advisory Group (MSAG) to Myeloma Australia, which consists of a panel of haematologists across Australia. Levels of evidence and grades of recommendations in this guideline are as outlined in table 1

Table 1: Level of evidence and grades of recommendations.

LEVELS OF EVIDENCE	
1A	Evidence from meta-analysis of randomised control trials
1B	Evidence from at least one randomised controlled trial.
2A	Evidence from at least one well-designed non-randomised trial, including phase II trials and case-control studies
2B	Evidence from at least one other type of well-designed, quasi-experimental study such as observational studies.
3	Evidence from well-designed non-experimental descriptive studies.
4	Evidence obtained from expert committee reports or opinions and/or of respected authorities.
GRADES OF RECOMMENDATIONS	
A	Recommendation based on at least one 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 increased bone marrow plasma cells[2]. There are three stages of disease: An initial premalignant stage termed monoclonal gammopathy of uncertain significance (MGUS), followed by smouldering (or asymptomatic) MM and MM (previously termed symptomatic MM) that is now defined by myeloma defining events including the presence of end organ damage (specifically hypercalcaemia, renal impairment, anaemia and bone lesions (CRAB features) and/or the presence of three specific biomarkers (so called SLiM CRAB criterias) in people with no CRAB features including: clonal bone marrow plasma cells ≥ 60%, serum free light chain (FLC) ratio ≥ 100 (provided involved FLC level is ≥ 100 mg/L), or more than one focal lesion on MRI (Table 3).

Multiple myeloma is almost always preceded by MGUS[2]. Table 2 and 3 outline the criteria for the diagnosis of MGUS, smouldering and symptomatic MM.

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

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)	SMOULDERING MYELOMA	MULTIPLE 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 κ 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. - Absence of myeloma defining events (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 (table 3) - No evidence of amyloidosis.	Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma **and** presence of Myeloma defining events (table 3).

Table 3: Myeloma defining events.

END ORGAN DAMAGE (CRAB)	
C-Increased calcium level	Corrected serum Calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
R-Renal insufficiency	Creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/dL)
A-Anaemia	Hb <100g/L or 20g/L below the lower limit of normal
B-Bone lesions	One or more osteolytic lesions on skeletal radiography, CT, or PET-CT
BIOMARKERS OF MALIGNANCY (SLiM-CRAB criteria)	
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. Genetic heterogeneity and disease biology across different patients and even between different myeloma clones within the same patients with MM is vast, and currently, the implication this has to therapy is still poorly defined. Nonetheless, using commonly available prognostic markers (table 5), a group of crudely defined high-risk patients can be identified that can in turn impact on treatment decisions. 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[3].

Currently, the most widely adopted prognostic model is the revised international staging system (R-ISS; table 4). This model is based on the traditional ISS that incorporates serum levels of ß2microglobulin (ß2M) and albumin, as well as LDH and high-risk FISH (del17p and t(4;14)) [4]. The R-ISS risk stratification system identifies 3 different MM prognostic groups in patients who were treated in the era of IMiDs and proteasome inhibitors and supersedes the conventional ISS staging system.

A number of molecular methods for risk stratification have emerged in recent years such as gene expression profiling, SNP (single nucleotide polymorphism)-based mapping arrays and comparative genomic hybridisation. At present, these techniques are only used in the setting of clinical trials.

Table 4: Revised International Staging System [4].

REVISED INTERNATIONAL STAGING SYSTEM (R- ISS)			
Stage	**Criteria**	**Med OS***	**5 Year OS**
R-ISS I	- ISS I (Serum ß2M <3.5mg/l and serum Albumin >35g/l) *AND* - Normal LDH *AND* - No high-risk FISH profile (defined as del17p and/or t(4;14) and/or t(14;16))	NR	81%
R-ISS II	Patients failing to meet criteria for R-ISS I or III.	83m	62%
R-ISS III	ISS III (Serum ß2 microglobulin >5.5mg/L) *AND* High risk FISH OR High LDH	43m	39%

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

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

HIGH RISK FACTORS	The following tests for high-risk disease are routinely available in Australia and are recommended.
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 (See section 2)

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

Figure 1: Initial diagnostic work up

ALL PATIENTS SUSPECTED OF HAVING MULTIPLE MYELOMA[1].

Haematology:
- Full blood count (FBC), differential & blood film.

Biochemistry:
- U&E, Ca^{++}, PO_4/Mg^{++}, urate
- LFT, Albumin
- ß2 Microglobulin, LDH, C-reactive protein (CRP)
- Serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE).
- 24 hour urine collection: protein excretion, CrCL, Bence Jones Protein.
- Serum free light chain (SFLC)[2].

Bone marrow aspirate and trephine.
- Morphology; immunohistochemistry: CD138 (κ and λ light chain expression, p53)
- Cytogenetics (if % plasma cells in the aspirate is >15%)[3]
- FISH for: t(4;14), t(14;16), t(14;20), t(11;14) 17p del, 1q21 amplification[3].
- Flow cytometry: CD138, CD19, CD56, κ and λ light chain expression[4].

Imaging:
- Skeletal survey or whole body low-dose CT.

SELECTED CASES:
- Full axial and pelvis MRI:
  - in patients with severe back pain, severe bony disease, suspected vertebral compression, or suspected solitary plasmacytoma (Grade B, level 3 evidence), or
  - in patients without myeloma defining events (ie. CRAB, section 3.1) but in whom positive biomarker of malignancy with MRI lesions is suspected.
- Tissue biopsy to diagnose extramedullary or osseous plasmacytoma
- Bone densitometry in patients with suspected osteoporosis.

MGUS and smouldering myeloma.
Follow up as per figure 2.

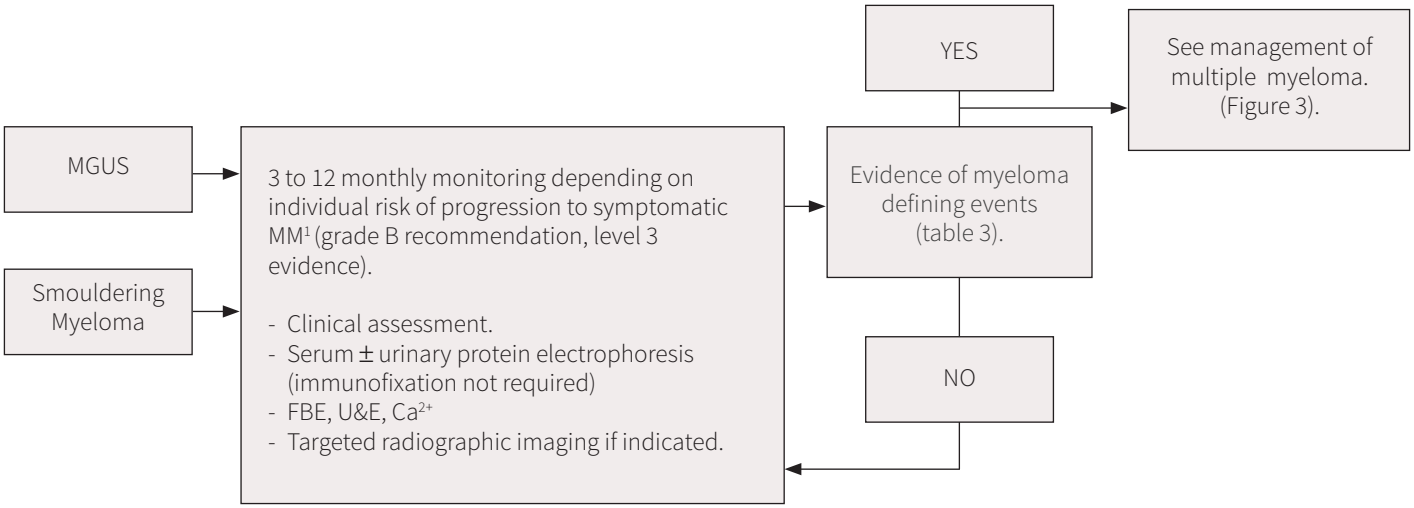
Multiple myeloma
(ie. presence of myeloma defining events (table 3)).

ADDITIONAL INVESTIGATION UPON REQUIREMENT OF TREATMENT:

SELECTED PATIENTS:
- Viral serology: Hep B, Hep C, CMV, VZV.
- HLA typing for siblings/extended family if aged <65 years
- Sestamibi scan[4] (Grade B, level 3 evidence)
- PET scan[4] (Grade B, level 3 evidence)
- Gated blood pool scan or echocardiogram in patients with cardiac history and considered for anthracycline therapy. (Grade C, level 4 evidence).
- Echocardiogram or cardiac MRI if amyloid is suspected (Grade C, level 4 evidence).

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 [5]
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 [6].
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. Additional markers for the standardised detection of minimal residual disease is as per the Euroflow-based next generation flow approach [7]
5. 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% [8]. MIBI is more sensitive in detecting soft and skeletal lesions compared to conventional radiography. In MGUS patients, MIBI is always negative [8-10]. Sensitivity of PET in detecting myelomatous involvement is ~85% and specificity is ~92% [10]. 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

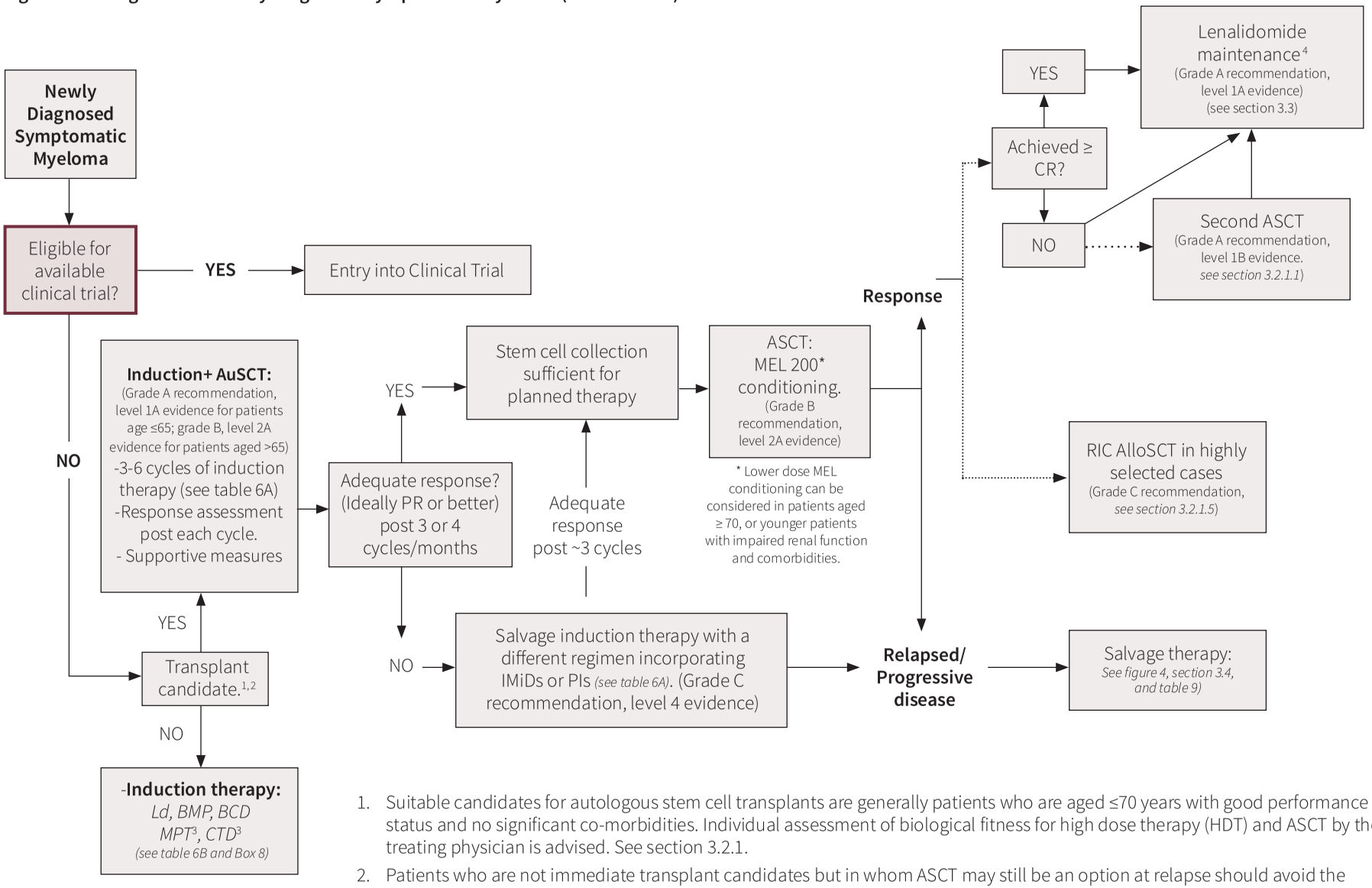
Figure 2: Management of MGUS and Smouldering Myeloma (see section 3.1).



[1]For MGUS:

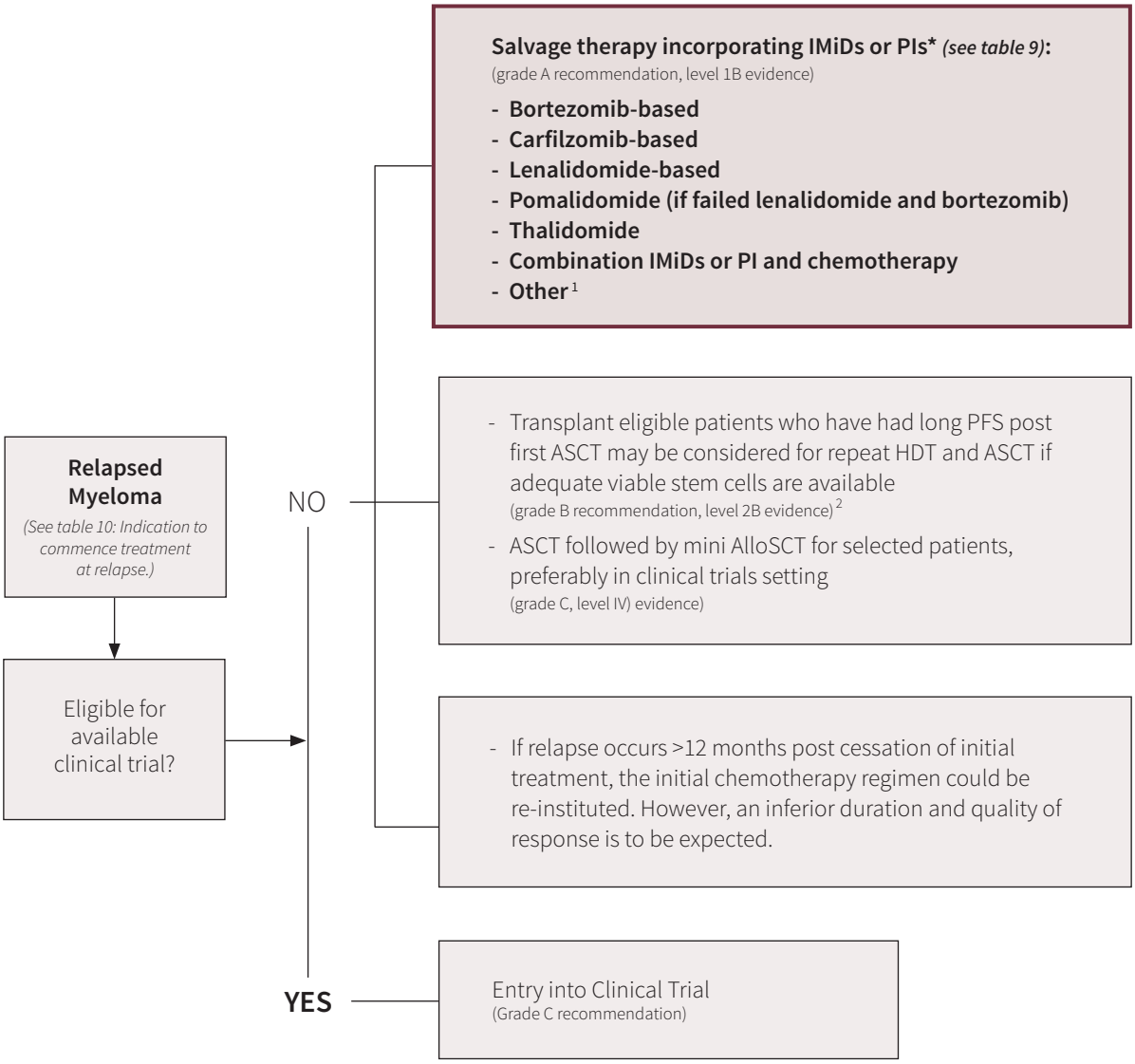
- When serum paraprotein level is ≤15g/l and stable, IgG type, and normal SFLC kappa: lambda ratio, SPEP can be repeated annually.
- When paraprotein value is >15g/l or there is an abnormal SFLC kappa:lambda ratio, a bone marrow aspirate and trephine is considered if paraprotein is rising to assess for 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 [11].

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



1. Suitable candidates for autologous stem cell transplants are generally patients who are aged ≤70 years with good performance status and no significant co-morbidities. Individual assessment of biological fitness for high dose therapy (HDT) and ASCT by the treating physician is advised. See section 3.2.1.
2. Patients who are not immediate transplant candidates but in whom ASCT may still be an option at relapse should avoid the alkylating agent melphalan so as not to compromise potential stem cell harvest. Induction regimens without melphalan are outlined in table 6A.
3. Thalidomide-based induction should only be used in patients in whom there is a contraindication to lenalidomide or bortezomib-based treatment.
4. In July 2019, lenalidomide received positive PBAC (pharmaceutical benefit advisory committee) recommendation for maintenance therapy for NDMM post ASCT. Until it is formally reimbursed on PBS, note that long consolidation with thalidomide post ASCT is recommended over no treatment (see section 3.3 and recommendation box 10).

Figure 4: Management of relapsed Myeloma (please see section 3.4)



1. Note: A number of novel agents have been approved by the US FDA (Food Drug Administration) and/or the Australian TGA (Therapeutic Goods Administration) for the treatment of RRMM (see section 4.0) but are currently not reimbursed by the Australian PBS for the treatment of MM. These include second generation proteasome inhibitor ixazomib, mAbs including daratumumab and elotuzumab, the HDACi panabinostat, and the novel eEF1A2 inhibitor Plitidepsin. Please refer to section 4.0.
2. Data from the British Blood and Bone Marrow Transplant Registry suggested that a PFS of at least 9 months to the first ASCT is associated with improved survival outcome to a second ASCT in relapsed MM (Cook et al. Biol Blood Marrow Transplant 2011). In the era of novel therapies, most myeloma experts in Australia would consider a second ASCT for salvage therapy upon at least 12-18 months to the first ASCT.

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

This table summarises the commonly used induction regimens and is not intended to be exhaustive.
Please refer to Box 3 Recommendation for induction therapy prior to ASCT.

REGIMEN	SCHEDULE	RESPONSES AND COMMENTS	
BORTEZOMIB-BASED			
CyBorD/BCD [52, 171, 172]	Bortezomib 1.3mg/m^2 IV D1,4,8,11 Cyclophosphamide 300mg/m2 po D1,8,15,22 (or cyclophosphamide 900mg/m2 IV D1) Dexamethasone 20mg po on day of and day after bortezomib. Cycles repeated every 21 days x for 3-4 cycles prior to ASCT	ORR 88%, ≥VGPR 61% post induction	This is the most commonly used induction regimen for TE patients in Australia, according to the Australian and New Zealand MRDR.
	Or Bortezomib 1.5mg/m^2 wc D1,8,15,22 Cyclophosphamide 300mg/m2 po D1,8,15,22 Dexamethasone 20mg po on day of and day after bortezomib. Cycles repeated every 28 days x for 3-4 cycles prior to ASCT	ORR 93%, ≥VGPR 60% post induction	
BD [48, 85]	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 [53, 107, 173]	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	
IMMUNOMODULATORY DRUGS-BASED			
CTD [50, 174]	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% Second most commonly used induction regimen for TE patients in Australia, according to the Australian and New Zealand MRDR.	
TAD [51]	Thalidomide 200mg po daily Doxorubicin 9mg/m^2 IV rapid infusion, D1-4 Dexamethasone 40mg po, days 1-4, 9-12, and 17-20 Cycles repeated every 28 days for 3-4 cycles prior to ASCT.	ORR with TAD 72% vs. 54% with VAD, p<0.001. CR+VGPR higher post ASCT in TAD arm (49% vs. 32%, p<0.001))	
TD [47, 175, 176]	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%. [47] When Thalidomide is used for TE patients, a triplet combination (eg. CTD) is preferable to TD as the response to the latter is not much better than that seen with conventional chemotherapy.	

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REGIMEN	SCHEDULE	RESPONSES	
Ld [177]	Lenalidomide 25mg po daily d1-21 every 28 days Dexamethasone 40mg po weekly. Cycles repeated every 28 days for 3-4 cycles prior to ASCT, otherwise, until disease progression.	CR/VGPR 42% post induction.	In Australia, lenalidomide is currently not reimbursed by the PBS for the initial induction in patients in TE patients with MM as of October 2019.
LCD [54, 130]	Lenalidomide 25mg po daily d1-21 every 28 days Cyclophosphamide 300mg/m^2 po daily D1,8,15 Dexamethasone 40mg po daily, D1,8,15, and 22 Cycles repeated every 28 days for 3-4 cycles prior to ASCT,	VGPR 38%, CR 2% post induction	
COMBINATION PI AND IMIDS			
BTD [55]	Bortezomib 1.3mg/m2 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	In Australia, combination of PI and IMID is not yet reimbursed by the PBS for induction therapy in TE patients with NDMM, as of October 2019.
(BTDC) [178]	Bortezomib 1.3mg/m2 IV D1,4,8,11, Dexamethasone 40mg po D1-4, 9-12 Thalidomide 100mg po daily Cyclophosphamide 400mg/m2 IV D1, 8. Cycles repeated every 21 days for 3 cycles prior to ASCT, or additional 4 cycles for patient who became ineligible for ASCT.	Post induction: ORR 96%; CR/nCR 44% post ASCT : ORR 100%; CR/nCR 78%	
BLD [31]	Bortezomib 1.3mg/m^2 IV D1,4,8,11, Lenalidomide 25mg po D1 to 14 Dexamethasone 20mg po, days 1,2,4,5,8,9,11,12 Cycles repeated every 21 days for 3 cycles prior to ASCT and additional 2 cycles post ASCT prior to maintenance.	ORR 99% ≥VGPR 59%	
CHEMOTHERAPY-BASED			
CID [179]	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 [180]	Doxorubicin 30mg/m^2 IV D1, Carmustine 30mg/m^2 IV D1, Cyclophosphamide 600mg/m2 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)	

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

SCHEDULE	SCHEDULE	RESPONSES AND COMMENTS	
LENALIDOMIDE-BASED			
Ld [87]	Lenalidomide 25mg po daily, days 1-21. Dexamethasone 40mg po daily, days 1,8,15,22 Cycles repeated every 4 weeks. Treatment until disease progression.	ORR 75% (CR15%)	Ld is reimbursed by the Australian PBS for the upfront treatment of MM. Continuous Ld is superior to fixed duration (18m) Ld with respect to PFS, and is superior to MPT in PFS and OS MPL is less well tolerated in patients over the age of 75. Note, PBS-reimbursed lenalidomide can only be used in combination with dexamethasone (Ld)
LCd [130]	Lenalidomide 25mg po daily, days 1-21. Dexamethasone 40mg po daily, days 1,8,15,22 Cyclophosphamide 300mg/m2 days1,8,15	ORR 85% ≥ VGPR 47%	
MPL-(L) [181]	Melphalan 0.18mg/kg po D1-4 Prednisone 2mg/kg po D1-4 Lenalidomide 10mg po daily Cycles repeated every 4 weeks x 9 ± lenalidomide continued until relapse.	ORR 77%, CR 16% Med TTP 24.7m 2 yr OS 86.2%	
BORTEZOMIB-BASED			
BMP [84, 86, 126]*	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 improves 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 [84, 86] or alternatively bortezomib 1.3mg/m^2 or 1.5mg/m2 weekly.[182]. **Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved toxicity profile[82].	CR 24-30% Med PFS 22-27m 2-year OS 85-87%.	Bortezomib is reimbursed by the Australian PBS for the upfront treatment of MM in Australia with or without alkylating agents. Triplet combination (bortezomib + alkylating agent + dexamethasone) is more efficacious compared to doublet combination (bortezomib + dexamethasone. Cyclophosphamide is often preferred over melphalan due to better tolerability and equivalent efficacy. Doublet combination may be more tolerable and is acceptable for the elderly frail patient.
BCD [52]*	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.	ORR 82% CR 12%	

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SCHEDULE	SCHEDULE	RESPONSES AND COMMENTS	
BORTEZOMIB-BASED… *CONTINUED*			
Bd [85]*	Bortezomib**: 1.3 mg/m² 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/m² IV D 1,8,15,22 every 5 weeks for nine cycles [84, 86] or alternatively Bortezomib 1.3mg/m2 or 1.5mg/m2 weekly.[181]. **Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved toxicity profile[82]. ***Low dose dexamethasone, 40mg weekly (or 20mg weekly for patients aged >75 years) have been shown to be more tolerable and has largely replaced the alternative dexamethasone schedule outline below.	ORR 88% (CR 6%)	Bortezomib is reimbursed by the Australian PBS for the upfront treatment of MM in Australia with or without alkylating agents. Triplet combination (bortezomib + alkylating agent + dexamethasone) is more efficacious compared to doublet combination (bortezomib + dexamethasone. Cyclophosphamide is often preferred over melphalan due to better tolerability and equivalent efficacy. Doublet combination may be more tolerable and is acceptable for the elderly frail patient.
THALIDOMIDE-BASED			
MPT [94]	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	Thalidomide is reimbursed by the Australian PBS for the upfront treatment of MM in Australia. Thalidomide-based regimens remain an effective treatment option for induction therapy in transplant ineligible patients, however, treatment is hampered by toxicities, mainly peripheral neuropathy. As such most patients will tolerate a maximum of 12 months of treatment. Doublet thalidomide and dexamethasone is not superior to MP owing to greater toxicities, particularly in patients age above 75 years, and is therefore not commonly used.
CTDa [95]	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 6 to 9 cycles every 3 weeks.	CR 13% Med PFS 13m Med OS 33m	

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SCHEDULE	SCHEDULE	RESPONSES AND COMMENTS	
COMBINATION BORTEZOMIB AND THALIDOMIDE OR LENALIDOMIDE			
BLd[92]	Eight 21-day cycles: Bortezomib: 1.3 mg/m² IV D 1, 4, 8, and 11 Lenalidomide: 25 mg orally on days 1-14 Dexamethasone: 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 Followed by 28-day cycles until disease progression, of: Lenalidomide 25 mg orally days 1-21 Dexamethasone 40 mg oral once a day for days 1, 8, 15, and 22.	CR 37% PFS at 18m 75% OS at 18m 97%	At the time of publication of this guideline, combination BLd received positive recommendation by the Australian PBAC for the upfront treatment of transplant ineligible patients with multiple myeloma, and is anticipated be reimbursed on the PBS.
BLd-Lite[93]	Nine 35-day cycles of: Bortezomib: 1.3mg/m² sc days 1,8,15,22, Lenalidomide: 15mg orally daily on days 1-21 Dexamethasone: 20mg orally on the day of and day after bortezomib (or days 1,8,15,22 for patients age >75 years) Followed by six 28-day cycles of: Bortezomib: 1.3mg/m² sc days 1 and 15 Lenalidomide 15mg po days 1-21.	ORR 86% ≥VGPR 66% PFS 35.1m OS not reached at med follow-up of 30m.	BLd-lite appears to have comparable efficacy with reduced toxicity, in particular, reduced peripheral neuropathy.
BTP[84]	Bortezomib: 1.3 mg/m² given IV D 1, 4, 8, 11, 22, 25, 29, and 32 (cycle 1), every 6 weeks, and 1.3 mg/m2 on days 1, 8,15, and 22 every 5 weeks (cycles 2 to 6). Thalidomide: 100 mg/day orally daily every cycle for 6 cycles. Prednisone: 60 mg/m² given orally on days 1-4 every cycle for six cycles	CR 28% Med PFS 31m 3 year OS 70%	
BLCd	Bortezomib: 1.3 mg/m² IV D 1, 4, 8, and 11 every 3 weeks for maximum 8 cycles. Lenalidomide: 15 mg orally on days 1-14 every 3 weeks for maximum eight cycles. Cyclophosphamide 500mg/m² orally on days 1, 8 every 3 weeks for maximum 8 cycles. Dexamethasone: 40mg orally days 1, 8, 15, every 3 weeks for maximum eight cycles.	CR 25% 1 year PFS 86%	Quadruplet-combinations of bortezomib BLCd or BMPT are not superior to triplet-combinations with respect to survival outcome, but is more toxic.
BMPT [86]	Bortezomib: 1.3 mg/m² IV days 1, 8, 22, 29, every 6 weeks for nine cycles Melphalan: 9 mg/m² orally on days 1-4 every 6 weeks for nine cycles Prednisone: 60 mg/m² 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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SCHEDULE	SCHEDULE	RESPONSES AND COMMENTS	
DARATUMUMAB COMBINATIONS			
Dara-BMP [157]	Daratumumab 16mg/kg IV weekly C1 Every 3 weeks C 2-9 Every 4 weeks C10+ Bortezomib 1.3mg/m² sc 1,4,8,9,15,16,22,25,29,32 every cycle for C1-9 Melphalan 9mg/m² po D1-4 every cycle for C1-9 Dexamethasone 20mg po/IV weekly C1 Every 3 weeks C2-9 Every 4 weeks C10+ Cycles repeated every 42 days during C1-9. Cycles repeated every 28 days during 10+ until disease progression.	≥CR 42.6% 18m PFS 71.6%	In Australia, daratumumab is TGA registered for NTE NDMM in combination with BMP. TGA submission for Dara-Ld has yet to occur as of June 2019. Daratumumab is currently not reimbursed on PBS for the treatment of MM as of March 2019
Dara-Ld [156]	Daratumumab 16mg/kg IV weekly C1 Every 2 weeks C 3-6 Every 4 weeks C7+ Lenalidomide 25mg po daily D1-21 Dexamethasone 40mg po weekly Cycles repeated every 28 days until disease progression.	≥CR 48% 30m PFS 71%	

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[12]; 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[13].
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, lenalidomide or pomalidomide 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[14]
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 guidelines. • Valaciclovir, aciclovir or famciclovir prophylaxis against Varicella Zoster reactivation in patients receiving proteasome inhibitors, especially when used in combination with dexamethasone. • Trimethoprim-Sulfamethoxazole prophylaxis against Pneumocystis Jiroveci in patients who are on high dose corticosteroids that is equivalent to at least 20mg of prednisolone daily for at least 4 weeks. Dapsone, Pentamidine or Atovaquone are possible second line prophylactic agents if Trimethoprim-Sulfamethoxazole is contraindicated. • Patients should be vaccinated against hepatitis B, pneumococcus, influenza and other pathogens deemed necessary because of epidemiologic prevalence. Live vaccines should be avoided. Non-immune close contacts of patients should also be vaccinated[15]
Other prophylaxis	• Proton pump inhibitor or histamine H2-receptor antagonist is recommended in patients receiving ongoing corticosteroids

3 MANAGEMENT OF MULTIPLE MYELOMA – AN OVERVIEW

Between 2012 to 2018, patients with MM in Australia had a median OS of 5 years according to data from the Australian Myeloma and Related Diseases Registry (MRDR; www.mrdr.net.au), but this is anticipated to improve with better standards of care and expanding treatment options. The expansion of effective treatments 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 [2]

The average risk of progression from monoclonal gammopathy of uncertain significance (MGUS) to symptomatic myeloma is approximately 1% per year[16]. For SMM, the median time to progression is between 12 to 32 months[17]. 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)[17] 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[18].

There are two schools of thought with respect to proposed future management of high-risk SMM. The first is that of an aggressive approach akin to that for active MM, with the ambitious aim to cure, given that myeloma cell clones may be more amenable to complete eradication at this stage. The second is that of a gentler approach with the aim of delaying progression and perhaps OS. The initial phase III QuiRedex study that showed improved OS with Rd compared to placebo for high-risk SMM is no longer interpretable in the context of SMM, as a proportion of the so called high-risk SMM in that study had MM based the SLiM CRAB criteria [19]. Following that study, the Spanish GEM-CESAR study adopted an aggressive approach for patients with HRMM (excluding patients with SLiM CRAB criteria), with 6 cycles of induction KRd (carfilzomib, lenalidomide and dexamethasone) followed by MEL200 ASCT, 2 cycles of KRd consolidation, then Rd maintenance), and reported ORR 100% with CR 75% and MRD negativity of 60%. This high rate of response ought to be weighed up with the potential morbidity and spectrum of long-term consequences of ASCT in what is smouldering disease. Meanwhile, the phase II CENTAURUS study of daratumumab (in three different schedules) for patients with HR-SMM reported a favourable safety profile and efficacy (ORR up to 56%) and has led way to an ongoing phase III AQUILA study of daratumumab monotherapy in patients with HR 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).

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

Monitoring should include a clinical assessment, full blood evaluation, renal function, electrolytes including calcium levels, serum ± urinary paraprotein, and targeted radiographic imaging when indicated. (Grade C recommendation).

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

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

While confirmatory studies are awaited, commencing anti-myeloma treatment for patients with HR-SMM ought to be part of clinical trials and is currently not recommended as part of standard of care. Figure 2 and Box 1 outlines the recommended follow up algorithm for patients with MGUS and SMM.

3.2 UPFRONT TREATMENT OF MULTIPLE MYELOMA – AN OVERVIEW:

Initial treatment for patients with newly diagnosed MM (NDMM) depends on their eligibility for high dose therapy (HDT) and autologous stem cell transplant (ASCT), that is in turn dependent on the patient's age, comorbidities and functional status. Whether or not ASCT is incorporated as part of initial treatment, the aim is to induce a maximal depth of response, especially complete response (CR), without unacceptable toxicities. CR is associated with prolongation of PFS and OS [20, 21]in both the ASCT[22-24] and non-ASCT setting[21, 25, 26], 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[27]. 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[28]. Currently, CR is considered an objective of initial treatment, provided there is no unacceptable toxicity. Amongst patients with CR, MRD (minimal residual disease) negativity as defined by multi-parameter flow cytometry, polymerase chain reaction or next generation sequencing, has been shown to correlate strongly with OS. MRD negativity is increasingly accepted as a surrogate correlate for improved OS[29]. At present, methods for assessment of MRD are not consistent across laboratories and generally only available in tertiary treatment centres in Australia. MRD is not generally used to influence treatment decisions and is therefore mainly used in the clinical trial setting.

3.2.1 Patients eligible for ASCT:

The superiority of ASCT (when used as part of initial therapy) over a non-transplant approach has now been confirmed in the era of IMiDs and proteasome inhibitors in four randomised phase III trials. In both the GIMEMA MM-RV-209[30] and EMN MM-RV-441 trial, patients age <65 years were given lenalidomide-dexamethasone induction prior to stem cell collection, then randomised to either ASCT or a further 6 cycles of MPL (Melphalan, Prednisone, Lenalidomide; GIMEMA trial) or CLD (cyclophosphamide, lenalidomide, dexamethasone; EMN trial). Both studies have demonstrated superiority of the ASCT approach as part of initial treatment with respect to PFS and OS. Similar results were seen in the phase III IFM 2009 study evaluating bortezomib lenalidomide dexamethasone (BLd) induction with or without upfront ASCT, then lenalidomide maintenance. Marked improvement in PFS was seen with the upfront ASCT approach (HR 0.69, p<0.001) [31]. Importantly, an impressive superiority in the rate of MRD negativity was seen with the ASCT approach (80% (ASCT arm) vs. 65%, p 0.001), which in turn is generally correlated with improved OS[29]. Finally, in the EMN02/HO95 study, incorporating ASCT as part of initial treatment was superior to ongoing VMP (bortezomib, melphalan, and prednisone) with respect to PFS[32] Meta-analysis of the major studies indeed confirmed superior PFS by incorporating ASCT to initial treatment[33]. However, longer-term follow up is required to delineate any OS benefit, which will also be affected by subsequent therapies.

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

3.2.1.1 Tandem vs. Single ASCT

Prior to the era of IMiDs, PIs, and other novel therapeutic agents, tandem ASCT (in which the second ASCT is planned to occur 3 to 6 months after the first) was found to benefit mainly patients who have not achieved at least VGPR to the initial transplant[37, 38]. The role of routine tandem ASCT in the era of effective induction (IMIDs and/or PI) and effective maintenance remains a matter of debate, but there is a stronger rationale for patients with high-risk disease.

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 that was not designed to compare single versus double ASCT, but rather single transplant plus thalidomide maintenance therapy versus tandem

transplant, ie. thalidomide maintenance post single ASCT improved PFS thus confounded the result [40]. Indeed when that study was retracted from the meta-analysis, tandem transplant resulted in improved EFS, but not OS.

In a more recent long-term follow up (median 117 months) analysis of data combined from three European phase 3 studies (GIMEMA MMY -3006, PETHEMA/GEM and HONVON65MM/GMMG-HD41), tandem ASCT resulted in superior PFS (HR 0.76 (p=0.001) and OS (HR 0.69 (p<0.001) compared with single ASCT. Subgroup analysis demonstrated superiority in the tandem ASCT arm particularly in patients with high-risk cytogenetics, higher ISS stage and in patients who have not achieved CR , but not in patients with low-risk disease (ISS 1)[41].

Conversely, the primary analysis of the ongoing BMT CTN 0702 – StaMINA trial, tandem ASCT had no impact on PFS and OS compared to single ASCT when effective induction (combination IMID and PI) and lenalidomide maintenance was incorporated (see section on consolidation)[42]. One criticism of the StaMINA study however, is that patients were allowed to receive more than 4 (up to 12) cycles of induction therapy prior to randomisation to second ASCT/other consolidation, which, in itself may have had a consolidative effect.

At present, tandem ASCT with its associated acute toxicity may be a reasonable strategy in selected patients who have had a suboptimal response to first transplant, and in particular patients with high-risk MM[43]. Otherwise, consolidation or maintenance therapies with newer agents, and effective salvage therapies in the current era, may well mitigate any OS advantage of tandem ASCT over single ASCT. Our recommendations for transplant eligible patients is as outlined in Box 2.

Box 2: Recommendation for transplant eligible patients:

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

Tandem ASCT may be considered particularly in patients with high-risk cytogenetics, who have not achieved CR after the first ASCT. (Grade A recommendation, level 1B evidence).

3.2.1.2 Induction therapy prior to ASCT

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 response is associated with better post-transplant outcome[44].

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

Immunomodulatory drugs (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 and Aiolos which alter downstream gene promotion of survival in plasma cells and immune regulatory genes in T cells[45]. Through cereblon, IMiDs increase T-cell costimulation and enhance NK cell activity, in addition to other antimyeloma activities including induction of apoptosis and antiangiogenesis[46].

Induction-regimens that incorporate IMiDs and /or proteasome inhibitors (table 6A) are superior to chemotherapy-only regimens, particularly in poor-risk patients such as those with poor cytogenetics or other adverse prognostic features[47-49]. As of October 2019 in Australia, the only IMiD that are reimbursed on PBS for induction therapy prior to ASCT is the first generation IMiD, thalidomide; lenalidomide is only reimbursed for induction therapy in non-transplant eligible (NTE) patients.

Three-drug combinations that incorportate a PI and/or IMiD is the current accepted standard of care for induction prior to ASCT. The addition of a chemotherapy agent, either cyclophosphamide or doxorubicin to thalidomide (CTD, TAD)[50, 51], bortezomib (CyBorD, PAD) [52, 53], or lenalidomide (LCD)[54] induces CR/VGPR rates between 37-65%. Impressive efficacy is also seen with three-drug regimens that combine IMiDs and proteasome inhibitors[55, 56], which enables omission of chemotherapy. Combination bortezomib, thalidomide and dexamethasone (BTd) is efficacious (CR/nCR 31% post induction) and is superior to Td[55]. Botezomib, lenalidomide and dexamethasone (BLd) is highly efficacious and when used as induction before and consolidation post ASCT, inducing a PFS of 50 months and a CR rate of 59%, according to the IFM 2009 study[31]. BLd will be the accepted standard of care for induction therapy for TE patients with NDMM once it is reimbursed by the PBS. However, as of October 2019, combination of IMiDs and proteasome inhibitors are not reimbursed by the PBS in Australia.

With respect to quadruplet combinations for induction therapy, no further advantage was seen with a four-drug combination of IMIDs, PI, cyclophosphamide and dexamethasone, which instead results in greater toxicity[56]. In contrast, a four-drug combination that incorporates the monoclonal antibody (mAb) daratumumab with the second generation PI, carfilzomib, lenalidomde and dexamethasone, appeared well tolerated and highly efficacious (ORR 100%, ≥VGPR 86%)[57] in an early phase clinical study, but requires further validation in ongoing phase III studies.

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[58], but this was not surprising given that the non-bortezomib comparator was VAD or TD, both of which are known to induce only modest responses. Nonetheless, bortezomib certainly induces rapid and quality responses, and given that it can partially mitigate the impact of adverse cytogenetics, bortezomib-based regimens are often used preferentially as first-line induction in transplant eligible patients. A weekly schedule of bortezomib 1.5mg/m2 appears to result in reduced toxicity without compromising efficacy compared to the traditional schedule of bortezomib 1.3mg/m2 days 1,4,8,11 every 21 days[52]. Similarly, it appears that weekly subcutaneous bortezomib is better tolerated than IV without compromising efficacy in transplant eligible patients, based on preliminary results of a phase II study[59]. 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 (TE) patients should be treated with 3-6 cycles of induction prior to ASCT (grade A recommendation, level 1B evidence).

The incorporation of proteasome inhibitors and/or immunomodulatory drugs as part of front-line induction therapy (table 1) improves quality of responses and is considered standard of care. Currently, only bortezomib or thalidomide but not lenalidomide are reimbursed by the Australian PBS for induction therapy for TE patients with NDMM. Note that the Australian PBS does not allow the concurrent use of bortezomib and thalidomide or lenalidomide as of October 2019..

Until combination bortezomib-lenalidomide-dexamethasone (BLd) is reimbursed by the Australian PBS for induction therapy for TE patients with NDMM, three-drug combinations incorporating a PI or IMiD with chemotherapy (cyclophosphamide or less commonly anthracycline) and dexamethasone is the accepted standard of care for induction therapy in Australia (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 1.3 mg/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.*

* *Once BLd is reimbursed by the PBS for upfront induction in patients with planned ASCT as part of first-line treatment, it will be the accepted standard of care in preference over triplet regimens that contain chemotherapy (level 1B evidence, grade A recommendation)*

3.2.1.3 Stem cell mobilisation

The most common regimens used to mobilise peripheral blood stem cells (PBSC) for MM patients is recombinant human granulocyte colony stimulating factor (rhG-CSF), such as filgrastim™, 10mcg/kg, or high dose cyclophosphamide with rhG-CSF. The addition of high dose cyclophosphamide for mobilisation does not necessarily improve depth of response over induction therapy, and does not improve CR rates or time to progression (TTP) in patients undergoing ASCT[60]. 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[61].

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[62]. Due to high cost, plerixafor is generally reserved for patients who fail to mobilise adequately as either a rescue strategy or during a second mobilisation attempt, under the PBS re-imbursement criteria in Australia (pbs.gov.au).

Bortezomib and thalidomide does not appear to impair stem cell mobilisation [63] 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 mobillisation 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[64]. 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[65], 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; stem cell mobilisation should be 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 mobilse adequately on cyclophosphamide plus rh-GCSF, or rhG-CSF alone (Grade B recommendation, level 2B evidence).

3.2.1.4 Monitoring of patients after ASCT:

The average time to progression for patients after HDT and ASCT is in the order of 2-4 years for younger patients, and shorter for older patients. The final magnitude of response post ASCT should be assessed after 2-3 months. Patients should be followed up with clinical and laboratory assessments, looking for evidence of relapse/progression. Testing should include serum or urinary paraprotein and SFLC levels (especially in patients with non-measureable 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[66]. Initial follow up for patients is usually monthly until stable, then 3 monthly or less frequent subsequently if there appears to be disease stability. Recommendation regarding follow up post ASCT are summarised in box 5.

Box 5: Recommendations regarding follow up post ASCT:

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

Follow up assessment should include:

- *Clinical assessment.*
- *Serum ± urinary protein electrophoresis (immunofixation not required)*
- *Serum free light chains.*
- *FBE, U&E, Ca^{2+}*
- *Targeted radiographic imaging if indicated.*

3.2.1.5 Allogeneic Stem Cell Transplant

"Graft versus myeloma (GVM)" effect does exist in the setting of allogeneic stem cell transplantation (alloSCT) [67]. However, while this may give rise to some long-term durable remissions [68], myeloablative alloSCT is associated with a high TRM of up to 50%. Reduced intensity conditioning (RIC) alloSCT lowers TRM to approximately 10-15% at 1 year, whilst maintaining the GVM effect, however chronic graft-versus-host disease remains a major problem in many survivors. A number of prospective trials have been published. The IFM99-03 study [69], included only patients with high-risk (del13q + B_2M>3mg/ml), and patients with available sibling donors underwent MEL200 ASCT followed by RIC AlloSCT with anti-thymocyte globulin, busulphan and fludarabine conditioning. Patients without a donor had a second ASCT in the companion IFM99-04 study. At the time of initial reporting median EFS and OS were similar in the two studies, EFS 35 months vs 32 months, p=ns, and OS 47 months vs 35 months, p=ns, in ASCT + RIC alloSCT vs. tandem ASCT respectively. However after longer follow up, OS was found to be significantly inferior in patients assigned to RICalloSCT [70]. An Italian randomised study, also comparing tandem ASCT vs. ASCT followed by RIC alloSCT (non-myeloablative total body irradiation conditioning), and not requiring poor prognostic features for selection demonstrated a superior long-term outcome in those who had available sibling donors (OS: 80 vs. 54 months, p=0.01; EFS: 35 vs.29 months. P=0.02) [71]. In the Spanish PETHEMA trial [72], comparisons were made between a second ASCT vs. RIC (melphalan and fludarabine) alloSCT in a group of patients who achieved < VGPR to their first ASCT. A higher rate of CR in favour of RIC alloSCT was seen (40% vs. 11%, p=0.001) and a plateau in PFS was also seen in this group. However, due to a higher TRM and GVHD, no statistical difference in EFS and OS was observed. Similarly, interim results from the BMT-CTN (Blood and Marrow Transplant Clinical Trials Network) 0102 Trial showed equivalent 3-year PFS and OS for tandem auto-auto vs. auto-allo stem cell transplant both high-risk [73], and standard-risk [74] MM patients. Two Gy total body irradiation was used as the non-myeloablative conditioning regimen in the allo-SCT arm. There was a suggestion of lower late PFS and time to progression/relapse in the auto-allo SCT arm in the high-risk group (p=0.09), however, no added benefit from auto-allo SCT was seen in the standard-risk group over tandem ASCT due to increased TRM. At present, a number of studies are ongoing to investigate the role of AlloSCT with novel immunological approaches. However, given the lack of consistent survival benefit to date, the use of AlloSCT should still be restricted to clinical trials, with the exception of selected cases of very high-risk MM (please see section 3.4: patients with high-risk MM)[75]. Recommendations regarding AlloSCT are summarised in box 6.

Box 6: Recommendation regarding AlloSCT:

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

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

3.2.2 Patients not eligible for ASCT:

3.2.2.1 Pre-treatment consideration: fit versus frail elderly patients

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

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

The traditional notion that patients aged above 65 years are ineligible for transplant is no longer appropriate. For patients aged between 65-75 who are 'very fit', induction therapy incorporating IMiDs or proteasome inhibitors followed by HDT+ASCT and subsequent maintenance can induce profoundly deep responses[78, 79] (Please refer to section on transplant eligible patients). Reduced-dose conditioning (melphalan 100-140mg/m^2)[78, 79] is tolerable and has been shown to induce a median PFS of 4 years in this group of patients[78].

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

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

- *Based on age, comorbidities, frailty and disability, elderly patients should be classified as either, very fit, fit or unfit to guide treatment choice.*
- *‘Very fit’ patients aged between 65-70 can be considered for full dose induction therapy incorporating IMiDs or proteasome inhibitors (see table 6A) followed by HDT+AuSCT. Reduced dose conditioning (melphalan 100-140mg/m^2) 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 (see table 6B) (Grade A recommendation, Level 1A evidence)*
- *Reduced-intensity treatment is suggested for those more frail 'unfit' elderly patients (see table 8) (Grade B recommendation, Level 2A evidence)*
- *Patients who are considered ineligible for any treatment should be referred early to a palliative care unit.*

3.2.2.2 Initial treatment for non transplant eligible (NTE) patients

Bortezomib-based regimen

In Australia, bortezomib is reimbursed on the PBS for the initial treatment of MM and at relapse subject to other eligibility criteria (please refer to http://www.medicareaustralia.gov.au). For non-transplant eligible (NTE) patients, combination bortezomib, melphalan and prednisone (BMP) is an accepted standard of care regimen based on the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) study that showed superiority of BMP over MP with respect to PFS and OS [80].

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[81]. For NTE patients, the weekly schedule of bortezomib is now considered standard of care (table 6B). Subcutaneous bortezomib is non-inferior to IV bortezomib with respect to efficacy, but has an improved safety profile[82]. The use of cyclophosphamide in place of melphalan is of comparable efficacy[52].

Combining an IMiD and PI is attractive; final results from the SWOG SO777 study demonstrated superiority of bortezomib, lenalidomide and dexamethasone (BLd) over lenalidomide and dexamethasone (Ld) with respect to PFS (HR 0.7, p=0.0018) and OS (HR 0.709, p=0.025) in patients without immediate intent for ASCT. Survival benefit was also seen in patients age >75 years. In contrast, combination bortezomib, thalidomide and dexamethasone does not appear superior to a simple (and cheaper) bortezomib and alkylkating agent combination in NTE patients, but is particularly toxic with respect to cardiac adverse events[83, 84]. Of note, IMiD + bortezomib combination is not reimbursed by the Australian PBS.

In unfit elderly patients in whom an alkylating agent may not be suitable, a doublet combination of bortezomib and dexamethasone is efficacious with RR and CR of up to 70% and 25%, respectively[85]. Conversely, a 4-drug regimen combining bortezomib, lenalidomide, cyclophosphamide and dexamethasone(BLCD) have been shown to be more toxic without added efficacy[56, 86].

Lenalidomide-based regimens

Lenalidomide and dexamethasone (Ld) is an accepted first-line induction regimen for transplant ineligible patients based on the phase III FIRST (Frontline Investigation of Revlimid and dexamethasone versus Standard Thalidomide) clinical study[87], which demonstrated superiority of continuous Ld (i.e. Ld until disease progression) over the hitherto standard of care MPT (melphalan, prednisone and thalidomide) with respect to PFS (4 year PFS 32.6 vs. 16.6 months (MPT), p<0.00001) and OS (predicted 4 year OS: 59% vs. 51% (MPT), p=0.0023)[88]. Of note, continuous Ld significantly improved PFS over fixed duration (18 months) Ld. Four year PFS was 32.6 months with continuous Ld vs. 14.3 months with fixed duration Ld. However, OS was similar (predicted 4 year OS: 59m (cont. Ld) vs. 58m (18m Ld), respectively). This may be partly explained by the fact that a significant proportion of patients in the fixed duration Ld arm were retreated with Ld again upon first relapse. At present, continuous Ld is considered as one standard of care for initial induction therapy in transplant ineligible patients. Lenalidomide is reimbursed in Australia for the initial treatment of NTE patients with MM.

Unlike bortezomib, the addition of alkylating agents to lenalidomide for NTE patients as triplet combination (eg. melphalan prednisone lenalidomide (MPL)) is less well tolerated in elderly patients mainly due to myelosupression, especially those over the age of 75 years as was evidenced in the MM105 study. This perhaps accounted for the absence of a PFS improvement with MPL (without L maintenance) despite higher ORR when compared to MP (27). As was seen in the FIRST study, the use of continuous lenalidomide (i.e. the addition of lenalidomide maintenance to MPL (MPL-L)) resulted in a profound improvement in PFS by 18 months compared to MP. Again, this was noted only for patients aged less than 75 years[89]. Overall, the addition of an alkylating agent (cyclophosphamide or melphalan) to Ld has not been found to improve ORR, PFS or OS in first line treatment of transplant ineligible patients[90]; when combined with Ld, melphalan is more myelotoxic compared to cyclophosphamide.

Unlike thalidomide and bortezomib, the risk of neurological toxicity with lenalidomide is significantly lower. Myelosuppression is common, especially in patients with impaired renal function. Like thalidomide, VTE prophylaxis is recommended (see supportive measures, table 7). Lenalidomide-associated secondary primary malignancies (SPM) have been a concern since increased rates of SPM were noticed in 3 major studies that assessed lenalidomide maintenance[89]. In a 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].

Combination bortezomib, lenalidomide and dexamethasone.

Combination bortezomib, lenalidomide and dexamethasone (BLd) has also emerged as a highly efficacious regimen for TIE patients with NDMM, based on the phase III randomised SWOG SO777 study[92]. Here, 525 patients with NDMM without intent for upfront ASCT (43% aged 65 years or above) were randomised to BLd versus Ld. BLd was proven superior with respect to PFS (43m vs. 30m, HR 0.71, p=0.0018) and OS (75m vs. 64m, HR0.7, p=0.025). In this study, bortezomib was given 1.3mg/m2 IV days 1,4,8,11, lenalidomide 25mg orally days 1 to 14, and dexamethasone 20mg oral days 1,2,4,5,8,9,11,12, in a 28-day cycle. The main adverse events from BLd, were haematological, mainly anaemia, neutropenia and thrombocytopenia. The common non-haematological adverse events include fatigue, sensory neuropathy, and hyperglycaemia. As expected, grade 3 or worse neurological toxic effects were more frequent in the BLd group (33 vs. 11%, p<0.0001).

Using the same combination of BLd in an attenuated dosing schedule, the so called BLd (or VRd)-lite, O'Donnelle and colleagues[93] reported an ORR 86% with median PFS 35.1m. Here, bortezomib was given at 1.3mg/m2 subcutaneously (sc) days 1,8,15,22, lenalidomide 15mg orally daily on days 1-21 and dexamethasone 20mg orally on the day of and day after bortezomib (or days 1,8,15,22 for patients age >75 years) for nine 35-day cycles, followed by 6 cycles of consolidation bortezomib (1.3mg/m2 sc days 1 and15) and lenalidomide (15mg po days 1-21) for six, 28-day cycles. This VRd-lite regimen was well-tolerated; neuropathy occurred in 61% of patients but was mainly grade 1.

In August 2019, combination BLd received positive recommendation from the Australian PBAC, for the treatment of patients with TIE NDMM. At the time of publication of this guideline, it is anticipated that combination BLd will be reimbursed on the PBS in the near future for TIE patients with NDMM. The decision to embark on triplet BLd or doublet Ld should be individualised taking into consideration of patient's fitness based on frailty, comorbidity and disability; given the fact that BLd is associated with a higher rate of grade 3 or more adverse events, it would be reasonable to use Ld in a subset of patients who are intermediate-fit or unfit, particularly those who are at risk of peripheral neuropathy

Thalidomide-based regimens:

In Australia, thalidomide is reimbursed on the PBS for the treatment of both NDMM and RRMM (relapsed refractory multiple myeloma). However thalidomide containing regimens are regarded as inferior to bortezomib or lenalidomide-based regimens which are preferred over thalidomide, unless there are contraindications to those drugs in the upfront treatment of MM.

Thalidomide is often used in a triplet combination, with an alkylating agent (either cyclophosphamide or melphalan) and corticosteroid (either dexamethasone or prednisolone); see table 6B. For transplant ineligible patients, the addition of thalidomide to melphalan and prednisolone (MPT) improves PFS and OS compared to MP by 5.4 and 6.6 months, respectively, according to a meta-analysis of 1682 patients from the 6 randomised clinical trials that compared MP to MPT[94]. 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[95](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[96]. Thus, when thalidomide is used, it is often used in triplet combination (eg. CTD or MPT) rather than doublet combination (Td). In the First (MM020) study, MPT was demonstrated to be inferior to Ld and so should be only used if lenalidomide or bortezomib combinations are contraindicated.

Table 6B outlines the more common induction treatment regimens for transplant ineligible patients. Recommendations for initial induction therapy for transplant ineligible patients are summarised in box 8.

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

- *The current accepted standard of care for the initial treatment of transplant ineligible patients with multiple myeloma include:*
  - *Bortezomib, lenalidomide and dexamethasone (BLd), once it is reimbursed by the Australian PBS* (Level 1B evidence, grade A recommendation)*
    - *BLd-lite appears to have comparable efficacy with reduced toxicity, in particular, reduced peripheral neuropathy (Level 2A evidence, grade B recommendation).*
  - *Continuous lenalidomide and dexamethasone (Ld) (Level 1B evidence, grade A recommendation).*
  - *Bortezomib, melphalan and prednisolone (BMP) (level 1B evidence, grade A recommendation.*
    - *Cyclophosphamide could be substituted for melphalan (CyBorD regimen)*
    - *For unfit elderly patients (section 3.3.1), bortezomib and dexamethasone (Bd) as doublet should be considered (level 1B, grade B recommendation)*
    - *For bortezomib, a weekly schedule is recommended for transplant ineligible patients.*
- *Thalidomide, melphalan and prednisolone (MPT) has now been shown to be inferior to Ld (Level 1B evidence) and should only be used if only used if lenalidomide or bortezomib combinations are contraindicated (Grade A recommendation).*

* *At the time of publication of this guideline, combination BLd received positive recommendation by the Australian PBAC for the upfront treatment of transplant ineligible patients with multiple myeloma, and is anticipated to be reimbursed on the PBS in the near future.*

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[97], 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[81]. In addition, one randomised trial in patients with RRMM has shown that the subcutaneous route of administration was associated with reduced peripheral neuropathy without compromising efficacy[82]. 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[98].

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

Standard-dose lenalidomide (25mg) is generally well tolerated in elderly patients. However, dose reduction is recommended in patients with impaired renal function. Finally, lenalidomide at 10mg, when combined with melphalan and prednisone (MPR) did not improve PFS, as compared with MP, in patients age ≥75 years, but dose reductions were required more frequently than for younger patients [89].

Table 8: Recommended dose attenuation in unfit elderly patients.

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

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

3.2.3 Patients with high-risk MM.

Several factors are known to confer a poorer prognosis in patients with MM (table 5). These include older age [99], higher ISS stage, high LDH, high plasma cell labelling index and the cytogenetic abnormalities: t(4;14), t(4;16) and 17p deletion (as identified by FISH) [100-102], 13q deletion (identified by standard cytogenetic), as well as hypodiploidy and complex (combination of ≥3) cytogenetic abnormalities. Amplification of chromosome 1q21 (by FISH) has also been shown to be associated with both shorter time to disease progression and poorer prognosis[103, 104].

In the assessment of primary genetic abnormalities, FISH remains the standard technique, whereas molecular approaches such as gene expression profiling or SNP (single nucleotide polymorphism) mapping arrays are only used in the context of clinical studies.[105]

In the era of IMIDs and PIs, patients with high-risk MM are defined as those with an expected OS of <3 years for transplant eligible or <2 years for transplant ineligible. For transplant eligible patients, those with an expected OS <2 years are classified as "ultra high-risk"[3, 105]. The most robust factors that are consistently associated with such poor survival are higher ISS stage and the cytogenetic abnormalities 17p deletion and t(4;14). The revised(R)-ISS risk stratification system now incorporates ISS stage, LDH and high-risk FISH (del17p and t(4;14)),(table 4). In the era of IMiDs and PIs, the R-ISS can clearly identify 3 different MM prognostic groups in patients and now supersedes the previous ISS staging system[3, 106].

With respect to treatment, thalidomide does not overcome HR cytogenetic abnormalities. Several reports have confirmed that bortezomib improves PFS and OS in the presence of poor risk cytogenetics (13q deletion, t(4;14), amp1q21, and perhaps even 17p deletion) [104, 107-110] although it does not overcome the entire adverse impact of these mutations, especially when t(4;14) and del17p are combined[43].

There are limited data for lenalidomide in patients with high-risk cytogenetics. For transplant eligible patients, lenalidomide maintenance post ASCT appears to improve PFS but not OS for t(4;14) and del17p lesions [30, 111-113]. For transplant ineligible patients, results from the major phase III studies of lenalidomide (MM015[89] and FIRST[87]) showed no strong evidence that continuous lenalidomide can curb the impact of high-risk cytogenetics. Limited data exist for pomalidomide[114]. There are some data supporting the combined used of bortezomib and lenalidomide in patients with high-risk cytogenetics[56, 115], however, most of these data are from small non-randomised studies and further confirmation is required. Of note, the combined use of IMiDs and PI is not reimbursed by the PBS in Australia.

Tandem ASCT may have a role in patients with poor prognostic features, as was suggested in an integrated analysis of phase III European studies, in which patients were prospectively assigned to receive either single or tandem ASCT. Tandem ASCT resulted in OS benefit compared to single ASCT, that was particularly evident in patients with high-risk cytogenetics and who failed to achieve CR post bortezomib-based induction (5-year OS estimate 70% vs. 17% with single ASCT, p<0.001[41].

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

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

Box 9: Recommendations for patients with high risk MM:

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

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

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

3.3. CONSOLIDATION/MAINTENANCE THERAPY

3.3.1 Consolidation/maintenance therapy post ASCT:

Short consolidation following ASCT refers to a short treatment-course (2 to 4 cycles) that improves depth of response[55]. To date, there has been insufficient data to determine whether a short consolidation improves long-term survival; studies of short consolidation post ASCT demonstrate improvement in depths of responses and PFS but none of which have shown OS benefit [55, 115]. The phase III BMT CTN StaMINA study looked specifically at the role of consolidation. Patients aged <71 years (n=758) were randomised after induction, 1:1:1 to either single ASCT, or consolidation with either a second (tandem) ASCT or 4 cycles of RVD (lenalidomide, bortezomib, dexamethasone), prior to maintenance lenalidomide therapy. The addition of consolidation, whether it be a second ASCT or 4 cycles of RVD was not found to be superior to no consolidation with respect to PFS or OS. Thus, if one gives effective induction and lenalidomide maintenance post ASCT, then there is little incremental benefit with consolidation. This conclusion may not be extrapolated to the Australian setting where IMiDs and PIs cannot be used in combination in induction (as was the case for the majority of patients in the StaMINA study), and lenalidomide is

not available for maintenance post ASCT. In addition, the major caveat to this study was that participants were allowed more than 4 cycles of induction (up to 12) prior to randomisation to consolidation versus not.

Thalidomide ± prednisolone post ASCT has proven to prolong both PFS and OS[116]. As thalidomide is generally tolerated for a median of approximately 12 months, it is more aptly termed a long consolidation as opposed to maintenance when used post ASCT. Toxicity, in particular peripheral neuropathy, is the main reason for early thalidomide discontinuation.

Lenalidomide on the other hand, is the only proven maintenance post ASCT that has been shown to improve PFS and OS based on meta-analysis of 3 large phase III randomised studies: CALBG (n=460), IFM (n=614) and GIMEMA (n=134) [117]. Grade ≥3 neutropenia is the most frequent adverse-event. Lenalidomide related secondary malignancies ([7.8-8.5% lenalidomide vs. approximately 3% placebo] was an initial concern, however, meta-analysis has shown that the risk pertains mainly 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 until disease progression outweighs the risks.

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[107]. As such, no firm conclusions regarding bortezomib consolidation or maintenance can be made. Importantly, the final results from the Australian phase III VCAT study (Bortezomib Consolidation with Thalidomide and Prednisolone Vs Thalidomide and Prednisolone Alone in Previously Untreated Subjects With Multiple Myeloma After VCD Induction and ASCT), showed the addition of bortezomib (1.3mg/m2) every two weeks for 32 weeks to thalidomide+prednisolone resulted in a non-statistically significant higher depth of response (≥VGPR 85.7% vs. 77.1%), that did not translate to an improved PFS or disease free survival[118]. The concurrent use of thalidomide and bortezomib is not reimbursed on PBS in Australia.

More recently, ixazomib, a second generation orally bioavailable PI, has emerged as a contender for maintenance post ASCT. In the preliminary analysis of the TOURMALINE-MM3 study, ixazomib (4mg (3mg in the first 4 cycles) po weekly for 3 weeks in a 4 week cycle) in a fixed 2-year maintenance pot ASCT, resulted in superior PFS (HR 0.72, p-0.002) compared to placebo[119]. In the absence of evidence for OS advantage, perhaps due to short follow up (median 30.9 months), ixazomib cannot be recommended over lenalidomide, but may be a viable alternative for patients who cannot tolerate the latter.

In Australia, prior to the PBS reimbursement of lenalidomide for maintenance therapy post ASCT, only thalidomide was reimbursed for consolidation therapy post ASCT. In July 2019, lenalidomide monotherapy received positive PBAC (Pharmaceutical Benefits Advisory Committee) recommendation for maintenance treatment of newly diagnosed patients with MM post ASCT. At the time of publication of this guideline, it is anticipated that lenalidomide will be reimbursed by the PBS (pharmaceutical benefit scheme) for this indication in the near future. Please see box 10.

Box 10: Recommendations regarding maintenance therapy post ASCT:

Short consolidation therapy (typically 2-4 cycles) is not routinely recommended in Australia as there is not yet firm evidence to show that a short consolidation post ASCT improves long-term survival, especially when effective induction (incorporating either IMiDs and/or PIs) before and maintenance post ASCT is given (grade B recommendation, level 2A evidence).

Lenalidomide maintenance post ASCT improves PFS and OS, and is recommended for maintenance post ASCT in Australia once it is reimbursed on PBS for this indication (Grade A recommendation, level 1A evidence)

Until lenalidomide maintenance post ASCT is reimbursed on PBS, a long consolidation therapy with thalidomide 100mg daily with or without corticosteroids is recommended over no treatment in patients following first line treatment with HDT and ASCT (Grade A recommendation, level 1A evidence).

- *Thalidomide±prednisolone consolidation post ASCT should continue for approximately 12 months. The benefit of thalidomide treatment beyond 12 months remains to be proven (Grade A recommendation, level 1A evidence).*

The dose schedule and role of maintenance bortezomib is still unclear, and bortezomib is not TGA registered nor PBS reimbursed for this indication. Bortezomib maintenance post ASCT is not routinely recommended. (Grade C recommendation, level 4 evidence)

Ixazomib maintenance post ASCT improves PFS (level 1B evidence), but lacking data for OS. Ixazomib cannot be recommended over lenalidomide for maintenance post ASCT, but may be a viable alternative maintenance. Currently ixazomib is yet to be registered with the US FDA or Australian TGA for this indication and is not available in Australia.

3.3.2 Maintenance therapy for non-transplant eligible (NTE) patients:

With respect to maintenance therapy beyond the induction phase of treatment for NTE patients, the strongest evidence exists for lenalidomide. Three pivotal randomised phase III trials have demonstrated the benefit of continuous lenalidomide beyond induction 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 not overall survival [89]. In the final analysis of the FIRST trial, continuous Ld until disease progression improved both PFS and OS compared to a fixed duration MPT (HR 0.69, p<0.00001 and HR 0.78, p=0.0023, respectively). Ld until disease progression was superior to fixed duration Ld with respect to PFS (HR 0.7) but not OS[88]. For elderly, intermediate fit patients with NDMM, preliminary data from the phase III RV-MM-PI-0752 study demonstrated that after 9 cycles of induction with standard Ld (lenalidomide 25mg po D1-21q28 days and weekly dexamethasone 20mg po), continuation of a lower dose of lenalidomide (10mg) without dexamethasone resulted in similar efficacy but with potentially improved tolerability compared to continuation with standard dose Ld until disease progression.

For NTE patients who received thalidomide or bortezomib, rather than lenalidomide during induction, the phase III Myeloma XI study (CTd or CLd induction followed by bortezomib-based salvage versus placebo upon inadequate response, then lenalidomide versus placebo maintenance post induction) indicated benefit of lenalidomide maintenance over placebo with respect to PFS (HR 0.44 in the NTE cohort, p 0.014) but not yet OS after a median follow up of 31 months[120]. In Australia, lenalidomide is reimbursed for continuous treatment until disease progression when Ld is used as initial treatment in NTE patients, but not for maintenance post thalidomide or bortezomib-based induction therapy.

Thalidomide, on the other hand, is reimbursed by the Australian PBS for any phase of treatment of MM in Australia. In the MRC Myeloma IX trial[116], 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 [116]. Neurotoxicity poses the main toxicity for prolonged thalidomide such that maintenance thalidomide is usually not tolerated beyond 12 months.

With respect to bortezomib maintenance for NTE patients, two randomised studies have been reported. However, these trials were not designed to assess the isolated impact of bortezomib maintenance. The GIMEMA study compared BMPT followed by BT maintenance to BMP alone. BT maintenance improved CR rate slightly from 58% (post BMPT induction) to 62%; 3-year PFS was higher in the BMPT-BT arm (56 vs. 41%, p=0.008). Five year OS was superior in the BMPT-BT arm compared to BMP (59 vs. 46%, p=0.04)[86]. 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%[84] but no difference with respect to PFS or OS was seen between BP or BT maintenance. Recommendations on maintenance therapy in patients who are not transplant eligible are summarised in box 11.

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

- *The benefit of maintenance therapy with respect to PFS and possibly OS for transplant ineligible patient is most evident for lenalidomide and dexamethasone combination.*
  - *For transplant ineligible patients initially treated with Ld, we recommend that this be continued until disease progression (level 1B evidence, grade A recommendation)*
    - *For elderly, intermediate fit patients, after 9 cycles of Ld, omission of dexamethasone and dose attenuation of lenalidomide to 10mg is not unreasonable in the context of poor tolerance, pending final analysis of the RV-MM-PI-0752 study.*
  - *For transplant ineligible patients initially treated with thalidomide or bortezomib-based induction regimen, maintenance lenalidomide has been shown improve PFS (Level 1B evidence, grade A recommendation). However in In Australia, lenalidomide is not registered or reimbursed by the PBS for maintenance therapy post thalidomide or bortezomib-based induction for TIE patients.*
- *Thalidomide maintenance improves PFS but OS impact in the non-transplant setting is unclear, and is therefore not recommended as 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 nor is it recommended for this indication (Grade A recommendation, level 1B evidence)*

3.4. TREATMENT OF RELAPSED MULTIPLE MYELOMA:

The management of patients with RRMM requires careful evaluation, taking into account prior treatments and associated toxicities, duration of response to prior treatment, and the patient's current clinical status and tempo of relapse. Relapsed MM refers to disease that has recurred after an initial response, and is objectively defined as per IMWG criteria[121]. The aim of treatment is not only to prolong survival, but to also treat or prevent development of myeloma related end organ damage.

Many but not all patients will require immediate treatment at first detection of relapse. For patients with relapse with worsening or new CRAB symptoms, immediate treatment is mandatory. In the absence of worsening or new CRAB symptoms, immediate treatment may also be warranted in patients with rapidly progressive paraprotein level or SFLC (table 9), to prevent the onset of irreversible end organ damage. Otherwise, for patients with slow indolent biochemical relapse without any overt worsening or new CRAB symptoms, careful monitoring until significant progression occurs is acceptable

Table 9: Indications to commence treatment for myeloma at relapse[122].

CLINICAL RELAPSE:
• Development of new soft tissue plasmacytomas or bone lesions • Definite increased (≥50%) size of existing plasmacytomas or bone lesions. • Hypercalcaemia (≥11.5mg/dl; 2.875mmol/l) • Decrease in haemoglobin by ≥20g/L or to <100g/L due to myeloma. • Rise in serum creatinine by >177 µmol/L (2mg/dL) due to myeloma.
SIGNIFICANT BIOCHEMICAL RELAPSE PRIOR TO THE ONSET OF END ORGAN DAMAGE.
• Doubling of paraprotein in two consecutive measurements less than two months apart with at least a 5g/L absolute increase or • Any of the following increases in two consecutive measurements: ◦ The absolute level of paraprotein by ≥10g/L or ◦ The increase of urinary M protein (BJP) by ≥0.5g per 24 hours or ◦ Increase of involved FLC level by ≥200mg/L (with abnormal K:L ratio) or 25% increase (whichever is greater).

There is no standard sequence or algorithm of treatment for patients with relapsed MM. The choice of salvage regimen takes into account patient factors (age and frailty), disease factors (tempo of relapse, risk-group stratification), and prior treatment-related factors (response or refractoriness to prior type of treatment.) Table 10 outlines the commonly used salvage regimens.

Table 10: Salvage treatment regimens for relapsed/refractory MM*

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

REGIMEN		EFFICACY	COMMENTS
THALIDOIMDE-BASED[A]			
TD **[183]**	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 **[50, 174]2, 3]**	Thalidomide 100mg po. Daily Cyclophosphamide 500mg po.weekly Dexamethasone 40mgpo. D1-4, 12-15 or 40mg po. weekly. Cycles repeated every 4 weeks until best response.	Phase II trial. ORR 79% CR 17%	Minimal infective complications. Moderate emesis, fatigue, myelosuppression.
ThaDD **[184]**	Thal 100mgpo. daily Dexamethasone 40mg po. D1-4, 9-12, Peg liposomal doxorubicin 40mg/m2IV 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/m² daily IV continuous infusion D1-4. Cyclophosphamide 400mg/m2 daily IV continuous infusion D1-4. Etoposide 40mg/m² daily IV continuous infusion D1-4. Doxorubicin 10mg/m² 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 **[185]**	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[C]			
Len-dex **[127, 128, 177]**	Lenalidomide 25mgpo. 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[177] 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%
LCD **[54]**	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[177]	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.
LAD **[186]**	Lenalidomide 25mgpo. D1-21 Adriamycin 9mg/m² IV D1-4 Dexamethasone 40mgpo. 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[E]			
Pom-dex **[114]**	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 treatments including bortezomib and lenalidomide)	Grade 3 and 4 anaemia 33% Grade 3 and 4 neutropenia 48% Grade 3 and 4 thrombocytopenia 22%
PBd **[145]**	Pomalidomide 4mg po D1 to 14 Bortezomib 1.3mg/ m² sc D1,4,8,11 (cycles 1-8); D 1,8 (cycles 9+) Dexamethasone 20mg (10mg for >75 years old) day of and day after bortezomib.	ORR 82% CR/sCR 16%	

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REGIMEN		EFFICACY	COMMENTS
BORTEZOMIB-BASED[B] **Note: Bortezomib, when given subcutaneously and/or as a weekly schedule have been shown to reduce neuropathy**			
Bortezomib and Dexamethasone **[141]**	Bortezomib1.3mg/m² IV D1,4,8,11 every 21 days for cycles 1-8 D1,8,15,22 every 35 days for cycles 9-12 Dex 20mg po. on day of and day after bortezomib	Phase III trial. (SUMMIT/APEX) ORR ~38% CR ~6%	Gde≥3 fatigue 5% Gde≥3 peripheral neuropathy 8% Gde≥3 thrombocytopenia 30% Gde≥3 anaemia 10% Gde≥3 neutropenia 14%
CyBorD/ VCD **[52, 143]**	Cyclophosphamide 300mg/m2po. weekly. Bortezomib 1.3mg/m² 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 ORR (CR+PR) 82%, CR 16%	Gde≥3 AE = leukopenia, thrombocytopenia infection, herpes zoster
PAD **[144, 187] [[188]**	Bortezomib 1.3mg/m² IVD1,4,8,11 , Doxorubicin 20mg/m² 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 **[189]**	Bortezomib 1mg/m² 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 **[166]**	Bendamustine 70mg/m² IV D 1,4 Bortezomib 1.3mg/ m² D1,4,8,11 Dexamethasone 20mg po D1,2,4,5,8,9,11,12 Cycles repeated every 21 days for 8 cycles.	Phase II trial ORR 60.8% VGPR/CR 35.5 Med PFS 9.7m	Gde≥3 thrombocytopenia 38% Gde≥neutropenia 17%. Gde≥3 anaemia 18% Gde≥3 peripheral neuropathy 6%

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REGIMEN		EFFICACY	COMMENTS
CARFILZOMIB-BASED[D]			
Carfilzomib + Dexamethasone **[190]**	Carfilzomib 20mg/m2 IV D1,2 56mg/m² IV D8,9,15,16 Dexamethasone 40mg D1,8,15 Cycles repeated every 28 days until disease progression.	Phase III trial. ORR 77% VGPR/CR 54% Med PFS 18.7m	Gde≥3 hypertension 9% Gde≥3 dyspnoea 5% Gde≥3 fatigue 5% Gde≥3 cardiac failure 5%
Carfilzomib + Cyclophosphamide + Dexamethasone **[191]**	Carfilzomib 20mg/m² IV D1,2 36mg/m2 IV D8,9,15,16 Cyclophosphamide 500mg/m² po D1,8,15 Dexamethasone 40mg po D1,8,15 Cycles repeated every 28 days for 6 cycles followed by carfilzomib-dexamethasone (Kd) maintenance until disease progression.	Phase II randomised trial. ORR 84% VGPR/CR 43.8% Med PFS 11.9 months; ~18m in patients who proceeded with Kd maintenance.	Not presented in detail in abstract.
Carfilzomib + Thalidomide + Dexamethasone **[148]**	Carfilzomib 20mg/m² IV D1,2 56mg/ m² IV D8,9,15,16 Dexamethasone 40mg D1,8,15 Thalidomide 100mg po daily. Cycles repeated every 28 days for 12 cycles followed by carfilzomib-dexamethasone (Kd) consolidation for 6 cycles.	Phase II trial. ORR 82% VGPR/CR 65% Med PFS not reached after med follow up 7.3m; 1 year PFS ~68%	Gde≥3 hypertension 3% Gde≥3 dyspnoea 16% Gde≥3 fatigue 3% Gde≥3 cardiac failure 3% Gde≥3 peripheral neuropathy 13%
DARATUMUMAB COMBINATIONS[G] **Daratumumab is TGA registered for the treatment of patients with RRMM who have had at least one prior line of treatment in combination with Bd or Ld, and for patients who had at least 3 prior lines of treatment including a PI and IMID or who are refractory to PI and IMId as monotherapy. It is not reimbursed by the PBS as of June 2019**			
Daratumumab + Bortezomib + Dexamethasone **[156]**	Daratumumab 16mg/kg IV weekly C1-3 Every 3 weeks C 4-8 Every 4 weeks C9+ Bortezomib 1.3mg/m2 sc D1,4,8,11 for cycles 1-8 only Dexamethasone 20mg po D1,2,8,9,11,12 for cycles 1-8 only Cycles 1-8 repeated every 21 days. Cycles 9+ repeated every 28 days until disease progression.	Phase III trial. ORR 84% VGPR/CR 62% Med PFS 16.7m	Gde≥3 neutropenia 12.8% Gde≥3 thrombocytopenia 45.5% Gde≥3 anaemia 14.4% Most Infusion-related reaction (45.3%) were grade 1+2 and was mainly during first infusion.
Daratumumab + Lenalidomide + Dexamethasone **[155]**	Daratumumab 16mg/kg IV weekly C1-2 Every 2 weeks C3-6 Every 4 weeks C7+ Lenalidomide 25mg po daily D1-21 Dexamethasone 40mg po weekly Cycles repeated every 28 days until disease progression.	ORR 92.9% VGPR/CR 75.8% 12m PFS 82.3%.	Gde≥3 neutropenia 51.9% Gde≥3 thrombocytopenia 12.7% Gde≥3 anaemia 12.4% Most Infusion-related reaction (47.7%) were grade 1+2 and was mainly during first infusion.
Daratumumab **[152]**	Daratumumab 16mg/kg IV weekly C1-2 Every 2 weeks C3-6 Every 4 weeks C7+ Cycles repeated every 28 days until disease progression.	In patients with median 5 prior lines of therapy (2-14) ORR 29.2% Med DOR 7.4m Med PFS 3.7m	Gde≥3 anaemia 24% Gde≥3 neutropenia 12% Gde≥3 thrombocytopenia 19% Most Infusion-related reaction (42%) were grade 1+2 and was mainly during first infusion.

REGIMEN		EFFICACY	COMMENTS
PLITIDEPSIN **Plitidepsin is TGA registered TGA for the treatment of RRMM after ≥3 prior treatment lines including an IMID or PI, or ≥2 prior lines upon refractoriness and/or intolerance to both IMID and PI. It is not reimbursed on the PBS as of June 2019.**			
Plitidepsin **[167]**	Plitidepsin 5mg/m² IV days 1, 15 Dexamethasone 40mg po days 1,8,15,22 Cycles repeated every 28 days until disease progression.	In patients who fulfil TGA treatment criteria: ORR 12% For responding patients (≥PR) PFS 9.6m; OS 37.8m	
CHEMOTHERAPY			
Non-myeloablative melphalan **[192]**	Melphalan 25mg/m^2 IV	–	Myelosupression.
High dose cyclophosphamide **[124]**	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 **[193]**	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.

A. Thalidomide is available for treatment of patients with MM through the Pharmaceutical Benefits Scheme (PBS).

B. Bortezomib, as monotherapy or in combination with a corticosteroid and/or cyclophosphamide, is reimbursed by the PBS for patients with MM who have progressive disease after at least 1 prior therapy, and who has undergone or is ineligible for a primary stem cell transplant.

C. Lenalidomide as monotherapy or in combination with corticosteroid is reimbursed by the PBS for patients with MM who has progressive disease after at least 1 prior therapy, and who has undergone or is ineligible for a primary stem cell transplant.

D. Carfilzomib in combination with corticosteroid is reimbursed by the PBS for patients with MM who has progressive disease after at least 1 prior therapy, and who has undergone or is ineligible for a primary stem cell transplant.

E. Pomalidomide in combination with dexamethasone is reimbursed by the PBS for the treatment of MM in patients who have failed two or more prior therapies including lenalidomide and bortezomib. Combination pomalidomide, bortezomib and dexamethasone (PBD) is approved by the Therapeutic Goods Administration (TGA) for the treatment of RRMM with at least 1 prior line of treatment including lenalidomide, but is not reimbursed by PBS as of June 2019.

F. Bendamustine is not registered by the TGA for the treatment of MM within Australia.

G. Daratumumab is TGA registered for the treatment of patients with RRMM who have had at least one prior line of treatment in combination with Bd or Ld, and for patients who had at least 3 prior lines of treatment including a PI and IMID or who are refractory to PI and IMId as monotherapy. It is not reimbursed by the PBS as of June 2019

In Australia, the main treatment options for relapsed/resistant disease are IMiDs (thalidomide, lenalidomide and pomalidomide), PI (bortezomib and carfilzomib), alkylating agents, anthracyclines, and corticosteroids, administered alone or in various combinations, with selected patients undergoing HDT with ASCT. These various agents can be used in different combinations within PBS restrictions (please refer to www.pbs.gov.au), and in different sequences. No best sequence has been defined (Figure 4; table 9).

We recommend enrolment into a clinical trial if one is available as first option. Otherwise, the generally accepted principles are as follows:

1. Switch drug class, especially if remission to prior drugs was short or patient had concerning associated toxicity.
2. Retreatment with a prior line of treatment is feasible if a long prior remission (eg. treatment free interval >1 year), was achieved with no concerning toxicity. However, an inferior duration and quality of response is to be expected.
3. HDT and ASCT can be considered in patients who have had a deep (at least PR) and durable response to this treatment modality in the past[123]. Data from the British Blood and Bone Marrow Transplant Registry suggested that a PFS of at least 9 months to the first ASCT is associated with improved survival outcome to a second ASCT in relapsed MM [123]. In the era of increased effective salvage options, most myeloma experts in Australia would consider a second ASCT for salvage therapy upon the achievement of at least 12-18 months PFS to the first ASCT.
4. In patients with a slow tempo of disease relapse, doublet PI or IMID with dexamethasone, or indeed ongoing observation in the absence of end-organ damage may be appropriate, especially if they cannot tolerate more intensive treatment.
5. In contrast, in patients with rapidly progressive, intensive regimens combining an IMiD or PI with one or more chemotherapy (table 9) can be considered if the patient has good performance status and organ function.
6. Finally, when all newer agents and different treatment combinations have been exhausted, conventional doses of cyclophosphamide[124], non-myeloablative doses of melphalan[125], or low-modest doses of corticosteroids remain viable options, as is palliation in patients who cannot tolerate any further therapy. Please see box 12.

In addition to these general principles, the choice of salvage also depends on pre-existing co-morbidities. In patients with pre-existing neuropathy, exacerbation may occur with bortezomib or thalidomide. For patients with a previous history of VTE, or who are at high-risk of VTE events, thalidomide and lenalidomide, although not absolutely contraindicated, should be avoided if other effective induction options are available. VTE risks are highest when these immunomodulatory drugs are used with high-dose dexamethasone or anthracycline chemotherapy. Prophylactic or therapeutic-dose anticoagulation should therefore be instituted as appropriate. Lenalidomide is 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[126].

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) [127, 128] compared dex 40mg/d (d1-4, 9-12,17-20) with or without len (25mg/d d1-21) every 28 days shows superiority in the len-dex arm. RR and CR rates were 61% and 27% in the MM-009, and 58% and 14% in MM-010 trial, respectively. Importantly, lower dose dexamethasone (40mg weekly as opposed to the traditional pulsed dexamethasone) should be used in combination with lenalidomide (Ld) as perthe ECOG E4A03 trial [129]. Ld is especially effective for lenalidomide naïve patients, however, retreatment can also be effective for patients who have had prior lenalidomide but have not progressed on or within 60 days of cessation of lenalidomide[130]. For patients who are vulnerable based on renal impairment, baseline cytopenia or elderly age, lower dose lenalidomide (15mg) at the outset decreases toxicity and appears not to compromise efficacy based on results from the Australian RevLite study[131]. Cyclophosphamide can be added to doublet Ld as a triplet salvage regimen. In Australia, lenalidomide is reimbursed by the PBS for lenalidomide-naïve patients with progressive MM who have had at least one prior line of therapy

Pomalidomide, a second generation IMiD has shown efficacy in patients with RRMM, even in patients with disease refractory to both lenalidomide and bortezomib. In a randomised phase III trial (MM003)[114], 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[114]. 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)[132]. In Australia, pomalidomide in combination with dexamethasone, is reimbursed by the PBS for the treatment of MM in patients who have failed two or more prior therapies including lenalidomide and bortezomib.

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

Thalidomide monotherapy can induce a ORR in relapsed MM in approximately 25% to 30%; responses are durable with median EFS of 6-12 months and median OS of 14 months.[133, 134] Thalidomide and dexamethasone is associated with a superior RR of approximately 50-55% in the relapse/refractory setting [135, 136]. The addition of an alkylating agent (e.g. cyclophosphamide or melphalan) increases RR to 75-80% [137, 138].Thus the use of thalidomide remains an option for patients with RRMM, especially if patients are thalidomide-naive, when oral treatment is needed or when patients are not otherwise eligible for Bortezomib, lenalidomide or pomalidomide.

Bortezomib monotherapy induces an ORR of approximately 35-40% in relapsed, refractory MM, with an average duration of response of 1 year [139-141].Dexamethasone ought to be added to bortezomib (Bd) upfront, which improves ORR by a further 20% according to the Australian BOMER study which compared up-front Bd to a matched cohort of patients on the APEX study[142]. Increased efficacy is seen with triplet combinations of Bd with either cyclophosphamide or anthracycline[143, 144] (table 9). In Australia, bortezomib is reimbursed by the PBS for the treatment of patients with progressive MM after at least one prior line of treatment; retreatment is allowed for patients who have had prior bortezomib treatment provided no prior bortezomib refractoriness (prior progression during or within 6 months of cessation of bortezomib) has occurred.

In patients who relapse after prior lenalidomide, the addition of pomalidomide to bortezomib and dexamethasone (PBd) is superior to Bd alone (med PFS 12.2 (PBd) vs. 7.1m (Bd), HR 0.61, p<0.0001), according to the randomised phase III OPTIMISMM study[145]. This combination is approved by the TGA for patients with RRMM post at least one prior line of treatment including lenalidomide, but is yet reimbursed by the PBS for this indication.

Carfilzomib is a second-generation PI that is now PBS reimbursed for the treatment of patients with relapsed MM after at least one prior line of treatment. This was based on the phase III Endeavor study that showed combination carfilzomib and dexamethasone (Kd) was superior to bortezomib and dexamethasone (Bd) with respect to PFS [18.7m (Kd) vs. 9.4 (Bd), HR 0.53, p<0.0001] and OS [47.6m (kd) vs. 40m (Bd), HR 0.79, p=0.01][146] Carfilzomib was given at a dose of 20/56mg per m2: 20mg/m2 IV on cycle 1 days 1 and 2, then 56mg/m2 from cycle 1 day 8 onwards; the standard schedule is twice weekly: day 1,2,8,9,15,16 in a 28-day cycle. According to the phase III randomised ARROW study, once weekly schedule of carfilzomib 20/70mg per m2 (ie. 20mg/m2 cycle 1 day 1 then 70mg/m2 cycle 1 day 8 onwards) was just as effective as twice weekly 20/27mg per m2 (ie. 20mg/m2 cycle 1 day 1 then 27mg/m2 cycle 1 day 8 onwards) with respect to response rates and PFS, and with comparable safety. Nonetheless, the once weekly 20/70mg per per m2 schedule should not be assumed to be equivalent to a twice weekly 20/56mg per m2 when carfilzomib is used as doublet with dexamethasone as is in the Endeavor study. The addition of cyclophosphamide to Kd (KCd) is safe and effective; preliminary data from the UK Muk Five study demonstrated superiority of KCd over VCd with respect to rate and depth of response in patients with 1st relapse (ORR 84% (KCd) vs. 68.1% (VCd), p=0.001), particularly those with high-risk cytogenetics del17p. Continuation of Kd beyond the initial 6 cycles of KCd for 18 months induced better PFS than no maintenance (from start of maintenance, 11.9 vs. 5.6m, HR 0.59, p=0.0086)[147]. In combination with thalidomide and dexamethasone (KTd), the Australian ALLG MM018 study demonstrated high ORR (82%; ≥VGPR 65%; CR 16%) with a median PFS not reached after median follow up of 7.2m (1 year PFS 67.7%)[148]. Of note on PBS, thalidomide is not reimbursed when used in combination with carfilzomib.

The most common side effects of carfilzomib are hypertension (14% grade≥3), fatigue (7% grade≥3), dypsnoea (6% grade≥3), anaemia and thrombocytopenia which are all manageable. Cardiac-related events including cardiac failure, dyspnoea, and arrhythmias were identified in early studies; in the Endeavor study, cardiac failure was more common on the carfilzomib arm (all grade ~6% vs. ~2% (Bd)). We suggest pre-treatment hydration be left to the discretion of treating doctor, but is not usually required beyond first cycle.

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

In general, incorporation of IMiDs or PIs at first relapse appear to produce a superior outcome compared to their use as later lines of salvage-treatment[149, 150]. Alkylating agents such as cyclophosphamide and melphalan have traditionally been the chemotherapy-backbone on which to add IMiDs and proteasome inhibitors.

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

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

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

We recommend enrolment into a clinical trial if one is available as first option.

Switch drug class, especially if remission to prior drug was short or patient had concerning associated toxicity

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

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

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

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

The landscape of treatment of MM continues to expand. Over recent years a myriad of new drugs and drug groups have made debut, some of which have been shown to successfully salvage heavily pre-treated patients who are double refractory (refractory to bortezomib and lenalidomide), triple refractory (refractory to bortezomib, lenalidomide cytostatic agent), quadruple refractory (refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide) and even penta-refractory (refractory to bortezomib, carfilzomib, lenalidomide and pomalidomide and an anti CD38 mAb (daratumumab or isatuximab). There is no doubt that with increasing effective salvage options, OS for patients with MM is set to soar in the not too distant future. The main issue for Australia, as is the case with many countries around the world is affordable drug access of novel agents.

In Australia, we are blessed with a national health care system that provides subsidised access to health care services through Medicare and prescription drugs through the Pharmaceutical Benefits Scheme (PBS). The regulatory approval of anti-myeloma therapeutics by the Australian Therapeutics Good Administration (TGA), in turn paves way for consideration for PBS subsidisation of a novel drug but usually lags behind that of the US Food and Drug Administration (FDA) which is the regulatory equivalent of the Australian TGA, approval of novel agents.

Below is a non-exhaustive overview of the most promising agents that may or may not be TGA approved but are not PBS reimbursed. Amongst these, that which have received TGA approval for the treatment of MM are the second generation PI ixazomib, the monoclonal antibodies (mAb) daratumumab and elotuzumab, and the histone deacetylase inhibitor (HDACi) panobinostat. The others are in early phase of development and include novel immune therapies, chimeric antigen receptors (CAR-T), bispecific T cell engagers (BiTEs), antibody drug conjugates (ADCs) as well as small molecules including the BH3-mimetic, venetoclax, the selective inhibitor of nuclear export (SINE), selinexor, and the eEF1A2 inhibitor, plitidepsin which has received TGA approval for the treatment of RRMM in Australia as of February 2018.

Second Generation Proteasome inhibitors (PI):

Second generation proteasome inhibitors include carfilzomib, ixazomib, marizomib and oprozomib.

Carfilzomib is PBS reimbursed in combination with dexamethasone (Kd) for patients with RRMM who have had at least one prior line of treatment. Its use in combination with lenalidomide (KLd) is not PBS reimbursed in Australia, but was TGA approved based on superiority of KLd over Ld in the the pivotal phase III ASPIRE study with respect to PFS (HR 0.69, p=0.0001) and OS with(HR 0.79, p=0.04)[151]. Carfilzomib is not TGA nor PBS reimbursed for front line treatment in MM. Triplet combination carfilzomib, melphalan, prednisolone (KMP) was not superior to the current standard of care bortezomib, melphalan and prednisolone (BMP) in the phase III CLARION study. Carfilzomib combined with other novel agents such as mAb (daratumumab or isatuximab) is being actively investigated in a number of ongoing studies in both front line and relapsed refractory disease.

Ixazomib (Ninlaro®, Takeda) is an oral second generation PI that is given weekly for 3 weeks in a 4-week cycle. Triplet combination of ixazomib and Ld (ILd) is superior to Ld doublet in the treatment of RRMM. ILd is superior to Ld with respect to PFS (HR 0.74, p=0.01) based on the phase II TOURMALINE-1 study[152]. In the upfront setting, combination ILd has been shown to be effective in a phase II study[153]; the TOURMALINE MM2 study that compares ILd to Ld is still ongoing. Ixazomib is a very well tolerated drug, and like carfilzomib is minimally associated with peripheral neuropathy. Because of this and the convenience of oral therapy, ixazomib was explored as maintenance therapy post ASCT in TE patients (TOURMALINE-MM3 study) and after induction in NTE patients (TOURMALINE-MM 4 study). Results of the TOURMALINE-MM3 study have been published showing superiority of ixazomib over placebo with respect to PFS[119] (see section 3.3.1); that for TOURMALINE MM-4 remains pending.

Currently, ixazomib is TGA registered for the treatment of patients with RRMM who have had at least 1 prior line of treatment, in combination with lenalidomide and dexamethasone. It is not PBS reimbursed.

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

Monoclonal antibodies (mAb):

Daratumumab (Darazalex®; Janssen) is the first in class human IgG1K against CD38 that induces myeloma cell killing via three mechanisms including induction of NK-cell mediated antibody dependent cytotoxicity (ADCC), complement dependent cytotoxicity and direct apoptosis by crosslinking and/or allosteric inhibition on CD38 enzymatic activity. As monotherapy, daratumumab induced an impressive ORR 31% (≥VGPR 13%) and PFS 19.9 months in a group of heavily pretreated patients who were mostly (86%) refractory to both IMIDs and PI[154]. When added to the backbone of Ld (phase III POLLUX study)[155] or Bd (phase III CASTOR study[156]), daratumumab improved rate and depths of response for RRMM, in particular impressive rates of MRD (10-5) negativity in the order of 14-23% and PFS (HR 0.37 (p<0.0001) for POLLUX study and 0.39 (p<0.0001) for CASTOR study, respectively). For upfront treatment in TIE patients, daratumumab in combination with the current backbone of BMP (phase III randomised ALCYONE study)[157] or Ld (phase III randomised MAIA study)[158] significantly improved PFS (HR 0.5 for Dara-BMP vs. BMP, p<0.001; HR 0.55 for Dara-Ld vs. Ld, p<0.0001).

In Australia, daratumumab is TGA registered for patients who have had at least one prior line of treatment in combination with Bd or Ld, and for patients who had at least 3 prior lines of treatment including a PI and IMID or who are refractory to PI and IMId as monotherapy. Daratumumab is also TGA registered for use in combination with BMP for TIE patients with NDMM. TGA submission for Daratumumab-Ld combination has yet to occur as of June 2019. Daratumumab is not reimbursed by the PBS as of June 2019.

Isatuximab (formally known as SAR650984, Sanofi) is another mAb against CD38, that has similar mechanism of action profile to daratumumab. A phase Ib trial evaluating the combination of isatuximab, lenalidomide and dexamethasone showed a robust response (ORR 56%) 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; median PFS was 8.5 months[159]. Other studies with isatuximab in combination with various novel therapeutic agents in both the upfront and relapse/refractory setting are ongoing. Currently, isatuximab is not TGA registered for the treatment of MM in Australia.

Elotuzumab (Empliciti®, Bristol-Myers Squibb) is a humanised mAb to SLAMF7 (also known as CS1; signalling lymphocytic activation molecule 7), 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 antibody dependent cytotoxicity (ADCC), its efficacy as monotherapy in MM is only modest due to defective NK cell function in patients with MM. However, when combined with lenalidomide, that is known to enhance NK cell function, the combination elotuzumab,lenalidomide and dexamethasone (ELd) in the phase III ELOQUENT-2 study [160] resulted an ORR of 79%, and is superior to Ld with respect to PFS (HR 0.7, p<0.001) and on long-term follow up, also OS (HR0.77, p=0.026). Based on this data, ELd has also received TGA approval for treatment of RRMM in patients who have received 1 to 3 prior therapies, to date has not been submitted for PBS reimbursement consideration.

Other mAbs 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[161]. Several HDACi have been tested in MM such as panobinostat (FarydakTM), 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[162]. Here, combination panobinostat, bortezomib anddexamethasone was superior to bortezomib anddexamethasone 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[163]. 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[161]. Currently panobinostat in combination with Bd is TGA approved for the treatment of RRMM in patients who have had at least 2 prior therapies.

Bendamustine:

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[164]. In phase I and II trials, bendamustine was efficacious as monotherapy, and in combination with thalidomide, lenalidomide or bortezomib[165]. 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[166]Currently, bendamustine is not TGA approved or reimbursed by the PBS for the treatment of myeloma.

Novel small Molecules:

A number of promising novel small molecules have emerged over recent years. Selinexor (Karyopharm) is an oral first in class selective inhibitor of nuclear export (SINE) which specifically blocks exportin-1 (XPO1), and ultimately results in both the nuclear retention and activation of tumour suppressor genes as well as translational suppression of oncogenes. Based on the phase 2b STORM study, selinexor was the first agent to have demonstrated clinically meaningful activity (≥PR 26.2%) in a group of penta refractory patients with otherwise dismal prognosis (expect median OS 1.3-3.5m) and no established beneficial therapies at current time[167]. As of October 2018, selinexor was granted FDA priority review designation for the application for accelerated approval of for patients with ≥ 3 prior lines of therapy.

Venetoclax (Venclexta®, Abbvie) is a BCL-1 inhibitor that has TGA approval for the treatment of patients with relapsed CLL. In multiple myeloma, venetoclax is particularly effective for patients with t(11;14) with high Bcl-2 expression, inducing an ORR of 86% in this population in a phase I dose escalation study[168], although venetoclax is not uniquely effective for this population. Venetoclax is currently being investigated in combination with PI (bortezomib or carfilzomib) and other novel therapeutics. As of June 2019, venetoclax is yet to be approved by FDA nor TGA for the treatment of MM.

Plitidepsin (Aplidin®, Specialised Therapeutics) is a novel molecule that targets the proto-oncogene eEF1A2 (human translation elongation factor 1α2) and mediates pleotrophic anti-myeloma affects including cell cycle arrest and apoptosis via alternations in a number of signalling pathways. The phase III randomised ADMYRE study demonstrated that combination plitidepsin and dexamethasone was superior to dexamethasone with respect to PFS (3.8m vs. 1.9m (dex), HR 0.61, p=0.004) and OS (11.6m vs. 6.4m, HR 0.64, p=0.0015) despite the fact that 44% of patients in the dexamethasone arm crossed over to the plitidepsin-dexamethasone arm[169]. Base on this, plitidepsin was approved by the TGA for the treatment of RRMM after ≥3 prior treatment lines including an IMID or PI, or ≥2 prior lines upon refractoriness and/or intolerance to both IMID and PI. It is not reimbursed on the PBS as of June 2019.

Other immune therapies.

In addition to mAbs, other immune therapies that are making rapid headways in the treatment of MM include chimeric antigen receptor T cells (CAR-T), bispecific T cell engagers (BiTEs) and antibody drug conjugates (ADCs) amongst others.

CAR-T cells are autologous T cells that are genetically engineered ex-vivo, to express an artificial receptor capable of recognising the antigen of interest on malignant cells. A number of competing products exists for MM, the forerunner of which is bb2121 (from Celgene and Bluebird bio) which received FDA breakthrough therapy designation in 2017. Reports from phase I CRB-401 trial showed that b12121 induced a ORR of 94% (56%CR) and a median PFS of 11.8m in heavily pre-treated patients with a median prior 8 lines of therapy[170]. While results are striking, CAR-T cells are still in its infancy in the treatment of MM, and logistical obstacles will limit its widespread use in the foreseeable future.

Unlike CAR-T cells, bispecific T cell engagers have the benefit of being an “off the shelf product”, but with equally striking efficacy, based on preliminary results on early phase studies. These are composed of a single chain variable fragment (scFV) of two linked mAb, one which targets CD3 on T cells and the other to a specific tumour antigen, thus enabling engagement between T cells and tumour cells. A number of competing products exists, targeting CD38 or BCMA on myeloma cells, all of which are in early phase clinical trials.

Currently, the only antibody drug conjugate that is in early phase clinical development for MM is belantamab mafodotin; this is humanised IgG1 anti-BCMA antibody conjugated to the microtubule disrupting agent monomethyl auristatin-F, which has received breakthrough therapy designation from the US FDA in 2017.

5 CONCLUDING REMARKS

The treatment for multiple myeloma has become more complex as the therapeutic landscape expands. What is considered as standard therapy will continue to change as trial data mature with respect to newer-therapeutic agents. It is important to note that the standard of care in Australia may differ from that in the US and Europe, and is based on what is reimbursed by the Australian PBS, which in turn, is subjected to rigorous evidence-based and cost analysis assessment. At present, MM remains an incurable disease. It is anticipated that survival for patients with MM will continue to improve as more effective novel agents are approved and made available for use in the clinic. The above treatment guideline from the Australian Medical Scientific Advisory Group (MSAG) to Myeloma Australia are based on current published data, local clinical experience and PBS-approved therapies. We believe that a national consensus of treatment algorithm for MM will not only improve patterns of care nationally, but will also establish a foundation for future clinical studies that are locally-relevant.

The above guideline is based on up-to-date information as of October 2019. Some aspect of this guideline may change in the future depending on emerging data from clinical studies. This guideline is due for review in October 2021.

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