Received: 1 November 2023 | Accepted: 12 February 2024

DOI: 10.1111/bjh.19353

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

REVIEW

The role of maintenance therapy following autologous stem cell transplantation in newly diagnosed multiple myeloma: Considerations on behalf of the Chronic Malignancies Working Party of the EBMT

Angela Hwang[1] | **Patrick Hayden**[2] | **Charlotte Pawlyn**[3] | **Donal McLornan**[1] | **Laurent Garderet**[4]

[1]Department of Haematology, University College London Hospital NHS Foundation Trust, London, UK

[2]Department of Haematology, St James's Hospital, Dublin, Ireland

[3]The Institute of Cancer Research, London, UK

[4]Département d'Hématologie, Hôpital Pitié Salpêtrière, AP-HP, Paris, France

Correspondence
Laurent Garderet, Service d'Hematologie, Hôpital Pitié Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.
Email: laurent.garderet@aphp.fr

Funding information
EBMT

Summary
Recent treatment advancements in multiple myeloma have led to significant improvements in patient outcomes. Maintenance therapy following autologous haematopoietic stem cell transplantation (AHCT) is now standard of care and has been demonstrated to prolong and deepen treatment responses. Currently, lenalidomide remains the single agent that has been approved for maintenance post-AHCT in Europe and the USA which, if tolerated, is continued until disease progression. The treatment landscape is rapidly expanding however, and the optimal personalised maintenance approach for a patient is becoming more complex. Treatment outcomes for patients with high-risk disease remain poor and choice of maintenance in this population also remains unclear. This review article evaluates up-to-date literature regarding established maintenance approaches. It further analyses ongoing studies exploring maintenance regimens using combination and novel agents, approaches to maintenance in patients with cytogenetic high-risk disease and minimal residual disease response-adapted strategies that reflect the current evolving treatment paradigm.

KEYWORDS
BMT, maintenance therapy, multiple myeloma, myeloma therapy, stem cell transplantation

INTRODUCTION

Despite considerable advances in the treatment of multiple myeloma (MM), most patients still ultimately relapse. Maintenance therapy has become the standard of care following autologous haematopoietic cell transplantation (AHCT) as it has been shown to prolong and, in some patients deepen, treatment responses.

At present, lenalidomide remains the only agent approved in Europe and the USA for maintenance post-AHCT. Whether one agent or more is required to achieve sustained remissions continues to be evaluated as does the duration of maintenance, particularly for patients who demonstrate sustained minimal residual disease (MRD) negativity. In this review, we aim to provide an up-to-date, practical approach to maintenance therapy in MM by evaluating the evidence for both established and novel agents, approaches in high-risk disease and the role of MRD in guiding maintenance treatment and duration.

ROLE OF MAINTENANCE: CONVENTIONAL AGENTS

Immunomodulatory drugs (IMiDs)

Lenalidomide

Lenalidomide is well-established and widely used as maintenance therapy post-AHCT. Randomised phase 3 studies have demonstrated that lenalidomide improves progression-free survival (PFS) and some studies reported improved overall survival (OS). The Co-operative Cancer and Leukemia Group B (CALGB) 100104 study was one of the first phase 3 studies to compare lenalidomide versus placebo from 100 days following first AHCT.[1] In this study, 460 AHCT-eligible patients with newly diagnosed MM who had received at most two induction regimens and who had achieved a response of stable disease or better, were randomised in a blinded fashion to either lenalidomide ($n = 231$) or placebo ($n = 229$). Initial results demonstrated a significant improvement in time to progression (TTP) of 46 months with lenalidomide compared to 27 months for placebo ($p < 0.001$). Updated data at a median follow-up of 91 months, despite a significant crossover of eligible patients in the placebo arm to the lenalidomide arm, demonstrated that the median TTP was 57.3 months with lenalidomide versus 28.9 months for placebo (HR 0.57, $p < 0.001$). Median OS was significantly longer for those patients who received lenalidomide compared to those who received placebo (113.8 vs. 84.1 months, $p < 0.0004$).[2]

The French IFM2005-02 trial randomised patients younger than 65 years of age to post-AHCT maintenance treatment with either lenalidomide or placebo. Here, the duration of maintenance was fixed at 1 year during the study due to concerns regarding the rates of secondary primary malignancies (SPM) in other studies. At a median follow-up of 45 months, the study demonstrated an improved median PFS with lenalidomide maintenance (41 vs. 23 months with placebo, HR 0.50, $p < 0.001$). However, OS 3 years postrandomisation showed no significant difference between the groups (80% vs. 84% with placebo, HR 1.25, $p = 0.29$).[3] This seems to indicate that 1 year of lenalidomide maintenance is insufficient to prolong survival.

The Italian GIMEMA group conducted a phase III trial that randomised patients to receive lenalidomide maintenance or no maintenance following either a high dose melphalan (HDM) (200 mg/m^2) 'MEL200' AHCT or consolidation with melphalan–prednisone–lenalidomide. At a median follow-up of 51.2 months, median PFS was significantly improved in the lenalidomide maintenance group (41.9 vs. 21.6 months, HR 0.47, $p < 0.001$). Again, OS estimates at 3 years were similar in the two groups at 88.0% versus 79.2% ($p = 0.14$) respectively.[4]

A subsequent meta-analysis of these three randomised controlled trials confirmed the significant improvement in PFS with lenalidomide maintenance post-AHCT of 52.8 versus 23.6 months for placebo/observation (HR, 0.48; 95% CI, 0.41 to 0.55). Initial discordant OS data between studies were felt to be due to a few factors, an important one being that some studies were underpowered for OS as a primary end-point. The analysis demonstrated a significant 25% reduction in the risk of death with lenalidomide maintenance versus placebo or observation with a median OS of 'not reached' versus 86.0 months respectively ($p = 0.001$). In subgroup analysis, the largest OS benefit was seen in patients who had achieved at least a very good partial response (VGPR) after HDM and AHCT, or who had received a lenalidomide-based induction strategy.[5] To further improve on these results, the effect of adding corticosteroids to lenalidomide maintenance was evaluated in a phase III study that randomised patients to lenalidomide plus prednisone 50 mg on alternate days versus lenalidomide alone following HDM and AHCT or cyclophosphamide, lenalidomide and dexamethasone. Toxicity profiles were comparable; however, the addition of prednisone did not provide an OS advantage or a statistically significant improvement in PFS.[6]

The UK Myeloma XI study further evaluated outcomes in both transplant-eligible and -ineligible patients who received lenalidomide maintenance or placebo. This was an open-label, randomised phase III trial with three randomisation stages: (1) induction as determined by transplant eligibility, (2) intensification as determined by response to induction and (3) maintenance versus none. A total of 1137 patients were assigned to lenalidomide maintenance and 834 to observation. At a median follow-up of 31 months, median PFS was improved in the transplant-eligible lenalidomide group (57 vs. 30 months, $p < 0.0001$). On subgroup analysis, there was a trend to increased PFS in all standard, high- and ultra-high-risk cytogenetic risk groups with no evidence of heterogeneity in outcome between groups suggesting all benefitted from the use of lenalidomide maintenance compared to observation. A significant improvement in 3-year OS was observed with post-AHCT lenalidomide maintenance (87.5% vs. 80.2%, $p = 0.014$), although this benefit was not seen in the transplant-ineligible group.[7]

Regarding the duration of lenalidomide maintenance, the German-speaking Myeloma Multicenter Group (GMMG)-MM5 trial evaluated 2-year fixed duration (LEN-2Y) versus a lenalidomide maintenance strategy which was response-adapted based on the achievement of complete response (CR) (LEN-CR). The median duration of maintenance in the LEN-2Y versus LEN-CR groups were 17.6 and 9.5 months respectively ($p < 0.001$). At a median follow-up of 60.1 months, OS was longer with LEN-2Y versus LEN-CR with 3-year OS rates of 84.1% versus 76.1% (HR 1.42, $p = 0.03$). There was a trend towards a shorter PFS of 56.1% versus 84.1% but this did not meet statistical significance (HR 1.15, $p = 0.2$). Continuing lenalidomide beyond CR reduced the negative prognostic effect of the presence of t(4;14) on PFS and OS, and del17p on PFS. The results, therefore, supported continuing maintenance beyond the achievement of CR.[8] More recently, the DETERMINATION study randomised patients to

triplet induction therapy with lenalidomide, bortezomib and dexamethasone (RVd) versus RVd followed by HDM, transplantation and consolidation.[9] Lenalidomide maintenance was given in both arms until disease progression, intolerable toxicity, or trial withdrawal. At a median follow-up of 76 months, median PFS was 46.2 months with RVd alone versus 67.5 months with HDM and AHCT followed by consolidation and maintenance. There was also a PFS benefit in those with high-risk disease, with a median PFS of 17.1 months with RVd alone versus 55.5 months with HDM and AHCT. The study highlighted the importance of long-term lenalidomide maintenance in maintaining a durable response. Comparing this trial, in which lenalidomide was given until progression, to the identical IFM2009 trial in which lenalidomide was fixed at 1 year, there was a strong benefit in favour of continuous maintenance with relative PFS in the two trial transplant arms of 67.5 versus 47.3 months respectively.[10] The UK Myeloma XI trial further observed improvements in PFS with continuous longer duration lenalidomide maintenance beyond 3 years, that support these findings.[11]

Summary

Lenalidomide has been approved by both the FDA and the EMA for maintenance post-AHCT. It is the only agent shown to confer an overall survival advantage in this setting though the optimal duration of maintenance remains under debate. Lenalidomide maintenance should commence before disease progression, as suggested by the CALGB 10014 study where patients on lenalidomide had significantly longer TTP despite those on the placebo arm being allowed to crossover. The initial recommended dose is 10 mg once daily for 21 days every 28 days (alternatively every day) and, if well tolerated, the dose may be increased to 15 mg once daily. In the DETERMINATION trial, lenalidomide was given until disease progression whereas it was given for a fixed duration of 1 year in the IFM2009 trial. The former approach resulted in 20.2-month improvement in Progression-Free Survival. Nonetheless, the need for maintenance beyond 2 years in patients with sustained MRD negativity is being evaluated in current trials. An exception is ultra-high-risk patients with two or more high-risk cytogenetic abnormalities, a group for whom intensified maintenance strategies are clearly required.

Thalidomide

Thalidomide was one of the earliest agents used as maintenance post-AHCT. The MRC IX study was a large phase 3 randomised study that compared post-AHCT thalidomide maintenance with observation. Thalidomide resulted in a significantly longer PFS compared to observation (30 vs. 23 months, HR 1.42 $p = 0.003$) although there was no OS benefit. There was greater benefit seen in patients with standard risk disease as defined by interphase FISH and worse OS in those with adverse cytogenetics.[12] The National Cancer Institute of Canada Clinical Trials Group MY.10 study also compared thalidomide and prednisone maintenance versus observation post-AHCT. At a median follow-up of 4.1 years, median PFS was significantly longer with 4-year estimates of 32% versus 14% ($p < 0.0001$) although, here again, there was no significant improvement in estimated OS. The toxicity profile, however, was significantly worse with poorer Quality-of-Life outcomes.[13] Lastly, the HOVON50 study was a phase 3 study that compared thalidomide with interferon-alpha maintenance post-AHCT until progression. At a median follow-up of 129 months, event-free survival was significantly longer in the thalidomide group ($p < 0.0001$). However, there was significant thalidomide toxicity including neuropathy, skin reactions and fatigue that limited treatment delivery in 42% of patients.[14] Due to this toxicity and the absence of a robust OS benefit signal, thalidomide maintenance did not become standard practice. It may, however, be used in resource-constrained countries with limited access to lenalidomide or other newer agents.

Pomalidomide

There is emerging evidence for the use of pomalidomide as maintenance post-AHCT as a 'salvage option' in a lenalidomide refractory group. The EMN011/HOVON114 trial studied salvage pomalidomide-based re-induction and maintenance in patients who had relapsed or demonstrated progressive disease following VCD (bortezomib, cyclophosphamide and dexamethasone) induction, HDM/ASCT or VMP (bortezomib, melphalan, prednisone), VRD consolidation and lenalidomide maintenance.[15] In the study, 111 patients received eight cycles of KPd (carfilzomib, pomalidomide and dexamethasone), followed by HDM and AHCT (if not previously received) and then maintenance pomalidomide with or without dexamethasone continued until progression. Of the group, 79% received their first HDM and ASCT. At a median follow-up of 40 months, the median PFS was 26 months and OS 67 months, demonstrating the feasibility of pomalidomide maintenance. In the IFM2013-01 study, patients received pomalidomide-based salvage in first relapse, then HDM and AHCT followed by pomalidomide and dexamethasone maintenance.[16] The median PFS was 33.2 months and median OS was not reached. Phase 3 studies comparing pomalidomide to standard-of-care lenalidomide for maintenance have not been conducted and would be required to compare their efficacy and tolerability. This may be of particular value for patients with renal impairment given its hepatic metabolism.

CELMoDs

Iberdomide

Iberdomide is a novel cereblon E3 ligase modulator that has demonstrated increased anti-proliferative activity

compared to IMIDs in preclinical studies.[17] There are ongoing phase II trials evaluating the efficacy and safety of iberdomide maintenance post-AHCT and results are awaited.[18,19]

Proteosome inhibitors

Bortezomib

Multiple studies have evaluated bortezomib maintenance post-AHCT. In the HOVON65/GMMG-HD4 two-arm study, newly diagnosed symptomatic MM patients received either vincristine, doxorubicin and dexamethasone (VAD) with thalidomide maintenance or bortezomib, adriamycin and dexamethasone (PAD) with bortezomib maintenance for 2 years post-AHCT to evaluate the efficacy of bortezomib in both induction and maintenance. CR rates were higher in the PAD and bortezomib maintenance group (49% vs. 34%; $p < 0.001$). Following HDM and AHCT, a longer PFS was seen in the bortezomib group: 31 versus 26 months.[20] Further subanalysis revealed that patients with del17p had derived the greatest benefit from bortezomib-based treatment with a median PFS of 26.2 versus 12 months ($p = 0.024$).[21] An issue with this study design, however, was that the two cohorts received different inductions and maintenance schedules hence the effect of either alone could not be assessed.

The phase 3 PETHEMA/GEM study (GEM05MENOS65) randomised 390 MM patients 65 years or younger to either thalidomide and dexamethasone, VTD or combination chemotherapy plus bortezomib followed by HDM and AHCT. They underwent a further maintenance randomisation to receive either thalidomide/bortezomib, thalidomide or alpha2-IFN. There was a trend towards improved CR rates with thalidomide/bortezomib (21%) over thalidomide (11%) and alpha 2 IFN (17%), which did not reach statistical significance. Regarding toxicity, however, a high rate of grade 2–3 peripheral neuropathy of 48.8% were observed in the thalidomide/bortezomib group.[22]

Bortezomib-based maintenance has also been specifically studied in high-risk disease. The Emory group examined RVd consolidation and 3 years of RVd maintenance post-AHCT in a high-risk group. Maintenance consisted of weekly bortezomib, lenalidomide on D1–21 of a 28-day cycle and weekly dexamethasone. With this approach, they demonstrated a median PFS of 32 months and a 3-year OS of 93%, superior to previous studies with either monotherapy or observation alone.[23] RVd maintenance was also studied in the Total Therapy IIIB trial where patients received VDT-PACE induction, tandem AHCT, consolidation and then 3 years of maintenance RVd.[24] The RVd maintenance schedule included bortezomib administered monthly in the first year and weekly in years 2 and 3, lenalidomide for all 3 years and dexamethasone on D1–4, 8–11 in the first year and then weekly with bortezomib in years 2 and 3. Of 177 patients, 22% had high-risk disease by gene expression profiling (GEP). After a median follow-up of 14.2 years, the median OS was 11.1 versus 2.8 years for GEP low-risk and high-risk respectively. Unlike the Emory study, this study did not result in improved outcomes for high-risk patients highlighting the significant unmet need for this patient group.

Ixazomib

Ixazomib, an oral proteasome inhibitor (PI), has been evaluated in the setting of maintenance. It may be a suitable agent given its convenient once-weekly oral dosing and lower toxicity profile. The Tourmaline-MM3 study was a phase 3 study evaluating the safety and efficacy of ixazomib for 2 years versus placebo as maintenance therapy following AHCT.[25] At a median follow-up of 31 months, the median PFS was longer with ixazomib versus placebo at 26.5 and 21.3 months ($p = 0.0023$) respectively. No increase in SPM was noted with ixazomib therapy, with an incidence of 3% in each group.

Further studies have hence sought to compare ixazomib with lenalidomide. The MMRC-066 trial commenced patients on ixazomib, lenalidomide and dexamethasone (IRd) consolidation post-AHCT and then randomised them to maintenance with either ixazomib or lenalidomide. Interim analysis at a median of 11 months follow-up demonstrated that ixazomib resulted in an estimated median PFS of 28.2 months whereas it was not reached in the lenalidomide cohort. Ixazomib was deemed not non-inferior to lenalidomide, randomisation ceased, and patients were advised to cross over to lenalidomide.[26] In the Spanish GEM2014MAIN study, patients were randomised to receive either IRd or Rd post-AHCT.[27] At a median follow-up of 69 months, the 6-year PFS rates were 55.6% and 61.3%, respectively (HR 1.136), with no significant difference between groups.[28]

The phase 2 IFM2013-06 study evaluated IRd induction followed by HDM and AHCT, early and late consolidation and then maintenance with single agent ixazomib.[29] In the intention-to-treat group, there was a high ORR of 92.3% with evidence of deepening responses at the end of consolidation when compared to those postinduction. At a median follow-up of 62.6 months, the median PFS was 41.8 months, and the 3-year OS was 92.8%. There was, however, no improvement in stringent CR (sCR) rates after 1 year of ixazomib maintenance and fixed-duration maintenance is likely to be a suboptimal approach. Overall, PFS outcomes appear to be inferior compared to RVd induction and lenalidomide maintenance strategies.

Combination ixazomib and lenalidomide maintenance is also being studied. In a phase 2 single-arm study of 64 patients on combination maintenance, the median PFS for all patients was 73.3 months with a 5-year OS of 88.4%. Patients with cytogenetically high-risk features, however, had a PFS of only 25.4 months. Although it was a single-arm study, results to date suggest a potential benefit for combination maintenance therapy when compared to single agent lenalidomide though further data are required.[30]

Carfilzomib

Carfilzomib, a second-generation PI, can induce deep responses and has been shown to prolong survival with manageable toxicity. The Italian FORTE study was the first to compare carfilzomib plus lenalidomide maintenance to lenalidomide alone in patients following carfilzomib-based induction, HDM and AHCT. Following the first randomisation to either (1) carfilzomib, lenalidomide and dexamethasone (KRd), HDM and AHCT, (2) 12 cycles of KRd or (3) carfilzomib, cyclophosphamide and dexamethasone (KCd) HDM and AHCT, patients then underwent a second randomisation to KR versus lenalidomide maintenance. KRd and AHCT had the highest rates of VGPR or better compared to other induction strategies (89% vs. 87% vs. 76%) and resulted in the highest rates of premaintenance MRD negativity (62% vs. 56% vs. 43%). Regarding maintenance, at a median follow-up of 37.3 months from the second randomisation, the rates of MRD conversion from positive to negative by next-generation sequencing (NGS) was higher with KR versus lenalidomide alone (56% vs. 30%, $p = 0.046$). The 3-year PFS was also longer with KR at 75% versus 65% ($p = 0.023$). Rates of non-haematological adverse event were higher with KR, including hypertension, thrombotic microangiopathy and cardiac events, although no increase in SPMs has yet been reported.[31]

The phase 3 ATLAS study is evaluating the efficacy of KRd versus lenalidomide post-AHCT until disease progression or intolerance. Patients with undetectable MRD and standard risk disease are switched to lenalidomide alone after cycle 6 if on the KRd arm. At a median follow-up of 33.8 months, the median PFS was 59.1 months in the KRd arm and 41.4 months in the lenalidomide arm ($p = 0.012$).[32] There is a legitimate concern regarding the treatment burden and the cumulative toxicity of three active agents compared to single agent lenalidomide. A higher frequency of grade 1–2 adverse events were seen in the KRd arm (93% vs. 83%) with higher rates of anaemia, respiratory tract infections and fever. Serious adverse events were higher in the KRd arm (30% vs. 22%) and were primarily due to lower respiratory tract infections (12% vs. 3%). There was one treatment-related death due to respiratory failure in the KRd arm. Longer term follow-up will be valuable to determine both the efficacy and deliverability of this approach.

The Phase 2 MMRC study was a single-arm study that evaluated KRd combination therapy for maintenance post-KRd induction, AHCT and consolidation. At a median follow-up of 56 months, the estimated overall 5-year PFS was 72% and 5-year OS 84%, the outcomes in those with high-risk disease being poorer at 57% and 72% respectively. In such high-risk patients, achieving MRD negativity was associated with superior PFS. Treatment toxicity was comparable to that seen in the FORTE study.[33]

Summary

Among the PIs, bortezomib and carfilzomib have shown the most convincing evidence of benefit in the maintenance setting, notably for patients with high-risk cytogenetics. However, toxicity is an issue, principally neurotoxicity for bortezomib and cardiac toxicity for carfilzomib. The recommended starting dose of bortezomib is 1.3 mg/m^2 subcutaneously in the absence of neuropathy and it is generally administered once every 2 weeks for a fixed duration of 2 years.

Anti-CD38 antibodies

Daratumumab

Daratumumab, an anti-CD38 monoclonal antibody, has become the standard of care for transplant-eligible patients with newly diagnosed MM and is an attractive maintenance agent given its tolerability. The CASSIOPEIA trial was a phase 3 study that randomised transplant-eligible patients to receive daratumumab, bortezomib, thalidomide and dexamethasone (D-VTd) or bortezomib, thalidomide and dexamethasone in induction and consolidation.[34] Daratumumab significantly improved the proportion of patients who achieved VGPR or better and MRD negativity following consolidation. The D-VTd group also had a significantly longer PFS. Those who achieved at least a PR were then randomised to daratumumab maintenance, dosed once every 8 weeks, versus observation for 2 years. At a median follow-up of 35.4 months, the median PFS had not been reached in the daratumumab group and was 46.7 months in the observation group (HR 0.53, $p < 0.0001$).[35] Notably, a statistically superior PFS with maintenance daratumumab was only seen in the patients who had received VTd induction. In other words, no significant benefit was seen with the use of maintenance daratumumab in patients who had received it during induction and post-transplant consolidation. Further follow-up will be required to determine whether there is any benefit of daratumumab maintenance post-D-VTd.

In the GRIFFIN study, daratumumab was further evaluated in a protocol consisting of (D)-RVd induction followed by HDM and AHCT, consolidation and then maintenance with Daratumumab-lenalidomide (Revlimid) (DR) or single agent lenalidomide. Patients were randomised to D-RVd or RVd and patients in the D-RVd group received maintenance IV daratumumab every 8 weeks or every 4 weeks following protocol amendment in addition to lenalidomide 10 mg on Days 1–21, or up to 15 mg if tolerated. Maintenance was capped to a maximum of 2 years or until disease progression. The primary end-point of sCR was reached in 42.4% of patients in the D-RVd arm and 32% in the RVd arm at the end of consolidation (OR, 1.57; one-sided $p = 0.068$).[36] At a median follow-up of 26.7 months, the D-RVd arm had higher rates of sCR (63.6% vs. 47.4%, $p = 0.0253$) demonstrating that DR maintenance resulted in deeper treatment responses.[37] There are ongoing studies evaluating daratumumab maintenance which will ultimately determine whether combination DR maintenance will become a standard of care. The AURIGA study is comparing subcutaneous daratumumab and lenalidomide maintenance with standard-of-care single agent lenalidomide and an end-point is the MRD rate after 1 year of

maintenance.[38] In this study, newly diagnosed MM patients who have received four or more cycles of induction followed by AHCT and who are daratumumab naive will be eligible for maintenance randomisation if they are MRD positive by NGS within 30 days of screening. The SWOGS1803 group will similarly compare combination daratumumab and lenalidomide maintenance with single agent lenalidomide and will evaluate overall survival and MRD for 2 years in the DRAMMATIC study.[39] The PERSEUS trial is comparing D-VRd induction, AHCT, consolidation followed by DR maintenance to VRd induction, AHCT, consolidation and R maintenance. Patients who receive DR maintenance and sustain MRD negativity for 1 year, will cease daratumumab and continue R maintenance.[40] The Daratumumab-containing arm was recently reported to have had a significantly improved PFS and increased depth of response (≥CR and MRD negativity), with consistent PFS benefit across clinically relevant subgroups.[41] The study authors have proposed that D-VRd followed by DR maintenance represents a new standard of care for transplant-eligible NDMM.[41]

Isatuximab

Isatuximab, another anti-CD38 monoclonal antibody, is being studied in the ongoing GMMG-HD7 trial in combination with RVd (Isa-RVd) versus RVd only. In the first part of this phase 3 study, patients were randomised to Isa-RVd versus RVd and received three cycles of a 42-day induction therapy. Isa-RVd reached the primary end-point of increased MRD negativity postinduction (50% vs. 36% in the control group, $p = 0.00017$).[42] Treatment was deliverable, with similar rates of grade 3 or 4 adverse events in the two arms. We await with interest the results of the second part of this study that will compare, after second randomisation, combination isatuximab and lenalidomide maintenance with single agent lenalidomide and the effect of the addition of isatuximab on both PFS and OS. Of note, the quadruplet combination of isatuximab with KRd (Isa-KRd) is also being studied in high-risk MM patients in the GMMG-CONCEPT study. This study has a transplant-eligible arm in which patients receive six cycles of Isa-KRd (28-day cycles) induction, followed by consolidation and Isa-KR maintenance. Interim analysis of the first 50 enrolled patients showed an ORR of 100% with 90% achieving a VGPR in a high-risk group.[43] After a median follow-up of 24.9 months, the median 12-month PFS was 79.6% and the 24-month PFS was 75.5%. Updated results are awaited.

Other monoclonal antibodies

Elotuzumab

Elotuzumab is a humanised IgG1 immunostimulatory monoclonal antibody against signalling lymphocytic activation molecule F7, a protein highly expressed on myeloma cells. The GMMG-HD6 trial was a phase 3 study which assessed the benefit of elotuzumab in combination with RVd in induction and consolidation and of maintenance elotuzumab and lenalidomide. At a median follow-up of 49.8 months, the addition of elotuzumab did not lead to a statistically significant improvement in PFS or OS.[44] A phase 2 study also compared combination elotuzumab and lenalidomide maintenance post-AHCT.[45] Of 100 patients, there was a 27% conversion rate from VGPR to MRD-negative CR. At a median follow-up of 41 months, the estimated 4-year PFS was 75%. Longer-term follow-up is required to consider its efficacy compared with that seen in the lenalidomide monotherapy trials indirectly. No direct comparison of elotuzumab to observation or randomised study of Elo-Len versus Len has been conducted post-ASCT. In the non-transplant setting, elotuzumab was evaluated in the randomised phase 2 SWOG-1211 trial that randomised patient to eight cycles of RVd or RVD-elotuzumab induction followed by maintenance in high-risk MM patients. At a median follow-up of 53 months, there was similarly no significant difference in PFS between the RVD and the RVD-elotuzumab arms (33.64 vs. 31.47 months, $p = 0.45$).[46]

Summary

Trials incorporating maintenance anti-CD38 monoclonal antibodies have recently been reported. Following the CASSIOPEIA trial results, the benefit of maintenance Daratumumab in those who receive it in induction and consolidation remains uncertain. In addition, neither the GRIFFIN nor the PERSEUS trials had a second randomisation before starting maintenance, so it is not possible to fully isolate the effect of their comparative maintenance approaches. On this basis, many clinicians may choose to continue to use single agent lenalidomide, certainly in standard risk disease, until the addition of Daratumumab (Dara-Len) has been clearly demonstrated to confer better outcomes.

Antibody-drug conjugates

Belantamab mafodotin

Belantamab mafodotin (belamaf) is a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate that has demonstrated activity in relapsed refractory (RR) MM though not yet in the front-line setting. The GEM-BELA-VRd trial is a phase 2 study currently evaluating the combination of belamaf and VRd induction followed by HDM and AHCT, consolidation, followed by lenalidomide and belamaf maintenance.[47] The BLAST study is another phase 2 study evaluating the efficacy and deliverability of reduced frequency belamaf every 3 months in addition to lenalidomide maintenance post-AHCT.[48] It is also being evaluated as single agent maintenance following salvage AHCT for relapsed MM and also as maintenance with lenalidomide in a MRD guided approach.[49,50] Outcomes from such maintenance strategies are awaited.

Summary

The significant corneal toxicity renders Belantamab mafodotin a poor candidate for use in maintenance. Although studies evaluating lower doses and lighter administration schedules are ongoing, it appears unlikely to be approved for this indication in the near future.

Bispecific antibodies

Teclistamab

Teclistamab is a novel bispecific antibody targeting both BCMA and CD3 that has demonstrated remarkable efficacy as monotherapy in triple-class exposed MM and in combination with daratumumab and lenalidomide in heavily pretreated patients.[51,52] The MajesTEC-4 (EMN30) study aims to enrol 1000 patients and randomise them to either combination teclistamab and lenalidomide maintenance or single agent lenalidomide in patients post-AHCT. Immunomodulatory agents have been proposed to improve the efficacy of immunotherapy and it is anticipated this combination may further improve efficacy.[53]

Elranatamab

Elranatamab is another anti-BCMA humanised bispecific antibody that has also shown efficacy in RR MM patients with a manageable safety profile.[54] The MagnetisMM-7 trial will compare two dosing regimens of elranatamab monotherapy with single agent lenalidomide as maintenance post-AHCT.[55]

Summary

Bispecific monotherapy has demonstrated remarkable single agent clinical efficacy, even in patients with late-stage disease and high tumour burden. The current hope is that their use in the setting of a complete or near complete remission may induce very deep responses and, in some, operational cures. Balanced against this enthusiasm is awareness of the increased risk of infections and the need for the routine use of intravenous immunoglobulins. It appears from reports that a better balance between clinical efficacy and risk can be achieved by their use as consolidation rather than as maintenance. Striking this balance, however, will likely require the additional logistical burden of close monitoring for MRD in such patients to allow for the intensity of treatment to be calibrated based on the results.

RISK-BASED MAINTENANCE STRATEGIES

There has been an increased focus on precision medicine and the development of personalised treatment strategies based on cytogenetic risk profiling (Table 1). High-risk cytogenetic abnormalities (HRCAs) include t(4;14), t(14:16), t(14:20), del17p13, gain or amplification of 1q and del 1p. The SKY92 gene expression classifier can also reliably identify NDMM patients with a poorer prognosis. Historically, post hoc subgroup analysis in landmark lenalidomide studies, prior to Myeloma XI, had not found a PFS or OS benefit with lenalidomide in high-risk cytogenetic groups. However, these studies were likely underpowered for this purpose. The FORTE study performed subgroup analysis of PFS based on KR versus R maintenance strategies and across cytogenetic abnormalities. In the KR group, the 3-year PFS was 90% in the absence of a HRCA, 69% with one HRCA and 67% with two or more HRCA. In the R group, this was 73%, 67% and 42% respectively. Results demonstrated trends favouring KR maintenance across all cytogenetic risk groups, including 2+ HRCA, although this did not reach statistical significance.[56] There is an ongoing need for further studies to optimise maintenance strategies for high-risk groups.

The Myeloma XI trial was a phase 3 multicentre UK study in which the third randomisation compared maintenance lenalidomide versus observation post-AHCT. Results support the PFS benefit of lenalidomide across all cytogenetic risk groups.[7] Extended analysis from the patients that underwent AHCT demonstrated that patients with a single adverse cytogenetic abnormality obtained greater benefit from lenalidomide maintenance compared to those with none (standard risk).[62] In the single hit group, those with del1p, del17p or t(4;14) derived the greatest benefit. Patients with del1p and t(4;14) relapsed early when on observation alone with median PFS rates of 7.5 and 9.9 months respectively. The same groups achieved PFS rates of 57.6 and 54.3 months, respectively, on lenalidomide maintenance. Gain 1q was the only cytogenetic subgroup that did not demonstrate a significant PFS benefit with lenalidomide versus observation alone (HR 1.5, $p = 0.2$). Outcomes remained poorest for patients with two HRCA (ultra-high risk) despite benefitting from lenalidomide maintenance, with a PFS of 22.5 on maintenance versus 10.6 months on observation ($p = 0.02$) and corresponding OS rates of 47.3 and 32.8 months respectively ($p = 0.7$).

A retrospective analysis assessed whether more intensive lenalidomide-based combination maintenance strategies improved PFS compared to lenalidomide alone. Lenalidomide combinations did not significantly improve PFS but a trend towards improved PFS was seen in the lenalidomide combination group, except for those with gain 1q.[63]

The OPTIMUM/MUK nine trial has also evaluated intensive induction in an ultra-high-risk MM group with two or more HRCA or primary plasma cell leukaemia.[64] A total of 107 patients across the UK received Dara-CVRd induction, Vel-Mel augmented AHCT, followed by 18 cycles of Dara-VR-based consolidation and monthly Dara-R maintenance until progression. The 30-month PFS estimate at the end of consolidation was 77%, superior to a matched-pair ultra-high-risk cohort in the previous Myeloma XI study for whom the corresponding 30-month PFS had been 39.8%. Estimated 30-month OS was 83.5% versus 73.5%. Further evaluation following maintenance and long-term follow-up

TABLE 1 Current trials examining cytogenetic risk-modified maintenance strategies.

Study number	Study	Phase	Intervention	Enrolment (*n*)	Primary outcome	Estimated completion
NCT03188172	MUK Nine b: OPTIMUM Treatment Protocol (MUK Nine)[57]	2	Induction CVRdD × 4–6 cycles followed by AHCT, consolidation 1 VRDd × 6 cycles, consolidation 2 VRD × 12 cycles, then maintenance lenalidomide and daratumumab	95	Progression-free survival	2023-06-30
NCT05722405	Ixazomib plus low-dose lenalidomide versus ixazomib alone for maintenance treatment of high-risk multiple myeloma[58]	4	Single agent ixazomib maintenance versus combination ixazomib plus low-dose lenalidomide maintenance post-AHCT	100	Progression-free survival	2025-07-31
NCT03641456	VRD as induction followed by VR maintenance in patients with newly diagnosed high-risk multiple myeloma[59]	2	VRd induction therapy followed by AHCT as per physician discretion and consolidation. Maintenance therapy with lenalidomide and monthly bortezomib	50	Very good partial response or better by IMWG criteria	2025-12-30
NCT03104842	Evaluation induction, consolidation and maintenance treatment with isatuximab, carfilzomib, lenalidomide and dexamethasone (GMMG-CONCEPT)[43]	2	Arm A: Transplantation—6 cycles I-KRd induction, after intensification another 4 cycles I-KRd, IKR maintenance Arm B: No transplantation—12 cycles I-KRd, IKr maintenance	246	MRD negativity	2026-09
NCT05665140	Expression-linked and R-ISS-adapted stratification for first-line therapy in multiple myeloma patients (ELIAS)[60]	2/3	Induction I-VRd × 3 cycles followed by HDM + AHCT versus I-VRd × 6 cycles Maintenance with IR	100	MRD negativity and CR rates	2027-08
NCT05776979	Post-transplant maintenance therapy with isatuximab plus lenalidomide for high-risk multiple myeloma patients[61]	2	Isatuximab and lenalidomide after AHCT	61	Incidence of adverse events, graded according to NCI CTCAE v5	2027-12-31

Abbreviations: AHCT, autologous haematopoietic stem cell transplant; C, cyclophosphamide; CR, complete response; D, daratumumab; d, dexamethasone; HDM, high dose melphalan; I, isatuximab; IMWG, International Myeloma Working Group; K, carfilzomib; MRD, minimal residual disease; R, lenalidomide; V, bortezomib (This list was composed using registered trial candidates on ClinicalTrial.gov, ISRCTN registry and the ANZCTR registry).

TABLE 2 Current studies looking at MRD-adapted maintenance strategies following AHCT with or without fixed duration.

Study number	Study	Phase	Regimen	Enrolment (*n*)	Primary outcome	Estimated completion
NCT03224507	Monoclonal antibody-based sequential therapy for deep remission in multiple myeloma (MASTER)[74]	2	Experimental arm: KRdD induction followed by AHCT, then 2 × 4 cycle blocks of KRdD consolidation. Patients with confirmed MRD negativity will not undergo maintenance and be monitored. After consolidation, MRD-positive patients will undergo lenalidomide maintenance Experimental arm: KRdD induction followed by 3 × 4 cycle blocks of KRdD consolidation. Patients with confirmed MRD negativity will not undergo maintenance and be monitored. After consolidation, MRD positivity patients will undergo lenalidomide maintenance	82	Percentage of patients with MRD-negative remissions at the completion of consolidation therapy	2023-09-30
NCT04221178	Stopping maintenance therapy in people with multiple myeloma in MRD-negative remission[71]	-	Cessation of maintenance therapy for participants in sustained MRD-negative remission whilst under careful observation	50	MRD negativity following 1 year of enrolment	2024-01-03
NCT04108624	Study to assess for measurable residual disease (MRD) in multiple myeloma patients (MRD2STOP)[72]	NA	Patients will undergo discontinuation of their maintenance therapy if they are MRD negative by PET/CT, flow cytometry and next-generation sequencing	56	MRD conversation rate Median progression-free survival rate Median overall survival rate	2024-12-01
NCT05091372	Minimal residual disease-guided maintenance therapy with belantamab mafodotin and lenalidomide after autologous haematopoietic cell transplantation in patients with newly diagnosed multiple myeloma[75]	2	Post-transplant maintenance therapy with belantamab mafodotin and lenalidomide	92	Conversion rate from MRD-positive to MRD-negative CR in participants with newly diagnosed multiple myeloma (NDMM) receiving post-transplant maintenance therapy with belantamab mafodotin plus lenalidomide	2025-03-31
NCT03477539	Daratumumab in treating transplant-eligible patients with multiple myeloma[76]	2	Patients receive pre-AHCT daratumumab consolidation for 2–4 cycles and then undergo AHCT 8 weeks later. Within 14 days after the day 100 visit post-AHCT, patients will then receive maintenance daratumumab and lenalidomide for up to 12 cycles. Patients who maintain response will continue daratumumab IV every 3 months	50	Rate of minimal residual disease (MRD) negative response at day 100 post-AHCT	2025-12-01

(Continues)

TABLE 2 (Continued)

Study number	Study	Phase	Regimen	Enrolment (*n*)	Primary outcome	Estimated completion
NCT03901963	A study of daratumumab plus lenalidomide versus lenalidomide alone as maintenance treatment in participants with newly diagnosed multiple myeloma who are minimal residual disease positive after front-line autologous stem cell transplant (AURIGA)[77]	3	Daratumumab plus lenalidomide maintenance versus lenalidomide for MRD-positive patients post-AHCT who are CD38 treatment naive	200	Percentage of participants with MRD negativity, that is MRD conversion rate from baseline to 12 months after maintenance treatment	2026-05-09
NCT04934475	Minimal residual disease adapted strategy (MIDAS)[78]	3	All patients receive Isa-KRd induction. Depending on MRD status, patients will be randomised to Arm A: MRD standard risk—Isa-KRd consolidation + 3 years maintenance lenalidomide; Arm B: MRD standard risk—AHCT + 2× Isa-KRd consolidation + 3 years maintenance lenalidomide; Arm C: MRD high-risk—AHCT + 2 × Isa-KRd consolidation + 3 years maintenance iberdomide and isatuximab; Arm D: tandem AHCT + 3 years maintenance iberdomide and isatuximab	716	Negative MRD rate	2028-09-01
NCT05192122	Free from maintenance drug therapy in multiple myeloma (The FREEDMM Trial) for minimal residual disease (HEME-20)[79]	1	Discontinuation of maintenance post-AHCT if in sustained MRD-negative VGPR or CR	50	Number of participants that have sustained MRD-negative VGPR or CR measured by bone marrow biopsy 12 months after stopping maintenance therapy	2029-01
NCT05344833	Postautologous transplant maintenance with isatuximab and lenalidomide in minimal residual disease-positive multiple myeloma (HEME-18)[80]	2	Isatuximab and lenalidomide maintenance if MRD positive after AHCT	50	Number of participants that have an MRD-negative CR rate at 1 year	2030-12
NCT04071457	S1803, Lenalidomide ± daratumumab/rHuPh20 as post-AHCT maintenance for MM w/MRD to direct therapy duration (DRAMMATIC)[39]	3	Randomisation to lenalidomide versus lenalidomide + daratumumab. After 2 years of maintenance, MRD+ participants to continue assigned treatment. MRD− participants to be randomised to continue or discontinue treatment	1100	Overall survival	2040-07-01

TABLE 2 (Continued)

Study number	Study	Phase	Regimen	Enrolment (*n*)	Primary outcome	Estimated completion
ISCRTN46841867	Risk and response-adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR) UK-MRA Myeloma XV trial[81]	2/3	Patients receive RCyBord × 4 induction followed by AHCT and then will go onto one of three arms: 1. De-escalation: Standard risk MRD-negative patients will receive 12 cycles of isatuximab maintenance. Those that remain MRD negative will be randomised to continue or stop treatment 2. Escalation: Standard risk MRD-positive patients will be randomised to R, RBord × 4 + R, R-Isa, or RBorDIsad × 4 + R-Isatuximab 3. Intensive: Patients will be randomised to RBorD × 4 + R or RBorIsaD × 4 + R-Isa	1400	Progression-free survival	Not listed

Abbreviations: AHCT, autologous haematopoietic stem cell transplant; Bor, bortezomib; CR, complete response; Cy, cyclophosphamide; D, daratumumab; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; R, lenalidomide; VGPR, very good partial response (This list was composed using registered trial candidates on ClinicalTrial.gov, ISRCTN registry and the ANZCTR registry).

will reveal the ultimate value of this approach in this poor prognostic group.

Overall single agent maintenance has been shown to ameliorate but not abrogate the impact of high cytogenetic risk features. More intensive approaches may be needed particularly in the context of ultra-high-risk disease (e.g. >1 high-risk lesion). The use of dual agent maintenance strategies with lenalidomide plus proteasome inhibition (bortezomib or carfilzomib) or anti-CD38 inhibition, when reimbursed, may help improve outcomes further.

MRD-ADAPTED STRATEGIES

Minimal residual disease evaluation during maintenance has been demonstrated in multiple studies to be a predictor of disease progression and a prognostic marker for long-term outcomes such as PFS.[65–67] Achieving an unmeasurable MRD state (MRD negativity) may also overcome the adverse effect of high-risk cytogenetics.[68,69] It has been proposed as a primary treatment end-point for trials and a guide to determine the duration of maintenance treatment. There are ongoing trials exploring MRD response-adapted maintenance and fixed duration strategies (Table 2). The GEM2014MAIN study discontinued post-AHCT IRd or Rd maintenance following 2 years of treatment if patients were MRD negative.[27] At an updated median follow-up of 69 months, there was a low progression rate of 17.2% at 4 years, even in high-risk patients.[70] Another phase 2 study is further evaluating outcomes following the cessation of lenalidomide maintenance after at least 3 years of MRD negativity. In an interim analysis of 23 patients at a median follow-up of 14.8 months, 87% have remained MRD negative 1 year after stopping maintenance.[71] The MRD2STOP study is investigating maintenance discontinuation after at least 1 year of therapy if MRD is unmeasurable through multiple modalities, that is PET-CT negative and unmeasurable MRD by flow cytometry or NGS in the bone marrow. At a median follow-up of 14 months, 5% of 38 patients have had disease progression with a sustained MRD negativity rate at 12 months of 84%.[72] A single centre prospective cohort study opted to discontinue lenalidomide maintenance in patients who had three consecutive MRD-negative results using next-generation flow, had a negative PET/CT and had a minimum 36 months of maintenance.[73] Twelve months after stopping, 36 out of 38 patients have remained MRD negative.

The MASTER trial is evaluating quadruplet induction with Dara-KRd followed by HDM and AHCT and Dara-KRd consolidation until the achievement of two consecutive MRD-negative results.[74] If MRD negativity is achieved, patients stop treatment and undergo observation; if they have persistent measurable MRD, they receive lenalidomide maintenance. At a median follow-up of 34.1 months, 123 enrolled patients with no, one or two or more HRCAs had 3-year PFS rates of 91%, 87% and 51%, respectively, and

3-year OS rates of 96%, 91% and 75% respectively. Of patients who achieved MRD negativity, 79% of patients remained off therapy; the corresponding proportions in the three cytogenetic risk groups were 88%, 83% and 47% in those having zero, 1 or 2+ HRCA respectively. This study has demonstrated the feasibility of using sustained MRD negativity to guide maintenance with comparable PFS and OS outcomes in high-risk patients. Lastly, the UK RADAR (Risk-Adapted therapy Directed According to Response) trial is a randomised multiarm phase 2/3 study that aims to recruit 1400 patients who will receive lenalidomide, cyclophosphamide, bortezomib, dexamethasone (RCyBoRD) based induction followed by HDM and AHCT with subsequent consolidation and maintenance based on cytogenetic risk and MRD status post-AHCT.[81] In standard risk patients, the study aims to assess the effect of stopping isatuximab maintenance in MRD-negative patients and the benefit of intensification of consolidation and maintenance with R-Isa in those with persistent measurable disease. In high-risk patients, the efficacy of intensified consolidation and maintenance (R or R-isa) will be evaluated.

It, therefore, appears clear that MRD assessment to inform maintenance treatment approaches is likely to enter routine clinical use soon. Most trials are not evaluating patients until after 2 years of post-transplant maintenance. Thereafter, some recommend annual assessment though the frequency of routine MRD testing outside of trials will probably be largely determined by the logistical constraints of busy clinics.

TREATMENT ALGORITHM

Whilst awaiting further study evidence, we propose in Figure 1, a pragmatic treatment algorithm based on both cytogenetic risk and MRD assessment that could be discussed with patients if they wish to follow an adapted duration approach. All patients should start on a lenalidomide-based regimen, either 3 months post-AHCT or immediately following post-transplant consolidation. In the presence of del(17p) or ultra-high-risk patients with two or more HRCAs combination maintenance approaches should be considered where available. Patients with ultra-high-risk disease should be considered for clinical trials as early relapse is common even with dual agent maintenance and many intensified maintenance strategies are not approved for routine use.

After 2 or 3 years of yearly MRD assessments, for those with sustained MRD negativity across two tests it may be reasonable to stop maintenance in those patients considered standard risk by tumour genetics. If MRD is detected, or MRD negativity is not sustained, treatment should be continued until disease progression. For patients with a negative MRD test and standard risk disease who have ceased maintenance therapy ongoing MRD monitoring and reinstituting maintenance therapy on re-emergence of detectable disease can be considered. The need to change treatment in this case, although intuitive, has not been clearly established as some patients may not have significant biochemical or clinical progression for years.

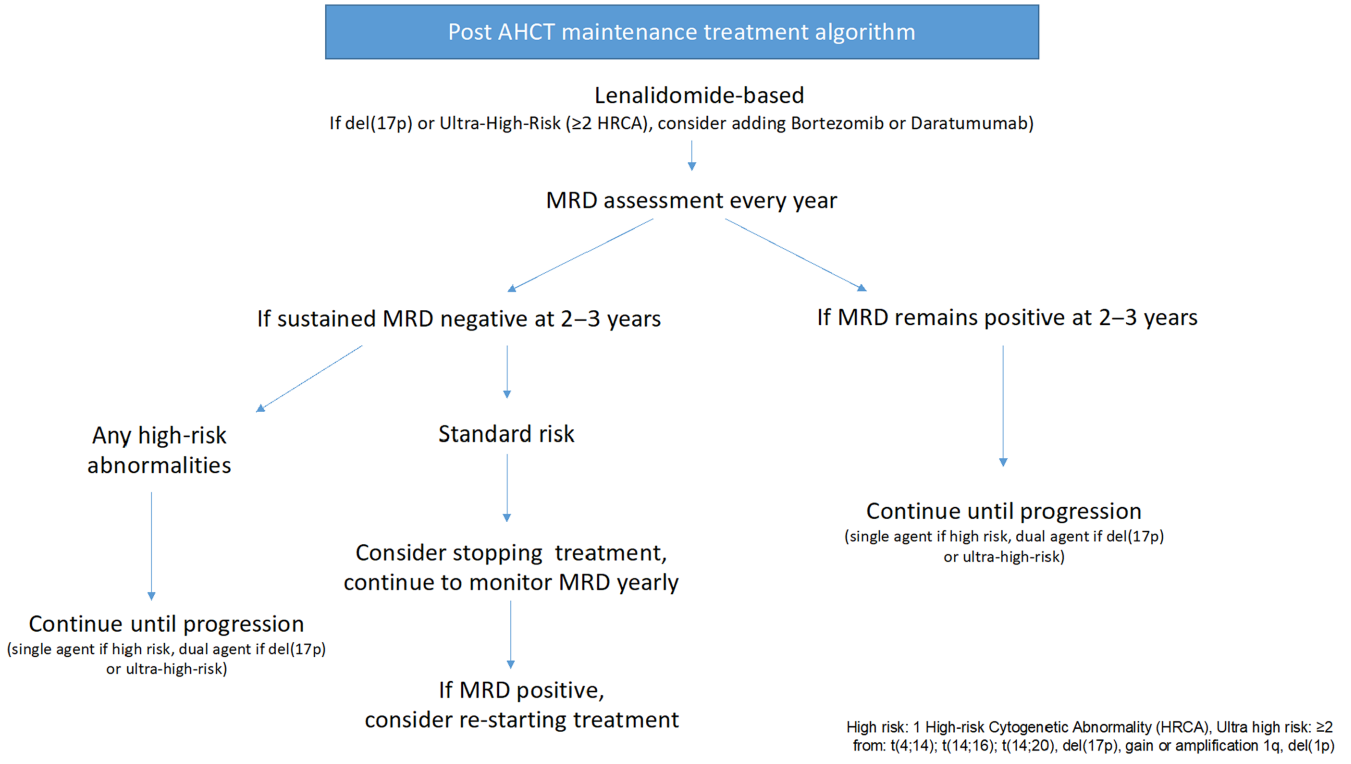

FIGURE 1 Proposed treatment algorithm. MRD, minimal residual disease.

TABLE 3 Current studies evaluating combination lenalidomide maintenance strategies post-AHCT.

Study number	Study	Phase	Regimen	Enrolment (*n*)	Primary outcome	Estimated completion
NCT02203643	Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE)[31]	2	Induction: KCd versus KRd followed by AHCT Maintenance: KR versus R	477	Efficacy as per IMWG criteria	2025-10
NCT04217967	Ixazomib, lenalidomide and combination for maintenance in newly diagnosed multiple myeloma patients[82]	4	Ixazomib monotherapy versus ixazomib and lenalidomide combination versus lenalidomide monotherapy maintenance	180	Progression-free survival Overall survival Time to next treatment	2022-10-01
NCT05243797	Phase 3 study of teclistamab in combination with lenalidomide and teclistamab alone versus lenalidomide alone in participants with newly diagnosed multiple myeloma as maintenance therapy following autologous stem cell transplantation (MajesTEC-4)[53]	3	Lenalidomide and teclistamab maintenance versus lenalidomide monotherapy	1572	Progression-free survival	2032-04
NCT05722405	Ixazomib plus low-dose lenalidomide versus ixazomib alone for maintenance treatment of high-risk multiple myeloma[58]	4	Control arm: Single agent ixazomib Experimental arm: Ixazomib plus low-dose lenalidomide	100	Progression-free survival	2025-07-31
NCT03104842	Evaluation induction, consolidation and maintenance treatment With isatuximab, carfilzomib, lenalidomide and dexamethasone (GMMG-CONCEPT)[43]	2	Arm A: Transplantation—6 cycles I-KRd induction, after intensification another 4 cycles I-KRd, IKR maintenance Arm B: No transplantation—12 cycles I-KRd, IKr maintenance	246	MRD negativity	2026-09
NCT04071457	Lenalidomide ± daratumumab/rHuPh20 as post-AHCT maintenance for multiple myeloma. with MRD to direct therapy duration (DRAMMATIC)[39]	3	Lenalidomide versus lenalidomide and daratumumab. After 2 years maintenance, MRD-positive participants to continue assigned treatment whilst MRD-negative participants to be randomised to continue or discontinue treatment	1100	Overall survival	2040-07-01
NCT03901963	A study of daratumumab plus lenalidomide versus lenalidomide alone as maintenance treatment in participants with newly diagnosed multiple myeloma who are minimal residual disease positive after front-line autologous stem cell transplant (AURIGA)[77]	3	Daratumumab plus lenalidomide maintenance versus lenalidomide for MRD-positive patients post-AHCT who are CD38 treatment naive	200	Percentage of participants with MRD-negative status, that is the MRD conversion rate from baseline to 12 months after maintenance treatment	2026-05-09
NCT02420860	Elotuzumab and lenalidomide after stem cell transplant in treating patients with newly diagnosed multiple myeloma[45]	2	Elotuzumab and lenalidomide maintenance	113	Progression-free survival	2024-04-30
NCT03948035	Elotuzumab in combination with carfilzomib, lenalidomide and dexamethasone (E-KRd) versus KRd in MM[83]	3	Induction and consolidation: E-KRd versus KRd followed by AHCT Maintenance: Elotuzumab and lenalidomide versus lenalidomide	576	MRD negativity rate postinduction PFS postmaintenance randomisation	2029-08

(Continues)

TABLE 3 (Continued)

Study number	Study	Phase	Regimen	Enrolment (*n*)	Primary outcome	Estimated completion
ACTRN 12620000291987	An ALLG phase 3 randomised trial of selinexor and lenalidomide versus lenalidomide maintenance postautologous stem cell transplant for patients with newly diagnosed multiple myeloma[84]	3	Selinexor and lenalidomide combination versus lenalidomide maintenance	232	Progression-free survival	2024-01-18

Abbreviations: AHCT, autologous haematopoietic stem cell transplant; Bort/V, bortezomib; C, cyclophosphamide; d, dexamethasone; I/Isa, isatuximab; IMWG, International Myeloma Working Group; K, carfilzomib; MRD, minimal residual disease; R, lenalidomide (This list was composed using registered trial candidates on ClinicalTrial.gov, ISRCTN registry and the ANZCTR registry).

EXPERT OPINION SUMMARY AND HORIZON SCANNING

In summary, maintenance therapy is established practice in the post-transplant setting. Though single agent lenalidomide is the standard of care, trial data are now available on drugs across the therapeutic spectrum including immunomodulatory agents, PIs, anti-CD38 antibodies and bispecific antibodies. This offers clinicians scope for a more individualised choice of maintenance therapy. More generally, there is increased recognition of the need to exert continuous pressure on aggressive disease clones and strategies are evolving towards risk-based combinatorial strategies, particularly using lenalidomide with either anti-CD38 and or bispecific antibodies (Table 3). Given the potent hypogammaglobulinaemia reported in patients receiving bispecific antibodies, it will be important to ensure that all trials incorporate QoL modules and carefully monitor for treatment-related toxicities such as infections as well as SPMs. This is especially pertinent for maintenance treatment the goal of which is to prolong remissions as opposed to achieving them. Another key advance in the latest suite of clinical trials has been the use of MRD to guide maintenance strategies. This may represent a landmark in our ability to target therapy to where it is most needed, and equally, to stop it where it is not required, thereby avoiding unnecessary toxicity. Taken together, these recent developments in the evolution of approaches to maintenance offer patients the prospect of more durable disease control using better-targeted, more potent and less toxic therapies.

AUTHOR CONTRIBUTIONS

All authors contributed to guideline writing, review and editing.

ACKNOWLEDGEMENTS

This work was supported by the Chronic Malignancies Working Party of the EBMT.

CONFLICT OF INTEREST STATEMENT

PH: Amgen—Travel Support, Janssen—Travel Support, Takeda—Travel Support; CP: Abbvie—Consultancy, Amgen—Consultancy, Honoraria and Travel Support, Janssen—Honoraria and Travel Support, BMS—Consultancy, Honoraria and Travel Support, Sanofi—Consultancy and Honoraria, iTEOS—Consultancy, Pfizer—Consultancy; LG: Amgen—Consultancy, Pfizer—Consultancy and Travel Support, BMS—Consultancy, Janssen—Consultancy, Takeda—Consultancy, GSK—Consultancy; the remaining authors have no conflicts of interest to disclose.

ORCID

Angela Hwang https://orcid.org/0009-0004-4938-0910
Patrick Hayden https://orcid.org/0000-0003-1374-4503
Charlotte Pawlyn https://orcid.org/0000-0002-7190-0028
Donal McLornan https://orcid.org/0000-0003-1224-091X
Laurent Garderet https://orcid.org/0000-0002-6138-8112

REFERENCES

1. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770–81.
2. Holstein SA, Jung SH, Richardson PG, Hofmeister CC, Hurd DD, Hassoun H, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol. 2017;4(9):e431–e442.
3. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782–91.
4. Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895–905.
5. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol. 2017;35(29):3279–89.
6. Gay F, Oliva S, Petrucci MT, Conticello C, Catalano L, Corradini P, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015;16(16):1617–29.
7. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(1):57–73.
8. Goldschmidt H, Mai EK, Durig J, Scheid C, Weisel KC, Kunz C, et al. Response-adapted lenalidomide maintenance in newly diagnosed myeloma: results from the phase III GMMG-MM5 trial. Leukemia. 2020;34(7):1853–65.
9. Richardson PG, Jacobus SJ, Weller EA, Hassoun H, Lonial S, Raje NS, et al. Triplet therapy, transplantation, and maintenance until progression in myeloma. N Engl J Med. 2022;387(2):132–47.
10. Perrot A, Lauwers-Cances V, Cazaubiel T, Facon T, Caillot D, Clement-Filliatre L, et al. Early versus late autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial. Blood. 2020;136:39.
11. Pawlyn C, Menzies T, Davies FE, de Tute RM, Henderson R, Cook G, et al. Defining the optimal duration of lenalidomide maintenance after autologous stem cell transplant-data from the myeloma XI trial. Blood. 2022;140(Suppl 1):1371–2.
12. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC myeloma IX results and meta-analysis. Blood. 2012;119(1):7–15.
13. Stewart AK, Trudel S, Bahlis NJ, White DJ, Sabry W, Belch A, et al. A randomized phase III trial of thalidomide and prednisone as maintenance therapy following autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM): the NCIC CTG MY 10 Trial. Blood. 2010;116(21):39.
14. van de Donk NW, van der Holt B, Minnema MC, Vellenga E, Croockewit S, Kersten MJ, et al. Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial. Lancet Haematol. 2018;5(10):e479–e492.
15. Sonneveld P, Zweegman S, Cavo M, Nasserinejad K, Broijl A, Troia R, et al. Carfilzomib, pomalidomide, and dexamethasone as second-line therapy for lenalidomide-refractory multiple myeloma. HemaSphere. 2022;6(10):e786.
16. Garderet L, Kuhnowski F, Berge B, Roussel M, Devlamynck L, Petillon MO, et al. Pomalidomide and dexamethasone until progression after first salvage therapy in multiple myeloma. Br J Haematol. 2023;201(6):1103–15.
17. Bjorklund CC, Kang J, Amatangelo M, Polonskaia A, Katz M, Chiu H, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. Leukemia. 2020;34(4):1197–201.
18. ClinicalTrials.gov. Iberdomide Maintenance Therapy in Patients With Multiple Myeloma [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05177536
19. ClinicalTrials.gov. Iberdomide (CC220) Maintenance After ASCT in Newly Diagnosed MM Patients [Internet]. 2022. Available from: https://clinicaltrials.gov/study/NCT04564703
20. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol. 2012;30(24):2946–55.
21. Neben K, Lokhorst HM, Jauch A, Bertsch U, Hielscher T, van der Holt B, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood. 2012;119(4):940–8.
22. Rosiñol L, Oriol A, Teruel A, De La Guía A, Blanchard M, De La Rubia J, et al. Bortezomib and thalidomide maintenance after stem cell transplantation for multiple myeloma: a PETHEMA/GEM trial. Leukemia. 2017;31(9):1922–7.
23. Nooka AK, Kaufman JL, Muppidi S, Langston A, Heffner LT, Gleason C, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia. 2014;28(3):690–3.
24. Hadidi SA, Ababneh OE, Schinke CD, Thanendrarajan S, Bailey C, Zangari M, et al. Three years (yrs) maintenance with bortezomib, lenalidomide, and dexamethasone (RVD) in multiple myeloma (MM): results of total therapy (TT) IIIB. J Clin Oncol. 2023;41(16_Suppl):e20053.
25. Dimopoulos MA, Gay F, Schjesvold F, Beksac M, Hajek R, Weisel KC, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019;393(10168):253–64.
26. Slade M, Martin TG, Nathwani N, Fiala MA, Rettig MP, Gao F, et al. Ixazomib, lenalidomide and dexamethasone consolidation with randomized ixazomib or lenalidomide maintenance after autologous transplant in newly diagnosed multiple myeloma. Leukemia. 2022;36(12):2917–21.
27. Rosinol L, Oriol A, Tamayo RR, Blanchard MJ, Jarque I, Bargay J, et al. Ixazomib plus lenalidomide/dexamethasone (IRd) versus lenalidomide/dexamethasone (Rd) maintenance after autologous stem cell transplant in patients with newly diagnosed multiple myeloma: results of the Spanish GEM2014MAIN trial. Blood. 2021;138:466.
28. Rosiñol L, Oriol A, Ríos-Tamayo R, Blanchard M-J, Jarque I, Bargay J, et al. Lenalidomide and dexamethasone with or without ixazomib maintenance TAILORED by residual disease status in myeloma. Blood J. 2023;142:1518–28.
29. Touzeau C, Perrot A, Roussel M, Karlin L, Benboubker L, Jacquet C, et al. All-oral triplet combination of ixazomib, lenalidomide, and dexamethasone in newly diagnosed transplant-eligible multiple myeloma patients: final results of the phase II IFM 2013-06 study. Haematologica. 2022;107(7):1693–7.
30. Patel KK, Shah JJ, Feng L, Lee HC, Manasanch EM, Olsem J, et al. Safety and efficacy of combination maintenance therapy with ixazomib and lenalidomide in patients with posttransplant myeloma. Clin Cancer Res. 2022;28(7):1277–84.
31. Gay F, Musto P, Rota-Scalabrini D, Bertamini L, Belotti A, Galli M, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol. 2021;22(12):1705–20.

32. Dytfeld D, Wrobel T, Jamroziak K, Kubicki T, Robak P, Walter-Croneck A, et al. Carfilzomib, lenalidomide, and dexamethasone or lenalidomide alone as maintenance therapy after autologous stem-cell transplantation in patients with multiple myeloma (ATLAS): interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023;24(2):139–50.
33. Jasielec JK, Kubicki T, Raje N, Vij R, Reece D, Berdeja J, et al. Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. Blood. 2020;136(22):2513–23.
34. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394(10192):29–38.
35. Moreau P, Hulin C, Perrot A, Arnulf B, Belhadj K, Benboubker L, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(10):1378–90.
36. Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020;136(8):936–45.
37. Kaufman JL, Laubach JP, Sborov D, Reeves B, Rodriguez C, Chari A, et al. Daratumumab (DARA) plus lenalidomide, bortezomib, and dexamethasone (RVd) in patients with transplant-eligible newly diagnosed multiple myeloma (NDMM): updated analysis of Griffin after 12 months of maintenance therapy. Blood. 2020;136:45–6.
38. Shah ND, Lutska Y, Pei H, Qi M, Krevvata M, Kane C, et al. Daratumumab (DARA) plus lenalidomide versus lenalidomide alone as maintenance treatment in patients with newly diagnosed multiple myeloma (NDMM) after frontline autologous stem cell transplant (ASCT): use of minimal residual disease (MRD) as a novel primary endpoint in the phase 3 Auriga study. Blood. 2019;134:1829.
39. Krishnan A, Hoering A, Hari P, Sexton R, Orlowski RZ. Phase III study of daratumumab/rhuph20 (nsc-810307) + lenalidomide or lenalidomide as post-autologous stem cell transplant maintenance therapy in patients with multiple myeloma (mm) using minimal residual disease to direct therapy duration (DRAMMATIC study): SWOG s1803. Blood. 2020;136:21–2.
40. Sonneveld P, Broijl A, Gay F, Boccadoro M, Einsele H, Blade J, et al. Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab (DARA) in patients (pts) with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): a multicenter, randomized, phase III study (PERSEUS). J Clin Oncol. 2019;37:8055.
41. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. Phase 3 randomized study of daratumumab (DARA) + bortezomib, lenalidomide, and dexamethasone (VRd) versus Vrd alone in patients (pts) with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplantation (ASCT): primary results of the Perseus trial. Blood. 2023;142:LBA-1.
42. Goldschmidt H, Mai EK, Bertsch U, Fenk R, Nievergall E, Tichy D, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol. 2022;9(11):e810–e821.
43. Leypoldt LB, Besemer B, Asemissen AM, Hänel M, Blau IW, Görner M, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. Leukemia. 2022;36(3):885–8.
44. Goldschmidt H, Mai EK, Bertsch U, Besemer B, Haenel M, Miah K, et al. Elotuzumab in combination with lenalidomide, bortezomib, dexamethasone and autologous transplantation for newly-diagnosed multiple myeloma: results from the randomized phase III GMMG-HD6 trial. Blood. 2021;138:486.
45. Thomas SK, Shah JJ, Morin A, Morphey AN, Lee HC, Manasanch EE, et al. Update of a phase II study of lenalidomide-elotuzumab as maintenance therapy post-autologous stem cell transplant (AuSCT) in patients (pts) with multiple myeloma (MM). Blood. 2020;136:46–7.
46. Usmani SZ, Hoering A, Ailawadhi S, Sexton R, Lipe B, Hita SF, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. Lancet Haematol. 2021;8(1):e45–e54.
47. Gonzalez-Calle V, Rodriguez Otero P, Rey-Bua B, De La Rubia J, De Arriba F, Cabañas V, et al. Belantamab mafodotin in combination with Vrd for the treatment of newly diagnosed transplant eligible multiple myeloma patients: results from the phase II, open label, multicenter, GEM-BELA-Vrd trial. Blood. 2022;140(Suppl 1):7286–8.
48. Cohen AD, Garfall AL, Susanibar-Adaniya SP, Vogl DT, Waxman A, De Mesa O, et al. Phase 2 study of belantamab mafodotin as pre-and post-stem cell transplant consolidation and maintenance (BLAST study) for multiple myeloma patients in first remission. Blood. 2022;140(Suppl 1):12628–29.
49. ClinicalTrials.gov. Belantamab Mafadotin Maintenance Therapy After Salvage Autologous Hematopoietic Cell Transplantation in Patients with Relapse Refractory Multiple Myeloma [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05065047
50. ClinicalTrials.gov. Minimal Residual Disease Guided Maintenance Therapy with Belantamab Mafodotin and Lenalidomide After Autologous Hematopoietic Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05091372
51. Usmani SZ, Garfall AL, van de Donk NW, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021;398(10301):665–74.
52. Searle E, Quach H, Wong SW, Costa LJ, Hulin C, Janowski W, et al. Teclistamab in combination with subcutaneous daratumumab and lenalidomide in patients with multiple myeloma: results from one cohort of MajesTEC-2, a Phase 1b, multicohort study. Blood. 2022;140(Suppl 1):394–6.
53. Zamagni E, Boccadoro M, Spencer A, Delforge M, Reece DE, Gyula Szabo A, et al. MajesTEC-4 (EMN30): a phase 3 trial of teclistamab + lenalidomide versus lenalidomide alone as maintenance therapy following autologous stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2022;140(Suppl 1):7289–91.
54. Sebag M, Raje NS, Bahlis NJ, Costello C, Dholaria B, Solh M, et al. Elranatamab (PF-06863135), a B-cell maturation antigen (BCMA) targeted CD3-engaging bispecific molecule, for patients with relapsed or refractory multiple myeloma: results from magnetismm-1. Blood. 2021;138:895.
55. Mateos Manteca MV, Grosicki S, Kim K, Negre E, Vandendries E. MagnetisMM-7: an open-label, multicenter, randomized phase 3 study of elranatamab versus lenalidomide in post-transplant patients with newly diagnosed multiple myeloma. J Clin Oncol. 2023;41:8066.
56. Mina R, Musto P, Rota-Scalabrini D, Paris L, Gamberi B, Palmas A, et al. Carfilzomib induction, consolidation, and maintenance with or without autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: pre-planned cytogenetic subgroup analysis of the randomised, phase 2 FORTE trial. Lancet Oncol. 2023;24(1):64–76.
57. Brown S, Sherratt D, Hinsley S, Flanagan L, Roberts S, Walker K, et al. MUKnine OPTIMUM protocol: a screening study to identify high-risk patients with multiple myeloma suitable for novel treatment approaches combined with a phase II study evaluating optimised combination of biological therapy in newly diagnosed high-risk multiple myeloma and plasma cell leukaemia. BMJ Open. 2021;11(3):e046225.

58. ClinicalTrials.gov. Ixazomib Plus Low-dose Lenalidomide Versus Ixazomib Alone for Maintenance Treatment of High Risk Multiple Myeloma [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05722405
59. ClinicalTrials.gov. VRD as Induction Followed by VR Maintenance in Patients with Newly Diagnosed High Risk Multiple Myeloma [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT03641456
60. ClinicalTrials.gov. Expression-linked and R-ISS-adapted Stratification for First Line Therapy in Multiple Myeloma Patients (ELIAS) [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05665140
61. ClinicalTrials.gov. Post-Transplant Maintenance Therapy with Isatuximab Plus Lenalidomide for High-Risk Multiple Myeloma Patients [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05776979
62. Panopoulou A, Cairns DA, Holroyd A, Nichols I, Cray N, Pawlyn C, et al. Optimizing the value of lenalidomide maintenance by extended genetic profiling: an analysis of 556 patients in the myeloma XI trial. Blood. 2023;141(14):1666–74.
63. Pasvolsky O, Milton DR, Rauf M, Tanner MR, Bashir Q, Srour S, et al. Lenalidomide-based maintenance after autologous hematopoietic stem cell transplantation for patients with high-risk multiple myeloma. Transplant Cell Ther. 2022;28(11):752.e1–752.e6.
64. Kaiser MF, Hall A, Walker K, Sherborne A, De Tute RM, Newnham N, et al. Daratumumab, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone as induction and extended consolidation improves outcome in ultra-high-risk multiple myeloma. J Clin Oncol. 2023;41:3945–55.
65. Paiva B, Manrique I, Dimopoulos MA, Gay F, Min CK, Zweegman S, et al. MRD dynamics during maintenance for improved prognostication of 1280 patients with myeloma in the TOURMALINE-MM3 and -MM4 trials. Blood. 2023;141(6):579–91.
66. de Tute RM, Pawlyn C, Cairns DA, Davies FE, Menzies T, Rawstron A, et al. Minimal residual disease after autologous stem-cell transplant for patients with myeloma: prognostic significance and the impact of lenalidomide maintenance and molecular risk. J Clin Oncol. 2022;40(25):2889–900.
67. Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv. 2020;4(23):5988–99.
68. Goicoechea I, Puig N, Cedena MT, Burgos L, Cordon L, Vidriales MB, et al. Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. Blood. 2021;137(1):49–60.
69. Avet-Loiseau H, Lauwers-Cances V, Corre J, Moreau P, Attal M, Munshi N. Minimal residual disease in multiple myeloma: final analysis of the IFM2009 trial. Blood. 2017;130:435.
70. Rosinol L, Oriol A, Rios-Tamayo R, Blanchard MJ, Jarque I, Bargay J, et al. Lenalidomide and dexamethasone with or without ixazomib maintenance tailored by residual disease status in myeloma. Blood. 2023;142:1518–28.
71. Korde N, Diamond B, Burge M, Hassoun H, Landau H, Hultcrantz M, et al. Maintenance therapy cessation for sustained MRD negative multiple myeloma patients. Blood. 2022;140(Suppl 1):2397–8.
72. Derman BA, Major A, Major S, Wolfe BD, Gorski M, Cooperrider JH, et al. Prospective trial using multimodal measurable residual disease negativity to guide discontinuation of maintenance therapy in multiple myeloma (MRD2STOP). Blood. 2022;140(Suppl 1):2108–9.
73. Malandrakis P, Ntanasis-Stathopoulos I, Kostopoulos I, Gavriatopoulou M, Theodorakakou F, Fotiou D, et al. P861: persistent bone marrow and imaging MRD negativity AS criteria to stop lenalidomide maintenance following ASCT: preliminary results of a single-center prospective cohort study. HemaSphere. 2023;7(Suppl):e4994547.
74. Costa LJ, Chhabra S, Medvedova E, Schmidt TM, Dholaria B, Godby KN, et al. Outcomes of MRD-adapted treatment modulation in patients with newly diagnosed multiple myeloma receiving daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) and autologous transplantation: extended follow up of the Master trial. Blood. 2022;140(Suppl 1):7275–7.
75. ClinicalTrials.gov. Minimal Residual Disease Guided Maintenance Therapy with Belantamab Mafodotin and Lenalidomide After Autologous Hematopoietic Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma [Internet]. 2023.
76. Ailawadhi S, Parrondo RD, Perez G, Kharfan-Dabaja MA, Murthy HS, Ayala E, et al. Peri-transplant and maintenance daratumumab for minimal residual disease (MRD) eradication in transplant-eligible multiple myeloma (MM) patients. Blood. 2022;140(Suppl 1):10165–66.
77. Lin T, Hampras S, Krey R, Pei H, Qi M, Krevvata M, et al. Daratumumab plus lenalidomide versus lenalidomide alone as maintenance treatment in patients with newly diagnosed multiple myeloma after frontline transplant: a multicenter, randomized, phase 3 study (AURIGA). Clin Lymphoma Myeloma Leuk. 2019;19(10):e199.
78. ClinicalTrials.gov. MInimal Residual Disease Adapted Strategy (MIDAS) [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT04934475
79. Sweiss K, Hofmeister CC, Zappia M, Frolov M, Benevolenskaya E, Quigley JG, et al. Free from maintenance drug therapy in multiple myeloma (the FREEDMM trial): a pilot study of minimal residual disease (MRD)-driven discontinuation of maintenance. Blood. 2022;140(Suppl 1):7304–5.
80. ClinicalTrials.gov. Post-Autologous Transplant Maintenance with Isatuximab and Lenalidomide in Minimal Residual Disease Positive Multiple Myeloma (HEME-18) [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT05344833
81. Yong K, Royle K-L, Ramasamy K, Parrish C, Hockaday A, Asher S, et al. Risk-adapted therapy directed according to response (RADAR, UK-MRA myeloma XV)-comparing MRD-guided treatment escalation and De-escalation strategies in patients with newly diagnosed myeloma suitable for stem cell transplantation. Blood. 2022;140(Suppl 1):1844–6.
82. Lu M, Liu A-J, Chen W-M, Wu Y, Fu R, Jing H, et al. P959: maintenance therapy followed autologous stem cell transplantation by IXAZOMIB and/or lenalidomide in patients with newly diagnosed multiple myeloma: a multicentered real world study in China. HemaSphere. 2023;7(Suppl):e3162941.
83. ClinicalTrials.gov. Elotuzumab in Combination with Carfilzomib, Lenalidomide and Dexamethasone (E-KRd) Versus KRd in MM [Internet]. 2023. Available from: https://clinicaltrials.gov/study/NCT03948035
84. Quach H, Lasica M, Routledge D, Kalff A, Lim A, Low M, et al. A randomized, open-label, phase 3 study of low-dose selinexor and lenalidomide (Len) versus len maintenance post autologous stem cell transplant (ASCT) for newly diagnosed multiple myeloma (NDMM): ALLG MM23, Sealand. J Clin Oncol. 2021;39:8055.

How to cite this article: Hwang A, Hayden P, Pawlyn C, McLornan D, Garderet L. The role of maintenance therapy following autologous stem cell transplantation in newly diagnosed multiple myeloma: Considerations on behalf of the Chronic Malignancies Working Party of the EBMT. Br J Haematol. 2024;204(4):1159–1175. https://doi.org/10.1111/bjh.19353