

CLINICAL PRACTICE GUIDELINE

Management of patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplantation

Georgia McCaughan, Simon Harrison and Hang Quach
on behalf of MSAG

MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG) TO MYELOMA AUSTRALIA (MA)
2026

Medical & Scientific Advisory Group (MSAG) Panel Members:

Georgia McCaughan – NSW

Doug Joshua – NSW

Miles Prince – VIC

Cindy Lee – SA

Silvia Ling – NSW

Hang Quach – VIC

Jessica Heenan – TAS

Wilfred Jaksic – SA

Adam Bryant – NSW

Anna Kalff – VIC

Simon Harrison – VIC

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Dipti Talaulikar – ACT

Andrew Spencer – VIC

Bradley Augustson – WA

Nicholas Weber – QLD

Christian Bryant – NSW

Nicole Chien – NZ

Wojt Janowski – NSW

Niri Anderson – QLD

MSAG Associate Members:

Dejan Radeski – WA

Shirlene Sim – VIC

Matthew Rees – VIC

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Introduction

Survival outcomes for patients with newly diagnosed multiple myeloma (MM) have improved dramatically over the past 2 decades.^{1,2} National and institutional registries have demonstrated that patients considered transplant eligible at diagnosis have a median overall survival (OS) of more than 10 years with modern induction regimens.^{3,4} Potent induction regimens incorporating immunomodulatory drugs and proteasome inhibitors, with or without a CD38-directed monoclonal antibody, are now considered standard of care in transplant-eligible patients.⁵⁻¹¹

These induction regimens achieve deeper pre-transplant responses than historical regimens, with 45% to 65% of patients receiving lenalidomide-bortezomib-dexamethasone (RVD) induction achieving a very good partial response (VGPR) or better. The incorporation of a CD38 monoclonal antibody further improves outcomes, with the addition of daratumumab to RVD resulting in a significant improvement in progression-free survival (PFS).¹² This was also demonstrated with the addition of daratumumab to bortezomib-thalidomide-dexamethasone (VTD), with an improvement in both PFS and OS.¹³ In CASSIOPEIA (Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma), the PFS in the Dara-VTD arm was close to 7 years.¹³ However, even in the era of combination immunomodulatory agents and proteasome inhibitors +/- an anti-CD38 monoclonal antibody, upfront high-dose therapy (HDT) and autologous stem cell transplantation (AuSCT) following induction remain the accepted standard of care.^{5,8,11,14}

HDT and AuSCT following RVD induction have been demonstrated to significantly prolong PFS, albeit without an improvement in OS, due to effective salvage therapy.^{5,8}

These guidelines have been developed by the Medical and Scientific Advisory Group (MSAG) of Myeloma Australia for patients deemed eligible for HDT and AuSCT in the Australian context.

Levels of evidence and grades of recommendations used in these guidelines are listed in **Table 1**.

Table One

Levels of evidence and grades of recommendations

LEVELS OF EVIDENCE	
1A	Evidence from meta-analysis of randomised controlled 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).

Recommendations for induction therapy

- Transplant-eligible patients should be treated with 3 to 6 cycles of induction prior to AuSCT, aiming for at least a partial response prior to transplant (Grade A recommendation, Level II evidence)
- Lenalidomide-bortezomib-dexamethasone is the recommended induction regimen in most transplant-eligible patients in Australia, given that a monoclonal CD38 antibody is not reimbursed in the upfront context (Grade A recommendation, Level II evidence)
Bortezomib should be given subcutaneously when possible. A twice weekly schedule of bortezomib is important when rapid disease control is required, particularly in the setting of renal failure associated with cast nephropathy, with particular care in monitoring for neuropathy symptoms and adjusting dose accordingly. Otherwise, a modified weekly bortezomib schedule is acceptable to minimise the risk of peripheral neuropathy at the outset (Grade B recommendation, Level III-3 evidence)
- For patients with acute, severe renal impairment, an alternative bortezomib-based regimen such as VD, VCD or VTD can be considered for induction prior to AuSCT (Grade B recommendation, Level II evidence)
- For patients with evidence of systemic light-chain amyloidosis, in whom standard-dose lenalidomide is not well tolerated, daratumumab-cyclophosphamide-bortezomib-dexamethasone is reimbursed by the Australian Pharmaceutical Benefits Scheme (PBS) and should be used (Grade A recommendation, Level II evidence)
- While the incorporation of an anti-CD38 monoclonal antibody in induction in newly diagnosed transplant-eligible MM, based on PERSEUS and CASSIOPEIA, is considered the global standard of care, daratumumab is not currently reimbursed for the upfront treatment of MM in Australia (Grade A recommendation, Level I evidence)

Comparing upfront versus deferred transplantation following RVD induction

Upfront AuSCT following induction remains the current standard of care.

Updated analysis of the IFM-2009 study comparing upfront versus deferred transplantation following RVD induction confirmed a significant improvement in outcome with upfront AuSCT, with a median PFS of 47.3 months versus 35 months ($P = 0.001$),^{5,17} but no OS advantage at a median follow-up of 89.8 months.¹⁷ A PFS benefit was also seen in the Phase III DETERMINATION study, with a median PFS of 67.5 months with upfront transplant compared with 46.2 months with deferred transplant,⁸ with notable benefits in those with high-risk cytogenetics (presence of 17p deletion, t(4;14) or t(14;16)): 55.5 months versus 17.1 months. As with IFM-2009, at a median follow-up of 76 months, no OS benefit was seen.⁸ Analysis of paired samples from IFM-2009 demonstrated that patients who underwent upfront AuSCT had significantly increased mutational burden at relapse; however, the clinical significance of this remains unclear.¹⁸

In addition to survival outcomes, health-related quality of life (HRQoL) is increasingly recognised as an important endpoint in the evaluation of treatment benefits. Consistent with other studies, data from the IFM-2009 demonstrate a temporary deterioration in HRQoL at the time of AuSCT with subsequent recovery to baseline,¹⁹⁻²¹ and in both treatment arms of this study they were sustained, clinically meaningful improvements in HRQoL.¹⁹⁻²¹

Although upfront AuSCT remains the standard of care, transplant deferral is a reasonable consideration in standard risk patients given the equivalent OS seen in IFM-2009 and DETERMINATION.^{5,8} However, it should be noted that those patients with standard-risk cytogenetics still had a significant PFS benefit at 82.3 months versus 53.2 months with upfront AuSCT in DETERMINATION.⁸ The rate of subsequent autologous transplantation in those patients randomised to deferred transplantation was 79% in IFM-2009 and 28% in DETERMINATION.^{5,8}

Taken altogether, when induction therapy incorporating an immunomodulatory agent and proteasome inhibitor is used, patients who are considered transplant eligible at diagnosis should undergo HDT and AuSCT as part of upfront therapy, given the significant PFS benefit, which is particularly marked in those with high-risk cytogenetics. Whether this will still hold true with the use of quadruplet induction with an anti-CD38 monoclonal antibody or when T cell-redirection therapies are incorporated into upfront treatment remains to be seen, in particular given the concerns regarding increased mutational burden and secondary primary malignancies with high-dose melphalan and AuSCT (**Table 2**).

Who is transplant eligible?

Assessment of transplant eligibility is individualised and must consider age, comorbidities, frailty, disability and patient preferences. Available tools that assess these factors include the IMWG Frailty Index,²² Myeloma Comorbidity Index²³ and HCT-CI,²⁴ which may inform a clinician's assessment of suitability for HDT and AuSCT but are not validated specifically for this purpose.

Clinical trials incorporating AuSCT have typically utilised an upper age limit of 65^{5,8}; however, in practice, fit patients older than 65 are often considered transplant eligible. There is both clinical trial and retrospective registry-based data that demonstrate that AuSCT can be safely performed in selected older patients up to age 75 without a significant increase in transplant-related morbidity.²⁵⁻²⁸

In summary, AuSCT should be performed in any patient with newly diagnosed myeloma who is considered eligible, which may include selected patients up to age 75 who are fit. However, concerns over increased transplant-related morbidity in those who are more elderly should be borne in mind, especially given daratumumab-lenalidomide-dexamethasone is now PBS reimbursed for transplant ineligible patients.

Induction regimens

Standard induction strategies for patients with newly diagnosed MM who are considered transplant eligible are summarised in **Table 2**.

The most frequently used induction strategy in patients considered transplant eligible in Australia is the triplet regimen RVD, which has not been directly compared to other induction regimens including bortezomib–cyclophosphamide–dexamethasone (VCD) or VTD in a Phase III study. A cross-trial comparison of GEM2005 and GEM2012 demonstrated a statistically significant improvement in rates of VGPR or better following six cycles of RVD compared to six cycles of VTD.²⁹ Given the improved response rates and better toxicity profile, RVD has been adopted as the standard of care induction therapy in most transplant-eligible patients. However, in the setting of severe renal impairment, there is an increased risk of lenalidomide-related adverse events and lenalidomide dose modification is required, making the use of RVD more complex and less optimal in some cases.²⁹ In this setting, bortezomib/dexamethasone alone³⁰ or, alternatively, another bortezomib-based triplet regimen such as VCD or VTD^{31,32} can be considered, and lenalidomide can be introduced upon sufficient recovery of renal function.

There are a variety of RVD protocols available, and MSAG previously published a statement on the use of these.^{33,34} Although most clinical trials have utilised a strategy of twice weekly dosing of bortezomib, a regimen incorporating weekly subcutaneous bortezomib is usually appropriate, particularly in light of the comparable efficacy and significantly reduced rate of peripheral neuropathy.^{35–37} Twice weekly bortezomib may be used in situations where rapid disease control is essential, in particular in patients who present with acute renal failure secondary to cast nephropathy.^{30,31,38} The number of induction cycles with RVD has varied from three to six in upfront Phase III trials.^{5,6,8}

The optimal number of cycles is unclear, although it was noted that in the Phase III PETHEMA/GEM2012 study, response rates continued to improve during induction, with 55.6% achieving a VGPR or better by cycle 3, and 70.4% at the completion of six cycles of induction; however, there is continued risk of treatment-related toxicities.⁶

Carfilzomib–lenalidomide–dexamethasone (KRd) has been utilised as an induction strategy in clinical trials, in particular in high-risk patients^{11,39,40}; however, there are no randomised trial data indicating that this approach is superior to RVD in transplant-eligible patients. In the Phase III ENDURANCE study, KRd did not improve PFS compared to RVD; however, this was in patients not being considered for AuSCT and excluded some high-risk patient groups, including t(14;16), t(14;20), del17p and high-risk GEP70 signature.⁴¹ The addition of a CD38 monoclonal antibody to induction treatment leads to improved response rates, minimal residual disease (MRD) negativity and PFS in transplant eligible patients.^{7,14,32,42} The PERSEUS study demonstrated a significant improvement in PFS with the addition of daratumumab to RVD with an estimated PFS at 48 months of 84.3% with daratumumab–RVD versus 67.7% with RVD (HR, 0.42; P < 0.0001).¹² It was also demonstrated in the CASSIOPEIA study that the addition of daratumumab to VTD induction improved PFS with a PFS of 83.7 months with daratumumab–VTD versus 67.7 months with VTD (HR, 0.61; P < 0.0001).¹³ Furthermore, in this study, the addition of daratumumab to VTD prolonged OS (HR, 0.55; P < 0.0001).

In alignment with the PBS reimbursement criteria, RVD is the standard of care induction in the Australian therapeutic context and patients should receive three to six cycles prior to proceeding with AuSCT aiming for a partial response prior to HDT and AuSCT.

The optimal approach in patients who do not achieve a partial response after RVD induction is unclear. Retrospective data suggest that proceeding to AuSCT is a reasonable approach in this high-risk group of patients.⁴³ Clinical trial enrolment or salvage therapy prior to AuSCT, particularly in the setting of progressive disease, may also be considered. Data from the ALLG MM17 study suggest that for patients who achieve a suboptimal response (<PR) to bortezomib-containing induction therapy prior to AuSCT, salvage therapy with a carfilzomib-based triplet (KTd: Carfilzomib, thalidomide, and dexamethasone) resulted in a high rate and depth of response prior to AuSCT (ORR 78%, CR 16%), with 3-year PFS and OS of 64% and 80% respectively.⁴⁴ However, such an approach is restricted in the Australian context, as the PBS will only reimburse a new treatment regimen if there is proven progressive disease.

For patients with evidence of systemic AL amyloidosis, in whom standard-dose lenalidomide is not well tolerated,⁴⁵ daratumumab-cyclophosphamide-bortezomib-dexamethasone (Dara-CVD) should be used as per the ANDROMEDA study.⁴⁶ Please refer to the MSAG AL Amyloidosis guideline.⁴⁷

The recommendations regarding induction therapy are summarised in **Box 1**. Given the complexities of induction treatment and the related supportive care, we recommend utilising available patient support tools including Myeloma Treatment Scheduler (MyeTx), an online patient education tool pre-populated with MM treatment schedules, to assist in scheduling and compliance (<https://rego.interact.technology/myetx>).

Table Two

Standard induction regimens for upfront treatment

Regimen	Schedule	Responses
RVD (5, 6, 8, 37)	21 day SC Bortezomib 1.3mg/m ² Day 1, 4, 8, 11 Lenalidomide 25mg Day 1-14 Dexamethasone 20mg 1, 2, 4, 5, 8, 9, 11, 12	Post-induction ORR 81.5-92% ³ VGPR 45-67%
	28 day (weekly) SC Bortezomib 1.3m/m ² Day 1, 8, 15, 22 Lenalidomide 15-25mg Day 1-21 Dexamethasone 20mg Day 1, 2, 8, 9, 15, 16, 21, 22	
	35 day (weekly) SC Bortezomib 1.3m/m ² Day 1, 8, 15, 22 Lenalidomide 15-25mg Day 1-21 Dexamethasone 20mg Day 1, 2, 8, 9, 15, 16, 21, m2	
VCD (41, 54, 55)	21 day SC Bortezomib 1.3mg/m ² Day 1, 4, 8, 11 Cyclophosphamide 300mg/m ² PO Day 1, 8, 15, 22 Dexamethasone 20mg Day 1, 2, 4, 5, 8, 9, 11, 12	Post-induction ORR 83.4-88% ³ VGPR 56.2-61%
	28 day SC Bortezomib 1.3mg/m ² Day 1, 8, 15, 22 Cyclophosphamide 300mg/m ² PO Day 1, 8, 15, 22 Dexamethasone 20mg Day 1, 2, 8, 9, 15, 16, 22, 23	
VTD (35, 54)	SC Bortezomib 1.3mg/m ² SC on Day 1, 4, 8, 11* Thalidomide 100mg daily Dexamethasone Cycle 1-2: 40mg Day 1, 2, 8, 9, 15, 16, 22 and 23; Cycle 3-4 40mg D1, 2 and 20mg Day 8,9, 15 and 16 *Weekly bortezomib will reduce the risk of peripheral neuropathy.	Post-induction ORR 89.8% ³ VGPR 56%

Regimen	Schedule	Responses
Dara-RVD (7)	<p>PERSEUS – 28 day SC Daratumumab 1.8g: Cycle 1-2 weekly; Cycle 3-6 every 2 weeks; maintenance every 4 weeks SC Bortezomib 1.3mg/m² on Day 1, 4, 8, 11* Lenalidomide 25mg Day 1-21 Dexamethasone 40mg Day 1-4, 9-12</p> <p>*In practice bortezomib would be administered weekly</p> <p>Dara-RVD is not TGA approved or PBS reimbursed</p>	
Dara-VTD (47)	<p>CASSIOPEIA – 28 day IV Daratumumab 16mg/kg Cycle 1-2: Day 1, 8, 15, 22; Cycle 2-4 Day 16* SC Bortezomib 1.3mg/m² SC on Day 1, 4, 8, 11** Thalidomide 100mg daily Dexamethasone Cycle 1-2: 40mg Day 1, 2, 8, 9, 15, 16, 22 and 23; Cycle 3-4 40mg D1, 2 and 20mg Day 8,9, 15 and 16</p> <p>*In practice daratumumab would be 1.8g SC **Weekly bortezomib will reduce the risk of peripheral neuropathy</p> <p>Dara-VTD is TGA approved but not PBS reimbursed</p>	<p>Post Induction ORR 92.7 ³ VGPR 64.9</p>
Dara-VCD (51)	<p>ANDROMEDA – 28 day SC Daratumumab 1.8g: Cycle 1-2 weekly; Cycle 3-6 every 2 weeks; Maintenance every 4 weeks until maximum of 24 cycles. SC Bortezomib 1.3mg/m² Day 1, 8, 15, 22 Cyclophosphamide 300mg/m² (500mg cap) Day 1, 8, 15, 22 Dexamethasone 40mg Day 1, 8, 15, 22*</p> <p>*Dexamethasone 20mg in patients aged > 70 or at discretion of physician</p> <p>Dara-VCD is TGA approved and PBS reimbursed only for patients with newly diagnosed AL amyloidosis</p>	

VCD = bortezomib-cyclophosphamide-dexamethasone

VTD = bortezomib-thalidomide-dexamethasone

RVD = lenalidomide-bortezomib-dexamethasone

Stem cell mobilisation

All patients considered transplant eligible should undergo stem cell mobilisation and collection, irrespective of whether the intent is to offer transplant upfront or deferred transplant is being considered, unless the stored cells are unlikely to be used (**Box 2**).

Given the potential effect of lenalidomide on stem cell mobilisation, this should be performed after 3 or 4 cycles of RVD.^{5,6} The recommended target CD34+ cell collection for one planned AuSCT is $\geq 2 \times 10^6$ CD34+ cells/kg. In selected patients, aiming to collect for two transplants is reasonable and should be guided by institutional policies.

It is noted that the increasing development of novel therapies and the potential effect of melphalan on the occurrence of second malignancies may reduce the potential benefit to risk ratio of second transplants. Collection of CD34+ cells surplus to AuSCT need may also be considered to facilitate CD34 top up in the setting of treatment-related cytopenias, which may become more relevant as patients are living longer and more treatment options become available.⁴⁹

The potential mobilisation strategies are as follows: G-CSF alone (\pm plerixafor rescue),⁵⁰ plerixafor and G-CSF⁵¹ or cyclophosphamide with G-CSF.

G-CSF in combination with plerixafor or cyclophosphamide is superior in terms of stem cell yield compared to G-CSF alone.⁵¹⁻⁵³ However, cyclophosphamide mobilisation is associated with more toxicity than the other approaches, including febrile neutropenia and hospitalisation.^{52,53} Lower doses of cyclophosphamide (1.5–2g/m²) have been demonstrated to have non-inferior stem cell yields with a trend to a reduction in febrile neutropenia and are preferred if this strategy is used.⁵³ While an upfront mobilisation strategy utilising G-CSF alone with plerixafor rescue based on pre-apheresis peripheral blood CD34 count or a planned strategy of G-CSF and plerixafor is reasonable, the PBS restricts use of plerixafor to failure of chemomobilisation. Therefore, many centres continue to utilise intermediate-dose cyclophosphamide (1.5–2g/m²) with G-CSF as the preferred strategy, in particular if higher target stem cell collection is planned.

BOX TWO

Recommendations for stem cell mobilisation

- Stem cell mobilisation should occur after 3–4 cycles of RVD whether an upfront or deferred transplant strategy is planned (Grade A recommendation, Level II evidence).
- Stem cells can be mobilised with G-CSF alone (10 mcg/kg), G-CSF with plerixafor or G-CSF with cyclophosphamide (1.5–2 g/m²).
- If chemotherapy-mobilisation is being performed, intermediate dose cyclophosphamide (1.5–2 g/m²) is preferred to high-dose cyclophosphamide (>2 g/m²) given that stem cell yields are similar (Grade B recommendation, Level III-3 evidence).
- Plerixafor should be utilised for patients who fail to mobilise adequately with G-CSF alone or cyclophosphamide/ G-CSF; plerixafor is reimbursed by the Australian PBS for the latter indication.

High Dose Therapy and Autologous Stem Cell Transplantation

Melphalan dosing

All patients undergoing HDT and AuSCT with normal renal function should receive a melphalan dose of 200 mg/m². Registry data suggest poorer outcomes with the use of 140 mg/m², although this in part reflects patient factors that led to the dose reduction.²⁶ In addition, there are randomised data demonstrating no benefit in terms of PFS or OS with the addition of melphalan 140 mg/m² + AuSCT following lenalidomide-dexamethasone induction compared with lenalidomide-dexamethasone alone, and hence if a patient is not considered fit for melphalan 200 mg/m², then careful consideration regarding the appropriateness of transplantation should occur,⁵⁴ in particular given the recent Pharmaceutical Benefits Advisory Committee's positive recommendation for the reimbursement of daratumumab-lenalidomide-dexamethasone. Patients with renal impairment benefit from AuSCT,⁵⁵ but a dose reduction to 140 mg/m² should be considered in those with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m².^{31,56,57}

Single versus tandem transplant

Tandem AuSCT is a strategy designed to deepen and prolong responses, whereby the second sequential HDT + AuSCT is performed within 3–6 months of the first. There are conflicting data regarding this approach with novel induction strategies and improved salvage regimens. The STaMINA study, in which the majority of patients received RVD induction (55%), did not show a benefit of tandem HDT and AuSCT over a single HDT and AuSCT in terms of PFS and OS.⁵⁸ However, on updated follow-up, in an as-treated analysis (rather than intention-to-treat), 6-year PFS was significantly higher in those who underwent tandem transplantation at 49.4% compared with 39.7% (RVD consolidation) and 38.6% (no consolidation).⁵⁹ This appeared to be driven by patients with high risk, with a 6-year PFS of 43.6% in those who underwent tandem AuSCT versus 26% who did not receive consolidation.⁵⁹ In contrast, the EMN02 study, in which patients had received VCD induction, demonstrated an improvement in 5-year PFS (53.5% vs. 44.9%, $P = 0.036$) and OS (80.3% vs. 72.6%, $P = 0.002$)⁶⁰ with tandem AuSCT. High-risk patients had a median PFS of 46 months versus 26.7 months that was not statistically significant ($P = 0.062$) and in the subgroup with del17p, the HR for progression or death favoured tandem AuSCT versus single AuSCT (HR, 0.24; $P = 0.006$).

The reason for the discrepant results between these two studies is not clear. One explanation is that most patients in STaMINA received a more potent induction regimen, including an immunomodulatory agent, which may have abrogated the benefit of the second AuSCT. It remains unclear if there is an ongoing benefit of tandem HDT and AuSCT with the use of an induction regimen incorporating an immunomodulatory agent and proteasome inhibitor. The possible impact of two doses of high-dose melphalan, especially in a relatively short time period, on second malignancy is also unknown. Currently, tandem AuSCT may still be considered appropriate in eligible patients with high-risk MM, including high-risk cytogenetics, in particular del17p.

Consolidation and Maintenance Strategies

Consolidation

The role of non-tandem AuSCT consolidation also remains unclear. All Phase III trials of RVD induction utilise two cycles of consolidation following HDT and AuSCT.⁵⁻⁸ The previously discussed STaMINA study demonstrated no benefit of four cycles of RVD consolidation following AuSCT, while the EMN02 study demonstrated a significant benefit with regards to PFS and OS in those receiving two cycles of RVD consolidation.^{58,60,61}

The lack of benefit in the STaMINA study may be related to the majority of patients receiving lenalidomide in induction, compared to those patients in EMN02 receiving VCD, and also the longer period of induction (median time since initiation of treatment to enrolment 5.2 months) compared to three or four cycles of VCD in EMN02. The uncertain benefit of consolidation after HDT and AuSCT should be discussed with patients. It is reasonable to offer consolidation to patients who have tolerated induction well and do not have peripheral neuropathy.

Maintenance

Maintenance lenalidomide has been demonstrated to improve OS and should be considered standard of care following AuSCT.⁶² The ideal duration of maintenance lenalidomide is not clear, and there are ongoing studies exploring planned cessation and response-adapted cessation. We recommend continuation until progression or unacceptable toxicity.⁸

Patients should be informed of the risk of second malignancies with appropriate discussion of the risks and benefits, especially after 2–3 years following AuSCT, at which time increased rates of secondary malignancy have been found in some studies.^{5,63} Age-appropriate malignancy screening should be performed.⁶² Bortezomib maintenance was evaluated in the Phase III 65/GMMG-HD4 study, which demonstrated a PFS benefit in patients receiving bortezomib maintenance compared to thalidomide; however, these patients also received different and historical induction regimens (vincristine-doxorubicin-dexamethasone (VAD) versus bortezomib-doxorubicin-dexamethasone (PAD)), making it difficult to extrapolate these data.⁶⁴ The combination of carfilzomib and lenalidomide (with or without dexamethasone) as maintenance has been evaluated in the ATLAS and FORTE studies and has been demonstrated to significantly improve PFS, with no evidence of an OS benefit.^{11,65} The combination of bortezomib and lenalidomide as maintenance following AuSCT has not been evaluated in a prospective clinical trial; however, a retrospective analysis utilising this approach in high-risk patients demonstrated a PFS of 42.4 months, which compared favourably with historical data.³ CD38-directed monoclonal antibody maintenance therapy has been studied.^{7,14,66} In CASSIOPEIA, following Dara-VTD or VTD induction, daratumumab maintenance improved PFS compared with observation alone (HR, 0.53; $P < 0.0001$).⁶⁶ Of note, in the patients who received Dara-VTD induction, PFS was not significantly improved in the group of patients randomised to daratumumab maintenance compared with observation.⁶⁶

The current standard of care for maintenance therapy is continuous lenalidomide until toxicity or progression. High-risk patients may benefit from an alternative, more intensive maintenance strategy. The benefit of the continuation of lenalidomide in the context of sustained MRD negativity, given the concern regarding secondary primary malignancies, is uncertain, and there are ongoing studies evaluating its cessation.^{67,68}

Monitoring post autologous stem cell transplantation

The median PFS with RVD induction, AuSCT and continuous lenalidomide maintenance in the DETERMINATION study was 67.5 months (95% confidence interval, 58.6 months—not reached). The post-transplant response should be assessed 3 months after transplantation. A bone marrow biopsy is required to confirm complete response and MRD assessment via next-generation flow cytometry or next-generation sequencing may be performed, although it is not currently reimbursed in Australia.

Premaintenance fludeoxyglucose positron emission tomography also provides prognostic information, although the results are unlikely to influence management.⁶⁹

Following AuSCT, patients are usually followed at least 3 months, including clinical assessment, serum and urine EPG/IFE (Electrophoretogram/Immunofixation), SFLC (Serum Free Light Chains), FBC (Full Blood Counts), EUC (Electrolytes, Urea & Creatinine), CMP (Comprehensive Metabolic Panel) and imaging as clinically indicated.

Role of allogeneic stem cell transplantation

In the era of upfront combination immunomodulatory agents, proteasome inhibitors +/- CD38 directed monoclonal antibody induction, there is a limited role for allogeneic stem cell transplantation in the management of MM outside of clinical trial. If allogeneic stem cell transplantation is being considered, it should be performed at centres with expertise in this area.

Patients with high-risk MM

Patients with high-risk MM continue to have inferior survival outcomes with the current standard of care.^{5,8} Available staging systems to identify these patients include ISS, R-ISS and R2-ISS, noting that the R2-ISS better predicts PFS and OS in those with high-risk disease.⁷⁰ Of these, R-ISS and R2-ISS incorporate cytogenetic information (del17p, t(4;14) and t(4;16) in R-ISS, in addition to gain1q in R2-ISS).

The IMS consensus on the genomic definition of high-risk myeloma proposed in 2024 defines high-risk disease as del17p in >20% of sorted plasma cells; TP53 mutation (with no threshold VAF); biallelic del(1p32) or two of the following: gain/ amplq, monallelic del(1p32) or t(4;14) or t(14;16) or t(14;20).⁷¹ Of note, there are also other features that can identify other patients with high-risk disease, including gene expression profiling,⁷² detection of circulating plasma cells and presence of extramedullary disease.^{73,74}

Achieving deep responses, including MRD negativity, is crucial for high-risk patients.⁷⁵⁻⁷⁹

The MASTER study, which had planned enrichment of patients with high-risk cytogenetic abnormalities, utilised daratumumab-KRD induction, AuSCT and MRD-adapted daratumumab-KRD consolidation.⁷⁵ At a median follow-up of 42.2 months, this study demonstrated favourable survival outcomes for patients with one high risk cytogenetic abnormality (3-year PFS 79% and OS 92%) compared with those with no high-risk cytogenetic abnormalities (PFS 88% and OS 94%). However, those patients with two or more high-risk cytogenetic abnormalities (considered 'ultra high risk') had inferior 3-year PFS at 50% and OS at 75%.⁷⁶ The GMMG-CONCEPT study enrolled high-risk patients defined by ISS II/III combined with del17p, t(4;14), t(14;16) or more than three 1q21 copies and evaluated isatuximab-KRD induction, consolidation and IsaKR maintenance with or without AuSCT.⁷⁷ This trial demonstrated a 3-year PFS of 68.9% in transplant-eligible patients and 58.4% in transplant ineligible patients.⁷⁷ Similarly to MASTER, patients with two or more high-risk cytogenetic abnormalities had inferior outcomes⁷⁷ even with this intensive induction and consolidation approach. As discussed previously, given the survival benefit seen with tandem transplantation in the EMN02 study and the supportive data in the high-risk cohort of STAMINA, we recommend consideration of tandem transplantation in young patients with high-risk disease followed by maintenance therapy. This is of particular importance in Australia, where upfront monoclonal CD38 antibodies are not reimbursed and MRD-adapted therapy is not feasible or accessible. Available international guidelines recommend combined proteasome inhibitor and immunomodulatory agent maintenance in patients with high-risk disease. As mentioned, the ATLAS and FORTE studies demonstrated an improvement in PFS with the addition of carfilzomib to lenalidomide maintenance (with or without dexamethasone),^{11,65} and while bortezomib and lenalidomide maintenance following AuSCT has not been evaluated in a prospective clinical trial, a retrospective analysis utilising this approach in high-risk patients demonstrated a PFS of 42.4 months, which compared favourably with historical data.³ The Emory RVD1000 retrospective analysis utilised risk-adapted maintenance with lenalidomide ± bortezomib and demonstrated excellent PFS of 65 months and OS of 126.6 months in the whole cohort.³ In Australia, dual maintenance is not reimbursed, and lenalidomide remains standard of care, and lenalidomide maintenance has been demonstrated to improve survival in these patients.^{62,80}

Conclusion

In the current era, where induction for fit patients consists of an immunomodulatory agent, proteasome inhibitor and dexamethasone with or without the addition of a CD38 monoclonal antibody, AuSCT remains the accepted standard of care in Australia for eligible patients. For patients with high-risk disease, achieving deep responses is particularly important, and tandem transplantation should be considered in young patients. We recognise the concern regarding genomic instability and secondary malignancies; however, the currently available evidence continues to support the benefit of upfront AuSCT for eligible patients. In the future, AuSCT may be superseded by the upfront use of CAR-T and bispecific antibodies, and this is being evaluated in ongoing clinical studies.

The above guideline is based on up-to-date information as of January 2026. Some aspect of this guideline may change in the future depending on emerging data from clinical studies. This guideline is due for review after January 2028.

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

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