Review Article

First Line Treatment of Newly Diagnosed Transplant Eligible Multiple Myeloma *Recommendations From a Canadian Consensus Guideline Consortium*

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Abstract

The availability of effective therapies for multiple myeloma (MM) has sparked debate on the role of first line autologous stem cell transplantation (ASCT), particularly in standard-risk patients. However, treatment for individuals with high-risk disease continues to display suboptimal outcomes. With novel therapies used earlier, practice is changing rapidly in the field of MM. Presently, quadruplet induction therapy incorporating an anti-CD38 monoclonal antibody to a proteasome inhibitor and an immunomodulatory drug prior to ASCT followed by maintenance therapy stands as the foremost strategy for attaining deep and sustained responses in transplant eligible MM (TEMM). This Canadian Consensus Guideline Consortium (CGC) proposes consensus recommendations for the first line treatment of TEMM. To address the needs of physicians and people diagnosed with MM, this document focuses on ASCT eligibility, induction therapy, mobilization and collection, conditioning, consolidation, and maintenance therapy, as well as, high-risk populations, management of adverse events, assessment of treatment response, and monitoring for disease relapse. The CGC will periodically review the recommendations herein and update as necessary.

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Introduction

Overview

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation and accumulation of malignant plasma cells mostly within the bone marrow. Despite recent therapeutic advancements, MM remains incurable for the vast majority of patients, emphasizing the importance of optimizing first line approaches to induce deep and durable responses, improve quality of life (QoL), and prolong survival. The goals of first line treatment in newly diagnosed transplant-eligible MM (TEMM) includes comprehensive eligibility assessment for autologous stem cell transplantation (ASCT) through consideration of individual patient characteristics (i.e., comorbidities; frailty status) that may impact treatment decisions and outcomes. It is particularly crucial to address the needs of patients with high-risk disease, characterized by cytogenetic abnormalities or other factors associated with poor prognosis, who may experience quicker disease progression and shorter survival times. Tailored treatment approaches are essential to optimize outcomes and mitigate relapse in this subgroup.

This consensus guideline aims to describe the best-practice approach to the first line treatment of TEMM. By providing

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concise and evidence-based recommendations, we seek to empower clinicians in making informed treatment decisions tailored to the individual needs and characteristics of their patients. Specifically, this review will focus on the management of first line ASCT-eligible patients, encompassing considerations related to induction therapy, stem cell mobilization and collection, conditioning regimens, consolidation strategies, and maintenance therapy among others.

Methodology

Members of the Canadian Consensus Guideline Consortium (CGC) were assigned sections of the manuscript. Each author reviewed the related literature and provided a written draft of their assigned section(s) with draft recommendations. Each topic was discussed and reviewed during regular online meetings that took place between April 2023 and May 2024.

The authors convened in-person in September 2023 and November 2023 to review, finalize, and grade the recommendations using a modified American Society of Clinical Oncology (ASCO) consensus approach. The authors voted to define the type of each recommendation as either evidence-based, consensus (informal), or no recommendation. The authors agreed to grade the recommendations by retaining the informal consensus process of the ASCO approach (Appendix 1). Next, the authors voted to rate the strength of each recommendation as either strong, moderate, or weak (Appendix 2).

To better inform the section on eligibility for ASCT in this manuscript, we conducted a survey to assess local ASCT practices across Canadian centers (see Acknowledgements section). Physicians practicing at Canadian transplant centers were surveyed regarding their center's ASCT age criteria, creatinine clearance thresholds, routine echocardiography including left ventricular ejection fraction (LVEF) thresholds, use of cardiac biomarkers, parameters for pulmonary function testing, pretransplant risk stratification tools, and geriatric assessment frailty testing.

Myeloma Canada members and additional leading Canadian MM clinicians had the opportunity to review the manuscript with the final consensus recommendations and their grading prior to submission for publication (see Acknowledgements section).

Interpretation and Use

When interpreting the recommendations, clinicians should bear in mind that each is based on clinical evidence, as well as clinical experience gained through daily practice and national and international collaboration with experts in the field of MM. Although the recommendations are intended to be a flexible tool to assist with timely and informed decisions, they should not replace sound clinical judgment or be used as a legal resource. The recommendations were finalized and graded based on available evidence at the time of development. Evidence updates are frequent and should be considered when consulting the recommendations. Clinicians with patient safety concerns or clinical care questions should seek the guidance from a MM specialist.

First Line ASCT for Newly Diagnosed MM

Rationale for First Line ASCT

High-dose chemotherapy followed by ASCT was pioneered as a therapeutic approach for MM patients the 1980s, and subsequently established as standard of care in the 1990s, based on a number of studies demonstrating superior responses, improved progression-free survival (PFS),[1–4] and in some cases an overall survival (OS) advantage.[2] The advent of novel agent based induction therapy, particularly triplet regimens incorporating a minimum of a proteasome inhibitor (PI) ± an immunomodulatory drug (IMID) has resulted in more patients achieving high quality responses prior to ASCT, with ≥ very good partial response (VGPR) rates typically exceeding 50%.[5–7]

The high efficacy of modern-day induction regimens has led to debate around the ongoing role of ASCT as part of frontline therapy in fit standard-risk patients. A number of large scale, randomized control trials (RCTs) have explored this question in patients treated with novel agent-based, triplet induction therapy, with almost all showing PFS advantage with ASCT.[5–9] In the phase 3 IFM 2009 RCT, patients were randomized to 3 cycles of VRD induction followed by ASCT and 2 cycles of VRD consolidation vs 8 cycles of VRD, with lenalidomide maintenance given in each arm for 1 year.[8] PFS was 50 versus 36 months for ASCT vs non-ASCT arm, but no OS benefit was observed. A meta-analysis of 4 phase 3 RCTs comparing combination therapy with novel agents vs. HDT/ASCT showed similar trends, with improvement noted in PFS (hazard ratio [HR] 0.55), but no difference in OS.[10] However, these data are not a true reflection of ASCT vs no ASCT approaches because the majority of patients in the IFM 2009 and the EMN02 studies received an ASCT at relapse.

It is likely that higher rates of deep responses, particularly of minimal residual disease (MRD) negative remissions underpin the superior PFS outcomes observed post ASCT. The IFM 2009 trial demonstrated advantage to ASCT only in the MRD positive group,[11] suggesting a potential role of response adapted decision making post induction. However, in the FORTE trial that employed a triplet combination incorporating the more potent PI carfilzomib as part of induction therapy, despite achieving initial equivalent rates of post ASCT MRD negativity for the KRD alone vs KRD plus ASCT arms (56 vs 62% respectively), the ASCT arm showed continuing PFS advantage. It is likely that higher rates of sustained MRD negativity achieved at 1 year (47% with KRD + ASCT vs 35% with KRD alone) post ASCT underpin the improved PFS.[7] Favorable impact on MRD was sustained across cytogenetic risk groups.[12] Although MRD currently remains a research tool, these data suggest that ASCT has the potential to achieve clinically meaningful deepening of responses, even in the era of modern day induction, and that post induction MRD status cannot be used for patient selection for ASCT outside clinical trial settings.

Timing of ASCT

MM is a heterogeneous disease, where clonal evolution exists at time of relapse, and therefore it is possible that deferral of any therapeutic modality, including transplant may result in increased

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treatment resistance, when applied in relapse state.[13] Prospective RCT data around deferral of ASCT to time of relapse is lacking for modern front-line regimens, and retrospective data is conflicting,[14–16] with some studies demonstrating benefit in PFS with upfront ASCT.[16] Long term follow-up of the IFM 2009, DETERMINATION, and the EMN02 trials showed no difference in OS between early and delayed ASCT; however 77% of patients in the IFM study and 63% in EMN02 proceeded to ASCT at the time of relapse, and analyses of the non-ASCT sub-groups was not specifically performed.

Eligibility for ASCT

ASCT eligibility criteria are generally in line with those employed in clinical trials, and patients are required to have a good performance status with ECOG of ≤2 and adequate organ function to be considered for ASCT. However, in the real-world setting, therapy is more individualized and select sub-groups of patients not routinely eligible for clinical trials, may be considered for ASCT.

Age

Most clinical trials have excluded patients greater than 65 years of age.[5–9] However, registry and population-based data show increasing number of older patients are being transplanted in SOC setting.[17,18] In an EBMT study, between 1 January 1995 and 31 December 2019, the median patient age at transplant increased from 55 years to 61 years, and the percentage of patients aged >65 years at transplant increased from 7% to 30%.[18] RCT data incorporating modern agent induction specific to older patients is lacking. The IFM 99–06 RCT compared IMID based triplet induction with MPT vs conventional chemotherapy with MP or ASCT (after 2 cycles of VAD) in patients aged over 65 and MPT arm was superior to ASCT.[19] However, none of the treatment arms are considered optimal by modern standards making results difficult to generalize.

Exploratory analysis in age matched cohorts to assess ASCT outcomes was performed in the UK Myeloma XI trial that randomized patients to induction with IMID based triplet (CTD or RCD) followed by ASCT consolidation for those deemed eligible.[20] This analysis revealed a significantly shorter PFS of 34.4 months for the 70-75 years age group, compared to <65 age group (50.8) months, but not significantly different to the 65-69 age group (40 months). However, comparison of ASCT vs no ASCT approaches within the same age cohort, using propensity score matching to adjust for potential confounders, showed a statistically significant improvement in both PFS (HR 0.44) and OS (HR 0.53) for patients undergoing ASCT, with no increase in day 100- or 1-year mortality.

Registry and population-based data also support safety of ASCT in older patients with most studies demonstrating no increase in ASCT related mortality,[17,18,21,22] with comparable event-free and OS outcomes across age cohorts.[17,21–23] Pooled analysis of observational studies has also shown an OS benefit with ASCT for older patients.[24]

While there is no specific age cutoff to determine transplant eligibility, emerging data demonstrating improved treatment tolerability of DRD in older adults may lead more patients and physicians to avoid treatment-related toxicity associated with ASCT. However, this approach is difficult to routinely recommend for otherwise fit, eligible patients because there is evidence of deepening MRD post ASCT even with the use of quadruplet regimens incorporating upfront anti-CD38 antibodies.

Renal Impairment

Patients with renal impairment have historically been considered a poor risk subgroup with increased risk of treatment related toxicity and have been excluded from clinical trials. The outlook of patients with renal impairment has improved with novel agent based combinations, particularly those incorporating PIs resulting in frequent rapid reversal of light chain nephropathy in newly diagnosed MM patients.[25–27] ASCT can further aid renal recovery,[28–30] with most recent studies demonstrating comparable PFS and OS outcomes post ASCT for patients with renal impairment compared with those without, including patients on dialysis.[31–33] ASCT eligibility should not be based on renal function alone.[32]

Cardiac/Pulmonary Function

In line with clinical trial eligibility, patients with symptomatic heart failure or respiratory failure are not routinely considered eligible for ASCT. Most centers in Canada routinely perform pre-ASCT echocardiography as part of their safety assessment, and a LVEF ≥ 50% is considered an acceptable threshold for ASCT. For LVEF between 40% and 50%, there is variability in practice with some Canadian centers considering patients for transplant if the LVEF is between 40% and 50% on a case-by-case basis, and others having a threshold of 40%-45% to define eligibility. Pulmonary function tests (PFTs), including spirometry and diffusion capacity are also a routine part of risk assessment. A diffusing capacity for carbon monoxide (DLCO) >50%-60% is generally deemed adequate for ASCT eligibility, with some centers having additional thresholds based on forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC). For patients with abnormal PFTs, computed tomography (CT) of the chest and respirology opinion may be sought for on a case by case basis for more precise risk stratification and optimization prior to ASCT.

Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI)

The HCT-CI is a composite index of organ co-morbidity and was prospectively validated for prediction of nonrelapse and overall mortality in allogeneic stem cell transplant (allo-SCT) recipients, and is often extrapolated to the ASCT population.[34] This is supported by data from retrospective analysis of 1730 patients receiving ASCT of whom 48% had MM.[35] Patients with high HCT-CI (score >2) had higher rates of 100-day composite end point of morbi-mortality (defined as death, need for intubation, dialysis or need for vasopressors) and nonrelapse mortality. In a CIBMTR analysis of 1156 MM patients, a HCT-CI of greater than 0 was associated with inferior OS, but not 1 year nonrelapse mortality.[36]

In another retrospective assessment of 126 patients with MM undergoing ASCT, any co-morbidity on the HSCT-CI or CCI (>0) was associated with an increased number of organ systems with serious toxicity (at least grade 2 toxicity using the Seattle criteria), an

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increased total sum of toxicity grades for all organs, and prolonged hospital length of stay.[37]

Most Canadian institutions perform the HCT-CI as part of their pre-ASCT assessments. Although this is most often used as a risk assessment tool to inform discussions with patients. Some institutions may use a high HCT-CI, in conjunction with age and other comorbidities to define eligibility.

Frailty Assessment

Frailty is increasingly recognized as an important determinant of outcomes in MM patients, and data on role of frailty assessments in elderly, transplant ineligible patients was reviewed by the Canadian Myeloma Research Group (CMRG).[38] However, few studies have assessed role of frailty in determining outcomes in the TEMM population. Although tools such as the Revised Myeloma Comorbidity Index (R-MCI) have predictive value for survival outcomes in TEMM, they have not been prospectively evaluated for patient selection. In an evaluation of 801 patients treated with standard of care therapy, and routinely eligible for transplant up to 70 years of age, ASCT in frail patients was associated with very poor PFS and OS.[39] The lack of a standardized definition of frailty makes comparison of treatment modalities across studies challenging, although emerging data support the upfront use of an anti-CD38 monoclonal antibody based regimen without ASCT in the frail population. This suggests a potential role for formal frailty evaluation in a subset of potentially frail MM patients being considered for ASCT.[40]

Although not standard practice, some Canadian centers do perform geriatric evaluations in older, frailer adults prior to ASCT on a case by case basis.

Exclusions and Temporary Deferral of ASCT

Disease Status. Depth of response post induction therapy has demonstrated predictive value,[41–44] likely due to correlation with depth of response achieved post ASCT. A partial response or better by International Myeloma Working Group Criteria is considered optimal for proceeding to ASCT, and is achieved in the majority of patients undergoing novel agent triplet or quadruplet-based induction therapy. In the rare cases where a partial response is not achieved, consideration should be given to switch treatment to an alternative regimen to deepen response; particularly in cases where alternative agents are feasible and the initial induction regimen did not include at least 2 novel agents.

Most centers do not proceed with ASCT in the setting of active disease progression, given the lack of clinical trial data to support this practice and retrospective data showing poor outcomes.[41] Given that ASCT remains an important component of MM treatment, patients should be referred for ASCT independent of depth of response, including those with stable disease. However, for patients with suboptimal response (stable disease or <PR) there may be consideration for optimizing induction therapy prior to ASCT where feasible.[45]

Infection. In line with clinical trials, all patients with evidence of active infection are deferred until clinical recovery.

Consensus Recommendations: First Line ASCT for Newly Diagnosed MM	Type of Recommendation (Strength of Recommendation)
ASCT remains standard of care for fit, consenting patients as part of first line therapy, outside of clinical trials.	Evidence-based (Strong)
There is no definitive age threshold when considering ASCT. Patients up to 70 years of age are routinely considered and fit, older adults otherwise meeting the eligibility criteria may be considered for ASCT.	Consensus (Moderate)
Renal impairment is not a contraindication for ASCT. Fit eligible patients, including those on dialysis, should be considered for ASCT.	Evidence-based (Moderate)
Patients with advanced cardiopulmonary disease should not be considered for ASCT.	Consensus (Strong)
ASCT in patients with active infection should be deferred until clinical recovery.	Consensus (Strong)
ASCT should proceed in patients with stable disease or better if stem cell collection is complete.	Consensus (Weak)

Abbreviations: ASCT = autologous stem cell transplantation; MM = multiple myeloma; HCT-CI = Hematopoietic cell transplantation-specific comorbidity index.

High-Risk Populations

Overview

The improvement in survival in patients with MM has not been consistent despite recent therapeutic advances because patients referred to as high-risk still experience poor outcomes even with the newest therapies.[46] These patients could be identified by patient- and disease-related characteristics such as extramedullary disease, cytogenetic abnormalities, suboptimal responses, plasma cell leukemia or circulating plasma cells, and early relapses. Furthermore, due to the lack of specific trials in this subgroup of patients (Table 1) and their underrepresentation in clinical trials (Table 2), the treatment of high-risk MM continues to be challenging. Recent evidence indicates that prognosis associated with high-risk features might be improved by reaching deep and sustained responses using the best available therapeutic options.

High-Risk Cytogenetic Abnormalities

Several cytogenetic abnormalities, including del(17p), del(1p32), gain 1q, t(4;14), and t(14;16), are considered high-risk in NDMM patients as they confer poor prognosis.[54] The inclusion of 3 genomic alterations [t(4;14), t(14;16) and del(17p)] in the R-ISS score, along with the levels of serum lactate dehydrogenase and serum β2-microglobulin stratifies patients in 3 categories, with significant distinct OS.[55] However, the definition of high-risk, based on 3 unweighted cytogenetic abnormalities, may be simplified and restrictive, and as such, may lead to misclassification. For example, a study by Walker using whole-genome and exome data from 784 patients identified a high-risk group of patients (6% of the population of NDMM), named double-hit, characterized

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Table 1 Select Published Clinical Trials Specifically Dedicated to High-risk ND MM According to Prespecified Definitions

Trial	Regimen	Study Design	Study Definition of High-risk	Response Rates	Median PFS
OPTIMUM[47,48]	Dara-CVRd vs KCRd or RCd	Phase 2b, first line TEMM and TIMM (MRD 100 days post ASCT and PFS)	Two or more of: t[4;14] **or** t[14;16], t(14;20), del(1p32), gain(1q) **or** del(17p), HR-GEP, PCL (>20% cPCs)	**At 30 months (Dara-CVRd):** ORR: 93% CR: 52% VGPR: 35% PR: 5% MRD-: 50%	**At 30 months:** Dara-CVRd: 87% KCRd/CRd: 39.8%
GMMG-CONCEPT[49]	Isa-KRd in induction, consolidation, and maintenance ± ASCT	Phase 2, TEMM (arm A) and TIMM (arm B) NDMM (MRD- 1025 post consolidation	del17p or t(4;14) **or** t(14;16) or >3 copies 1q21 **and** ISS 2 or 3 stage disease	**At 44 months (TEMM):** ORR: 94.9% sCR/CR: 72.8%v VGPR: 18.2% MRD-: 67.7% **At 33 months (TIMM):** ORR: 88.5% sCR/CR: 57.7% VGPR: 30.8% MRD-:54.2%	**At 44 months (TEMM):** NR (approximately 70%) **At 33 months (TIMM):** NR (approximately 70%)
SWOG 1211[50]	VRd vs VRd-Elo	Phase 2, TIMM (PFS)	HR-GEP, t(14;16), t(14;20), del (17p), amp(1q21), pPCL, or elevated serum LDH (>2 X ULN)	**At 53 months (VRd):** ORR: 88% ≥CR: 6% **At 53 months (VRd-Elo):** ORR: 83% ≥PR: 2.1%	**At 53 months:** VRd: 33.64 months (95% CI; 19.55-NR) VRd-Elo: 31.47 months (18.56–53.98)
EMN12[51]	KRd ± ASCT followed by KR maintenance	Phase 2, nonrandomized, TEMM and transplant ineligible pPCL	del(17p), t(4;14), t(14;16), del(1p), ampl(1q), ISS stage 3; elevated LDH	**At 43.5 months (younger adults; best response on protocol)**: ≥CR: 50% ≥VGPR: 83% ≥PR: 86% **At 32.0 months (older adults; best response on protocol)**: ≥CR: 36% ≥VGPR: 68% ≥PR: 80%	**Younger adults at 43.5 months:** KRd ± ASCT: 15.5 months (95% CI 9.4–38.4) KRd + ASCT: 26.2 months (95% CI 9.4–54.7) KRd + 2 ASCT: 31.2 months (95% CI 12.8-NE) KRd + allo-SCT: 49.2 months (95% CI 3.6-NE) **Older adults at 32.0 months:** 13.8 months
EMN02[5]	VCd then ASCT or VMP ± VRd consolidation followed by lenalidomide maintenance	Phase 3, 2 randomizations	>10% t(4;14),t (14;16), amp 1 q, >2-% del (17p)	**1st randomization at 60.3 months (ASCT):** sCR:22% CR:22% ≥VGPR: 84% **1st randomization at 60.3 months (VMP):** sCR: 21% CR: 19% ≥VGPR:77% **2nd randomization at 42.1 months:** ≥CR (VRd consolidation): 55% ≥CR (no consolidation): 40%	**1st randomization at 60.3 months:** ASCT: 56.7 months (95% CI; 49.3–64.5) VMP: 41.9 months (37.5–46.9) **2nd randomization at 42.1 months:** VRd consolidation: 58.9 months (54.0-NE) No consolidation: 45.5 months (39.5–58.4)

Abbreviations: ND = newly diagnosed; MM = multiple myeloma; Dara = daratumumab; C = cyclophosphamide; V = bortezomib; R = lenalidomide; d = dexamethasone; TEMM = transplant eligible multiple myeloma; TIMM = transplant ineligible multiple myeloma; t = translocation; del = deletion; PFS = progression-free survival; PCL = plasma cell leukemia; pPCL = primary PCL; ASCT = autologous stem cell transplantation; ORR = overall response rate; CR = complete response; sCR = stringent CR; VGPR = very good partial response; PR partial response; MRD = minimal residual disease; Isa = isatuximab; K = carfilzomib; Elo = elotuzumab; cPCs = circulating plasma cells; AEs = adverse events; N/A = not available; NE = could not be estimated; PD = progressive disease; HR-GEP = high-risk gene expression profiling; LDH = lactate dehydrogenase; ULN = upper limit of normal; NR = not reached; mo = months; ISS = international staging system; pts = patients.

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Table 2 Efficacy of Current Treatment Approaches for ND TEMM With High-Risk Features del(17p), t(4;14), or t(14;16)

	SWOG-1211[50]	CASSIOPEIA[52]		FORTE[12]		PERSEUS[53]	
Population	High-risk[a]	ITT	High-risk	ITT	High-risk	ITT	High-risk
Treatment	Elo + VRd vs VRd	Dara + VTd vs VTd		KRd + ASCT/KRd12		Dara + VRd vs VRd	
PFS (m) / HR	31 vs 34 / 0.96	NR / 0.47	NR / 0.67	NR / 0.64	NR / 0.51	NE / 0.42	

[a] High-risk definition: gene expression profiling high-risk, t(14;16), t(14;20), del(17p), amp1q21, plasma cell leukemia, elevated serum LDH (2 × upper limit of normal.Abbreviations: ND = newly diagnosed; TEMM = transplant eligible multiple myeloma; del = deletion; t = translocation; m = months; PFS = progression-free survival; HR = hazard ratio; NA = not available; NE = could not be estimated; NR = not reached; ITT = intention-to-treat; NR = not reached; Elo = elotuzumab; VRd or RVd = bortezomib + lenalidomide + dexamethasone; Dara = daratumumab; VTd = bortezomib + thalidomide + dexamethasone; KRd = carfilzomib + lenalidomide + dexamethasone; KRd12 = 12 × 28-day KRd cycles; + ASCT.

by either a biallelic TP53 inactivation or 1q amplification (≥4 copies) in addition to ISS stage 3, with a dismal prognosis (median PFS, 15.4 months; OS, 20.7 months).[56]

The gain of the long arm of chromosome 1 (+1q) is a frequent cytogenetic abnormality seen in approximately 30% of NDMM.[57,58] A retrospective analysis that included 201 patients with NDMM treated with VRD reported that patients with +1q had a shorter median PFS and OS compared with those without +1q (PFS 41.9 months vs 65.1 months; $P = 0.002$; OS not reached in both groups; $P = 0.003$). The negative impact of +1q on survival is more profound when there is amplification of 1q, defined by the presence of ≥ 4 copies (median PFS of 25.1 months).[59]

In the context of recent evidence and uncertainties regarding the definition and prognostic value of high-risk cytogenetic abnormalities and outcomes of patients with high-risk MM who achieve negative MRD, the role of tandem ASCT is debatable. According to the prospective CMRG database that included 302 single and 125 tandem transplants, followed by maintenance therapy in 190 (63%) and 96 (77%) patients, respectively, there was no difference in PFS or OS after a single or tandem transplant when maintenance was given.[60] 83% of patients were induced with cyclophosphamide, bortezomib, and steroids but 47 (11%) required an alternative re-induction regimen prior to first ASCT. Maintenance, in general, included more than 1 drug (eg, lenalidomide ± PI ± steroids). PFS for single or tandem ASCT with maintenance at 3 years was 53.7% and 46.3%, respectively ($P = 0.527$). Three-year OS rates were 76.7% and 85.6% ($P = 0.0962$); however, PFS was better with tandem compared to single ASCT when no maintenance was given. This study demonstrates the potent anti-MM effect of post ASCT maintenance and raises the question of the optimal role of tandem ASCT in the modern treatment era.[60] On the other hand, in the EMN02/HOVON95 trial, high-risk patients who received 1 ASCT had more limited outcomes compared to those who received tandem ASCT with a 3-year estimated PFS of 73% versus 64% (HR 0.70 [95%CI 0.50–0.98]; $P = 0.040$). A long-term update on the benefit of tandem transplant is still pending.

Extramedullary Disease (EMD) or Plasma Cell Leukemia (PCL)

The presence of extramedullary disease (EMD) or primary plasma cell leukemia (pPCL) in NDMM is rare accounting for approximately 0.5%-2% of MM cases.[61,62] PCL has traditionally been defined by > 2 × 10^9 cells/L and 20% circulating PCs in the peripheral blood[63]; however, some suggest that the criteria are too restrictive.[64] Recently, the International Myeloma Working Group proposed that the new criterion should include patients with ≥ 5% of circulating PCLs given 2 retrospective series demonstrated poor OS of 6%-13% in this population similar to patients with ≥ 20% of circulating PCLs.[65,66]

Patients with EMD or PCL are difficult to treat, and their outcomes are poor.[61,67] Although the introduction of IMIDs and PIs has significantly improved outcomes of primary PCL, the survival benefit is less pronounced compared to MM.

The European Blood and Marrow Transplantation Group (EBMT) retrospectively analyzed 751 pPCL patients transplanted between 1998 and 2014, comparing 4 frontline transplant strategies: single ASCT, single allo-SCT, or a combined transplant, either tandem ASCT/allo-SCT or double ASCT.[68] With a median follow-up of approximately 4 years, the median PFS and OS of all patients, irrespective of transplant type, were 14 and 33 months, respectively. Dhakal et al. retrospectively reviewed 348 patients with pPCL receiving ASCT ($n = 277$) or allo-SCT ($n = 71$) between 2008 and 2015.[69] Four years after allo-SCT or ASCT, the PFS (19% vs. 17%), nonrelapse mortality (12% vs.7%), relapse rate (69% vs. 76%) and OS (31% vs. 28%) were similar in the 2 groups.

Two prospective trials assessed outcomes of ASCT in patients with pPCL, one by the Gruppo Italiano Malattie de Ematologiche dell'Adulto (GIMEMA)[70] and one by the Intergroupe Francophone du Myelome (IFM).[71] In the GIMEMA study, patients received lenalidomide and dexamethasone for induction followed by ASCT and the median PFS and median OS were 14 and 28 months, respectively. In the IFM study, the median PFS and median OS were 15 and 63 months, respectively. Patients who underwent tandem ASCT/allo-SCT had a lower relapse rate but high nonrelapse mortality (particularly during the first 100 days) that negatively affected survival outcomes, at least for the first 2-3 years post ASCT. In addition, the relapse rate post tandem ASCT/allo-SCT was 35%. Importantly, the role of allo-SCT in an era where T-cell engagers and novel immunotherapeutics have shown promising efficacy is unknown, and the role of immunotherapies in this patient population needs to be evaluated further. While there is no uniform consensus on the optimal evidence-based treatment strategy for PCL, consolidation with allo-SCT may be considered as part of frontline treatment in younger (< 65 years) patients with pPCL with an available fully matched sibling or unrelated donor. As the benefits of allo-SCT are yet to be fully understood and to improve efficacy and safety, allo-SCT should be performed in the setting of a clinical trial, in which new induction, conditioning, and maintenance regimens may be explored.

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Consensus Recommendations: Specific Populations	Type of Recommendation (Strength of Recommendation)
Tandem ASCT should be considered for high-risk disease as defined by the EMN02 study.	Evidence-based (Weak)
Tandem ASCT should be considered for PCL.	Evidence-based (Weak)

Abbreviations: ASCT = autologous stem cell transplantation; PCL = plasma cell leukemia.

Induction

Objectives of Induction Therapy, Recommended Regimens, and Duration. The goals of induction therapy are to get quick disease cytoreduction, reverse or at least prevent further end-organ damage, and improve performance status regardless of the ASCT eligibility. Regimens for induction therapy commonly include a PI, dexamethasone, and an IMID or cyclophosphamide. Currently, 3-drug regimens such as bortezomib, thalidomide, and dexamethasone (VTD); bortezomib, lenalidomide, and dexamethasone (VRD); bortezomib, cyclophosphamide, and dexamethasone (VCD); and carfilzomib, lenalidomide, and dexamethasone (KRD); have shown improved efficacy compared with 2-drug combinations.[72,73]

Two RCTs compared the use of a PI plus an IMID and dexamethasone versus PI plus cyclophosphamide and dexamethasone as induction therapy in ASCT-eligible patients.[74,75] In the FORTE trial, KRD was superior to KCD; after 4 cycles of induction therapy, 74% of patients treated with KRD reached VGPR or better compared to 61% of those treated with KCD ($P = 0.01$).[75] In the prospective IFM 2013–04 trial, a total of 340 patients were randomly assigned to receive VTD or VCD.[74] After 4 cycles, 66.3% of the patients in the VTD arm achieved at least a VGPR (primary endpoint) vs 56.2% in the VCD arm ($P = 0.05$). In addition, the overall response rate (partial response [PR] or better) was significantly higher in the VTD arm (92.3% vs 83.4% in the VCD arm; $P = 0.01$). These trials supported the 3-drug regimens with a PI, an IMID and dexamethasone as the preferred induction therapy in ASCT-eligible patients. In instances where an IMID is not readily available, cyclophosphamide is an acceptable substitute. An integrated analysis supports the benefit of VRD over VTD, with higher rates of VGPR and MRD negativity after 6 cycles of induction therapy followed by ASCT.[76]

A 4-drug combination with the anti-CD38 monoclonal antibody daratumumab was also evaluated. In the CASSIOPEIA trial that randomly assigned 1085 patients age <66 years between VTD and daratumumab plus VTD (D-VTD), the addition of daratumumab to VTD during induction and consolidation before and after ASCT induced significantly higher VGPR, CR and MRD negativity rates that translated into a significant improvement in PFS in the daratumumab arm.[52] Similarly, the GRIFFIN and PERSEUS trials showed improved results with the addition of daratumumab to VRD induction, compared to VRD alone, despite increased infection risk.[53,77] A similar improvement was observed with the addition of isatuximab to KRD in the IsKia trial.[78] The CMRG is conducting a phase 2 trial (CMRG-008) to assess the benefits of adding isatuximab to the current Canadian standard of care (CyBorD induction/ASCT/maintenance lenalidomide).[79] The early results of this trial show that isatuximab added to CyBorD is well tolerated and effective.[80]

Currently, there are no RCTs that identified the optimal number of induction cycles prior to stem-cell collection, and most clinical trials have arbitrarily included 4 cycles of induction therapy.[81] Significant improvement in the depth of response has been achieved with triplet therapy with or without anti-CD38 agent. Furthermore, within 4 cycles of triple therapy, the majority of patients achieve at least a VGPR response, with the largest incremental decrease in paraprotein levels after the first cycle. After that, a decline is less steep, with very small incremental decreases in paraprotein seen beyond 3 to 4 cycles of therapy. Therefore, it is recommended to administer 3 to 4 cycles of induction therapy in patients in whom ASCT is planned. Although retrospective cohort-based studies do not support second-line induction therapy compared with immediate ASCT, there are limitations in applying these data to modern era salvage regimens, and there may be consideration of optimization of induction therapy where feasible.[82,83]

Patients With Suboptimal Response. The clinical significance of ASCT in patients with suboptimal response post induction therapy, including stable disease (SD) and progressive disease (PD), has not been established. Furthermore, suboptimal response and early PD within 12 months is considered a poor prognostic factor. In a multicenter retrospective study conducted in Japan that included 3898 newly diagnosed TEMM patients who underwent ASCT between 2007 and 2020, the suboptimal response rate was 4.7%, including 1.7% of patients with PD.[8] A significant difference in PFS but not OS was observed between the VGPR and PR groups. Additionally, there was no significant difference in OS or PFS between the PR and SD groups. A total of 558 patients (38.0%) received reinduction therapy. There were 229 patients (37.7%) with high-risk cytogenetics. After a median follow-up of 31.7 months, 30-month OS rates among the PR, SD, and PD groups were 86.3%, 78.5%, and 39.4%, respectively; $P < 0.001$). OS was significantly shorter in patients with high-risk cytogenetic abnormalities ($P < 0.001$) who achieved SD compared to those with PR and patients treated with reinduction therapy ($P = 0.013$). The 30-month PFS rate in patients with PD was 17.9%. Early PD within 12 months after ASCT was predictive of short OS, whereas OS without early PD, even in the PD group, was similar to that in the SD and PR groups. This indicates the importance of post ASCT maintenance to prevent early relapses. The study conducted by the CMRG confirmed the importance of post ASCT maintenance.[84] Because of suboptimal response or progression on the first induction, and based on the physician's decision, 10% of the patients received a second induction regimen before proceeding to auto-SCT. Patients treated with a second induction regimen had an ORR of 72.9% and $a \geq$VGPR rate of 35.4%. However, they had significantly inferior outcomes (median PFS 27.9 vs 36.2 months [$P = 0.001$]; median OS 118 vs 126 months [$P = 0.011$]). Yet, when maintenance was used, results were similar regardless of the number of induction regimens given (median PFS 55.3 vs 51.1 months [$p = 0.11$]; median OS 158.6 months vs not reached [$p = 0.13$]). This study highlights the contribution of post ASCT maintenance, particularly lenalidomide given

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until progression, in multiple subgroups, including those with high-risk features as well as those receiving a second induction.

Consensus Recommendations: Induction	Type of Recommendation (Strength of Recommendation)
Prior to stem-cell collection, ASCT-eligible patients should receive 3–6 cycles of an induction regimen.	Consensus (Strong)
The induction regimen should include a PI, an IMID and, if available, an anti-CD38 monoclonal antibody.	Evidence-based (Strong)
For patients receiving induction therapy, the level of minimal response required to proceed to ASCT is not firmly established. Patients should be referred for ASCT independent of depth of response.	Consensus (Strong)

Abbreviations: PI = proteasome inhibitor; IMID = immunomodulatory drug.

Stem Cell Mobilization and Collection

Successful hematopoietic stem cell (HSC) mobilization is a prerequisite of ASCT. Stem cell mobilization is a process by which, in response to cytokines or chemotherapy, HSCs are released from the bone marrow to the peripheral blood. Stem cells collected from the peripheral blood are preferred over those from the bone marrow due to ease of collection and faster engraftment time after high-dose melphalan. The CD34 cell surface marker is normally used as a surrogate marker for HSCs.[85] A sufficient number of CD34+ stem cells are required from the mobilization and collection processes to ensure adequate engraftment, and to therefore proceed safely with ASCT.[86] A particular number of CD34+ cells/mL are required (between 8 and 20) to start the collection process and to increase the likelihood of collecting enough CD34+ cells/kg in a single apheresis.[85]

A minimum threshold of 2×10^6 CD34+ cells/kg are recommended to support 1 cycle of high-dose melphalan therapy/ASCT.[87,88] The use of more CD34+ cells/kg may result in a faster engraftment,[88] but has not been consistently associated with significant clinical benefit.[89] If multiple ASCTs are planned, a higher collection target (at least double) is necessary for a possible salvage ASCT at relapse or planning for a tandem ASCT.[88] For each ASCT, we recommend aiming to collect 3-5 $\times 10^6$ CD34+ cells/kg of cells.

Different mobilization techniques are available, including administration of granulocyte-colony stimulating factor (G-CSF; e.g., filgrastim) alone, G-CSF plus chemotherapy, or G-CSF plus plerixafor. Each center should develop and implement their own algorithms for various mobilization strategies, with the goal of optimizing collection yield.[88]

There are no data to support a specific time off therapy (e.g., lenalidomide) prior to G-CSF administration to enhance the likelihood of successful mobilization.[89] Most MM specialists recommend a 2-4 week washout period from the last dose of lenalidomide to the start of apheresis.[88]

Filgrastim is the most commonly used G-CSF mobilization agent at a dose of 10 mg/kg/d x 5-10 days. Data with pegfilgrastim is limited and mixed for the moment.[88] When chemotherapy is added to the mobilization process, there is less likelihood of a collection failure; however, the approach is overall less attractive due to side effects and increased risk of complications.[90] The chemotherapy agent that is usually used is cyclophosphamide. In this setting, low-dose cyclophosphamide (1-2 g/m^2) has been shown to be as effective as intermediate and high doses.[91] Plerixafor reversibly inhibits the binding of stromal cell-derived factor 1 (CXCL12) to its CXCR4 receptor. Disruption of the CXCL12-CXCR4 interaction mediates the release of HSCs into the peripheral blood, favoring a better mobilization and collection yield.[92] A uniform mobilization regimen using plerixafor has not yet been established; however, it can be used pre-emptively or on-demand, usually with G-CSF. Plerixafor has been used more widely since lenalidomide became a standard part of induction therapy prior to ASCT for the majority of TEMM patients. Motixafortide, another inhibitor of CXCR4 with extended clinical activity, in combination with G-CSF, has shown better phase 3 efficacy for mobilization when compared to G-CSF alone.[93]

Induction therapy before ASCT for patients with MM typically consists of 3-6 cycles of a lenalidomide-based regimen. To achieve successful CD34+ stem cell harvest, lenalidomide exposure before collection should be limited because prolonged exposure can negatively impact subsequent peripheral blood stem cell collection.[94–96] An increased duration of lenalidomide therapy (more than 6 cycles) is usually associated with a lower count of PBSC collected and a higher number of apheresis sessions required. Therefore, to minimize the risks of mobilization failures, it is generally recommended to proceed with collection of PBSC within 6 months, ideally after 4 cycles, of initiation of a lenalidomide-containing therapy.[94–97] Following a lenalidomide-based induction, a mobilization strategy of G-CSF plus plerixafor (upfront or as a rescue therapy) is often used. Indeed, prior lenalidomide use is a significant risk factor associated with failed mobilization when filgrastim alone is used.[98] On the other hand, plerixafor has been shown useful to overcome the negative impact of lenalidomide on mobilization. A retrospective study of 89 patients,[99] using the following mobilization protocol: filgrastim or pegfilgrastim ± preemptive plerixafor according to a previously validated algorithm based on day 4 peripheral blood CD34+ cell count and mobilization target, showed that plerixafor was needed in 45% of the patients with no prior exposure to lenalidomide, in 63% of the patients with 1-4 cycles and in 84% of the patients with more than 4 cycles of a lenalidomide-based therapy ($P = 0.01$). Also, a higher proportion of patients with no prior exposure to lenalidomide met the mobilization target: 100% vs 90% vs 79% ($P = 0.008$); even though all patients yielded at least 2×10^6 CD34+/kg. A recent retrospective study,[100] in the COVID-19 era, looked at 94 patients with 40 of them who received prolonged induction with more than 6 cycles of lenalidomide. Mobilization protocol used G-CSF in combination with cyclophosphamide, plerixafor or both. Despite the fact that patients receiving a prolonged induction were more likely to require more than 1 day of apheresis (38 vs 15%, $P = 0.0154$), there was no difference in regard to CD34+ stem cell yields at completion of apheresis

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Table 3 Risk Factors for Mobilization Failure or Poor Mobilization

Risk Factors
Patient and Disease Related
• Increasing/older age[94,99,103]
• Low bone marrow reserve or low platelet count at the time of mobilization[103]
• Presence of bone marrow disease[86]
• Previous radiotherapy[86,91]
Therapy Related
• Number of months of previous chemotherapy[88]
• Prior melphalan[91,104]
• Prior lenalidomide[98,103]
• Increased duration of lenalidomide exposure before collection[94,95,99]
Mobilization Related
• Mobilizing regimen used[88]
• Mobilization more than 1 year after diagnosis[98,103]
• Low number of CD34+ cells/μL preapheresis[88]
• Previous mobilization failure[91]

Consensus Recommendations: Stem Cell Mobilization and Collection	Type of Recommendation (Strength of Recommendation)
Mobilization	
Stem cell mobilization should include G-CSF ± plerixafor. Plerixafor may be used upfront or on-demand based on peripheral CD34+ cell concentration.	Evidence-based (Strong)
In cases of mobilization failure, plerixafor should be used (if not used previously) with or without chemomobilization.	Consensus (Strong)
For lenalidomide-based induction, stem cells should be collected after 3–6 cycles, or ideally after 4 cycles.	Evidence-based (Moderate)
For daratumumab-based induction, stem cells should be collected after a maximum of 4 cycles with plerixafor.	Evidence-based (Moderate)
Collection	
Sufficient stem-cell collection (for more than 1 ASCT) should be considered upfront, due to potential limited ability for future stem-cell collection after prolonged treatment exposure.	Evidence-based (Strong)
CD34+ cells/kg threshold For 1 ASCT: Minimum of 2 x 10^6 CD34+ cells/kg For 2 ASCTs: Minimum of 5 x 10^6 CD34+ cells/kg	Consensus (Strong)
Indications to collect for 2 ASCTs upfront If tandem ASCT, salvage ASCT or a long life expectancy, consider collecting a minimum of 5 x 10^6 CD34+ cells/kg	Consensus (Strong)

Abbreviations: ASCT = autologous stem cell transplantation; G-CSF = granulocyte-colony stimulating factor.

(9.99 vs 10.46 cells/kg, $P = 0.5513$).[88] Our expert consensus was to use G-CSF mobilization with plerixafor either routinely or on demand, based on the institutional policy.

Of interest, lenalidomide exposure before ASCT has no effect on the collected PBCS's quality as well as on engraftment post ASCT.[94,95] The impact of the addition of daratumumab on stem cell mobilization and collection and the need for more plerixafor is well established.[52,77,101,102]

Mobilization failure is defined as failure to collect a minimum of 2 million (x 10^6) CD34+ cells/kg. Nowadays, mobilization failure is rare, especially with algorithms allowing for the use of plerixafor. Indeed, rates have reduced to below 10%.[88] There are some well identified risk factors for poor mobilizers (Table 3). For patients who failed initial mobilization, remobilization should include plerixafor or chemotherapy with filgrastim and is usually successful in these patients.[88,98]

Conditioning: High-Dose Therapy

Introduction. Conditioning is a preparative regimen of high-dose chemotherapy administered to patients prior to the infusion of hematopoietic stem cell products. The first phase 3 RCT documenting improved CR and OS rates with high dose melphalan was reported by Attal et al. in 1996.[1] 200 previously untreated patients were randomized to receive either conventional chemotherapy or high-dose therapy with stem cell rescue. 81% of patients in the high-dose therapy group obtained VGPR or greater, compared with 57% in the conventional therapy group, and 5-year OS rates were 52% vs 12% respectively.

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Despite advances in MM therapy including the introduction of potent "novel" agents, high-dose therapy with ASCT continues to show a significant, although less marked, survival benefit over standard chemotherapy and remains the standard of care for ASCT-eligible patients, and MEL200 remains the most common conditioning regimen of choice.[5,105]

Conditioning Regimens. Outside of clinical trials, the standard conditioning regimen prior to ASCT is MEL200 (melphalan 200 mg/m^2), given as a rapid infusion the day prior to stem cell reinfusion.[1,106]

The inclusion of total body irradiation as part of the conditioning regimen does not improve outcomes and increases toxicity, and is therefore not recommended.[107,108]

Reduced dose regimens (MEL140 or MEL100) show a minimal decrease in toxicity but also decreased response rates.[109,110] Thus, the goal should be to administer MEL200 if tolerated, though melphalan dose reductions are appropriate in patients with renal failure (eGFR < 30 mL/min/1.73 m^2).

Other agents have been investigated as either adjuncts to or replacements for HDM. Combining busulfan and melphalan may improve PFS, but does not improve OS and can be associated with higher rates of mucositis and infection.[111,112] Adding novel agents, such as bortezomib, to high dose melphalan has not been shown to improve either PFS or OS.[113] Adding bendamustine to HDM as been shown to increase CR rate in a phase 2 RCT, but evidence of improvement in PFS and/or OS is still lacking.[114] Similarly, a phase 2 trial of BeEAM (bendamustine, etoposide, cytarabine and melphalan) conditioning showed it to be effective and tolerable, but no significant differences in PFS or OS were observed compared with a historical HDM-conditioning cohort.

Supportive Care

ASCT-associated morbidity and mortality has improved with aggressive supportive care. This includes:

- Antiemetics
- Prophylaxis and management of mucositis
- Gastric protection
- Growth factor support
- Antimicrobials (antifungals, antivirals, ± antibacterials)
- Close monitoring of volume status with ins/out and daily weights, with hydration support as required
- Thromboprophylaxis
- Blood product support

Consensus Recommendations: Conditioning	Type of Recommendation (Strength of Recommendation)
The standard conditioning regimen prior to ASCT is MEL200.	Evidence-based (Strong)
MEL140 should be used in patients with creatinine clearance <30 mL/min.	Consensus (Strong)

Abbreviations: ASCT = autologous stem cell transplantation; MEL200 = melphalan 200 mg/m^2; MEL140, melphalan 140 mg/m^2.

Consolidation Post ASCT

Several previous studies have explored the use of consolidation chemotherapy as a means of achieving a deeper response in a shorter treatment duration. Among these studies, bortezomib-based consolidation therapy has been utilized.[115]

Consolidation therapy typically involves administering the same combination of agents used during induction therapy prior to ASCT, typically for a fixed number of cycles, most commonly ranging from 2 to 4.[72,116]

To date, numerous phase 2 and 3 studies have compared 3- versus 2-drug consolidation regimens, as well as quadruplet versus triplet therapies, all of which have demonstrated the efficacy of consolidation therapy in increasing the rate of high-quality responses, including stringent complete response (CR) and minimal residual disease (MRD) negativity.[117]

The role of consolidation therapy with VRd versus no consolidation has been studied in 2 RCTs, both of which have produced conflicting results. While the EMN02 study reported positive outcomes, these were not confirmed by the STaMINA study, leading to heterogeneous recommendations across different guidelines. The question of whether the impact of post ASCT consolidation therapy on subsequent outcomes is influenced by the length of induction therapy received before ASCT remains a topic of debate.[118,119]

Given the ongoing debate around the efficacy of consolidation therapy post ASCT, recent practice guidelines do not strongly recommend its use.[120,121]

In the phase 3 EMN02/HOVON-95 trial, a second random assignment compared post ASCT consolidation with VRD versus no consolidation, with both groups subsequently receiving prolonged lenalidomide maintenance. The trial demonstrated a PFS benefit with consolidation therapy (median PFS of 58.9 months versus 45.5 months in the no-consolidation group, with a *P*-value of 0.014), while OS at 5 years was comparable between the 2 groups.[5]

The results of the EMN02/HOVON-95 trial differed from those of the BMT CTN 0702 STAMINA phase 3 trial that compared 3 strategies after ASCT: no consolidation and lenalidomide maintenance only, consolidation with 4 cycles of VRD followed by lenalidomide maintenance, and consolidation with a second ASCT followed by lenalidomide maintenance. In an intent-to-treat analysis of 758 patients, the 3-year PFS, OS, and conversion rates to CR were similar across all 3 groups. However, with extended follow-up and a focus on the per-protocol high-risk patients who received consolidation therapy, the 5-year PFS increased to 43.7% for those receiving tandem ASCT versus 37.3% for those receiving ASCT/VRD (4 cycles) and 32% for those receiving only 1 ASCT before maintenance (*P*-value of 0.03 for comparison between tandem ASCT and no consolidation).[122] Another important consideration are variable induction regimens used in STAMINA participants, with 55% of patients receiving VRD, while the EMN02 trial used a more standardized induction regimen of 3-4 cycles of bortezomib, cyclophosphamide, and dexamethasone.

Although many clinical trials looked at post ASCT consolidation, the approaches used were generally heterogeneous and thus conclu-

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sions are difficult to extrapolate from the data. For patients who are ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least 2 cycles may be considered.

Consensus Recommendations: Consolidation Post ASCT	Type of Recommendation (Strength of Recommendation)
Consolidation therapy post ASCT is not routinely recommended.	Evidence-based (Weak)

Abbreviation: ASCT = autologous stem cell transplantation.

Maintenance

The distinction between consolidation and maintenance therapy is often blurred; however, maintenance is a long-term treatment at reduced intensity with the aim of keeping the disease under control for as long as possible before progression, and ideally to improve OS without affecting QoL.

In the past, many maintenance therapy attempts were hampered by significant complications such as the development of acute leukemia with melphalan,[123,124] or excessive toxicity with steroids,[125] interferon,[126] and thalidomide.[127]

However, with the advent of novel drugs with significantly less adverse effects such as second-generation IMIDs, PIs and now anti-CD38 monoclonal antibodies, maintenance therapy has been revisited. Lenalidomide, due to its oral convenience and its efficacy in first line[128,129] and relapse settings,[130,131] has received particular attention for its potential role in maintenance therapy. A meta-analysis demonstrated a median PFS of 52.8 months for lenalidomide maintenance and 23.5 months for placebo or observation (HR 0.48 [95% CI 0.41-0.55]).[132] Furthermore, an additional meta-analysis showed a significant OS benefit and confirmed the PFS benefit for lenalidomide maintenance post ASCT when compared to placebo or observation.[133]

PIs have also been evaluated for their role in maintenance therapy. The phase 3 HOVON-65/GMMG-HD4 trial comparing bortezomib versus thalidomide post ASCT for 2 years demonstrated a significant PFS and OS improvement with bortezomib;[134,135] however, the benefit was mainly driven by patients with high-risk cytogenetics, especially del17p.[136] One major limitation of the trial is that the induction regimen was different between the 2 groups, making it difficult to assess the real benefit of maintenance therapy. In the context of high-risk disease, there is no evidence to suggest that maintenance with bortezomib monotherapy cannot be used beyond 2 years. Ixazomib, as an oral PI, has also been evaluated in maintenance therapy post ASCT in a phase 3 trial. TOURMALINE-MM3 compared ixazomib versus placebo and showed a modest but significant 28% reduction in the risk of progression or death in favor of ixazomib (median PFS 26.5 months [95% CI 23.7-33.8] vs 21.3 months [18.0-24.7]; HR 0.72 [95% CI 0.58-0.89]; $P = 0.0023$); however, there was no significant improvement in OS.[137] In a recent phase 2 trial in ASCT-eligible patients without progression post consolidation, patients were randomized between ixazomib or lenalidomide maintenance. Though the difference in median PFS was not statistically significant between study arms, the median PFS tended to be lower with ixazomib (median PFS 28.2 months [95% CI 19.2-37.2]) versus lenalidomide (NR; HR 1.70; $P = 0.062$).[138] Carfilzomib has also been evaluated in maintenance therapy post ASCT. In the FORTE trial, a second randomization aimed to evaluate maintenance treatment with carfilzomib plus lenalidomide versus lenalidomide alone. The 3-year PFS was 75% (95% CI 68-82) with carfilzomib plus lenalidomide versus 65% (95% CI 58-72) with lenalidomide alone (HR 0.64 [95% CI 0.44-0.94]; $P = 0.023$), and no differences in OS to date with limited follow up.[7] Similarly, the ATLAS trial compared maintenance therapy with carfilzomib, lenalidomide, and dexamethasone versus lenalidomide alone. The median PFS was 59.1 months (95% CI 54.8-NR) in the carfilzomib, lenalidomide, and dexamethasone group versus 41.4 months (33.2-65.4) in the lenalidomide group (HR 0.51 [95% CI 0.31-0.86]; $P = 0.012$).[139]

Anti-CD38 monoclonal antibodies have also been evaluated for their potential role in maintenance therapy. Daratumumab maintenance was compared to observation in the CASSIOPEIA phase 3 trial. The median PFS was not reached (95% CI NR-NR) with daratumumab versus 46.7 months (95% CI 40.0-NR) with observation (HR 0.53 [95% CI 0.42-0.68]; $P < 0.0001$).[140] The study is still immature and limited by the fact that daratumumab is being compared to observation. Ongoing trials comparing daratumumab plus lenalidomide versus lenalidomide alone are underway (DRAMMATIC trial ClinicalTrials.gov Identifier: NCT04071457 and AURIGA trial ClinicalTrials.gov Identifier: NCT03901963).

Based on the clinical evidence, our expert consensus is that lenalidomide monotherapy should be the standard of care maintenance therapy post ASCT. For patients with high-risk cytogenetics, the addition of bortezomib to lenalidomide maintenance has been considered based on a single-center study that included 45 patients[141] and a *post hoc* analysis of the HOVON-65 trial. Both trials demonstrated that early ASCT, followed by VRD maintenance, is a promising strategy for high-risk MM patients, resulting in excellent response rates and promising PFS and OS. In the HOVON-65 trial, bortezomib maintenance was associated with a significant improvement in both the PFS and OS of patients with del(17p) compared to thalidomide.[142] The superiority of bortezomib maintenance compared to lenalidomide has not been shown in a prospective randomized trial incorporating novel agent induction. However, the combination of lenalidomide and bortezomib in maintenance has shown a trend towards improved PFS in observational studies,[143,144] which has supported the recommendations to consider doublet maintenance with bortezomib and lenalidomide in high-risk patients. The optimal duration of maintenance therapy is yet to be determined.

The FORTE and ATLAS trials comparing carfilzomib plus lenalidomide versus lenalidomide alone demonstrated improved PFS with the combination;[7,139] however, the studies have not yet reported significant improvements in PFS/OS outcomes among high-risk cytogenetic patients, though the median follow-up is still relatively short. There is no universally accepted maintenance therapy for high-risk patients, and this remains an area of active investigation.

For patients that are lenalidomide refractory at induction, the choice of maintenance is limited to PIs or anti-CD38 monoclonal antibodies. Although bortezomib,[134,135] ixazomib,[137] or daratumumab[140] may be reasonable choices, none of the agents have

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shown an OS benefit in maintenance. In this clinical situation, the ideal maintenance approach is unknown.

The optimal duration of maintenance therapy is not well established. Clinical trials that showed the best benefits continued maintenance until disease progression or intolerance.[145,146] Moreover, the STaMINA trial comparing 3 years of maintenance versus continuous maintenance until progression with lenalidomide monotherapy demonstrated inferior PFS with limited maintenance duration (79.5% vs 61% at 5 years; HR 1.91; $P = 0.0004$).[122] Furthermore, IFM2009[8] and DETERMINATION,[9] which were similarly designed trials with the exception of maintenance duration, potentially suggests a longer 4-year survival with maintenance until progression (DETERMINATION) versus 1 year of maintenance (IFM2009). These observations suggest that maintenance therapy should be continued until disease progression if otherwise well tolerated; however, ongoing trials are assessing if maintenance therapy could be stopped based on MRD status.[147,148]

Maintenance is intended to be a long-term treatment, and thus it should be well tolerated. Lenalidomide maintenance is associated with adverse events and the discontinuation rate due to toxicity varies from 5% to 27%.[145,146,149–152] Depending on the clinical context, nonhematologic adverse events (≥ grade 2) or hematologic adverse events (≥ grade 3) should prompt dose modification to improve treatment compliance as much as possible.

Consensus Recommendations: Maintenance	Type of Recommendation (Strength of Recommendation)
Maintenance therapy is a standard of care after ASCT	Evidence-based (Strong)
Lenalidomide monotherapy is the first-choice maintenance therapy after ASCT and should be given until progression or intolerance.	Evidence-based (Strong)
Bortezomib monotherapy as maintenance therapy after ASCT may improve outcome for patients with high-risk genetic disease especially del17p.	Consensus (Weak)
If accessible, double maintenance with lenalidomide and a PI may improve outcomes for patients with high-risk disease.	Consensus (Moderate)

ASCT = autologous stem cell transplantation; OS = overall survival; SC = subcutaneous; PI = proteasome inhibitor.

Management of Key Adverse Events of ASCT

Overview

Existing Canadian consensus guidelines describe the best-practice approach to managing MM-related manifestations and complications, aiming to mitigate their impact.[153] The guidelines cover the management of bone disease, renal insufficiency, tumor lysis syndrome, hematologic complications, and peripheral neuropathy, amongst other disease-related complications. However, the guidelines do not address adverse events and concerns associated with MM treatments, including the risk of secondary primary malignancy (SPM), infections and other acute toxicities and the impact of treatment on patient QoL.

Prevention and Management of Infections

Infections remain the main cause of morbidity and mortality in patients with MM due to the effect of both the disease and its treatments. Given that infectious risk is cumulative through the course of the disease, prevention is the key. To that end, several groups have developed consensus guidelines and recommendations regarding infection prevention and management.[153–157] Risk of infection is particularly high during induction therapy, with serious bacterial infection occurring in one third of patients and infection contributing to half of the early mortality.[158] The TEAMM study demonstrated the effectiveness of levofloxacin in reducing the risk of febrile episodes or death in patients with newly diagnosed MM during the first 12 weeks of treatment.[159] However, when considering prophylaxis with levofloxacin or other fluoroquinolones, one should also consider the risk of long-term tendon damage, neuropsychiatric concerns, and hypoglycemia, especially in older adults.

Patients undergoing ASCT are also at increased risk for bacterial infections during pre-engraftment. Furthermore, the incidence and risk factors of bacterial infection are variable and depend on patient demographics, local bacterial patterns, conditioning regimens, and prophylaxis strategies.[160] According to the German Society of Hematology and Medical Oncology, prophylactic antibiotics can be considered in ASCT recipients during pre-engraftment when the duration of profound neutropenia is expected to be at least 7 days.[161] The most common approach in Canada is fluoroquinolone prophylaxis starting on day 7 until neutrophil recovery; however, it should be noted that although antibacterial prophylaxis has reduced the incidence of fever and bloodstream infections, this has not translated into increased survival.

Historically, the use of fluconazole prophylaxis led to a significant decrease in invasive fungal infections among patients undergoing ASCT[162] and it is responsible for the elimination of *C. albicans fungemia*, which was a common infection, due to the extensive use of steroids in MM. However, recent data do not support the prophylactic use of antifungals to prevent invasive fungal disease—mainly because no reduction in mortality has been found post ASCT,[163] although due to an increased risk for *pneumocystis jiroveci* infection, prophylaxis with trimethoprim-sulfamethoxazole is recommended.

The burden of viral infection in MM falls into 2 categories: 1) reactivation of latent infection (e.g., herpes and hepatitis viruses); and 2) acquisition of new acute viral infections (e.g., respiratory viruses; SARS-CoV-2). Disrupted viral antigen processing associated with PI treatment and the depletion of cellular immunity due to melphalan conditioning, both pose a risk for reactivation of latent infection. Antiviral prophylaxis effectively reduces the risk of herpes simplex and varicella zoster virus reactivation associated with ASCT or PI treatment.[164]

An important issue to be considered when selecting infection prophylaxis in patients receiving chemotherapy, IMIDs, or other immunosuppressive treatments is the interaction of concomitantly used drugs. The key to reducing the burden of infectious complications in patients with MM undergoing ASCT is an individualized treatment plan based on treatment regimens, clinical history (in

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particular vaccination and previous infections), as well as patient's fitness and functional status.[153–156]

Vaccination guidelines for ASCT recipients have been published by 3 major societies: the American Society for Blood and Marrow Transplantation (ASBMT), the European Society for Blood and Marrow Transplantation (EBMT), and the Infectious Diseases Society of America (IDSA).[165,166] Given that antibody titers to vaccine-preventable diseases are known to decrease post ASCT, vaccination with most inactivated vaccines should be initiated 6–12 months post ASCT regardless of the patient's actual antibody titer levels. The administration of live vaccines, including measles, mumps, and rubella (MMR), is considered safer if given more than 2 years post ASCT, more than 1 year following the discontinuation of systemic immunosuppressive treatment, and more than 8 months after intravenous immunoglobulin (IVIG) therapy—often referred to as the "2–1–8 rule". Without data documenting an increased risk of MMR vaccination in patients on maintenance therapy, MMR vaccination can be given to patients on maintenance lenalidomide monotherapy > 2 years post ASCT.[153]

As of 3 months post ASCT, it is recommended for ASCT recipients to be revaccinated with a full primary series (3 doses) of an mRNA SARS-CoV-2 vaccine.[167] While both SARS-CoV-2 and MMR vaccination should be considered for patients on lenalidomide maintenance, MMR vaccination data are lacking with regards to anti-CD38 monoclonal antibody maintenance therapy.

Management of Hematological Toxicities

Hematologic toxicities occurring in the ASCT population are similar to those seen in the general MM population and have been discussed in detail in our supportive care guidelines.[153]

MM Treatment and the Risk of SPM

SPM is a potential complication following ASCT. Although late mortality post ASCT has declined over a 30-year period, an improvement in the mortality associated with SPM has not been observed.[168]

Multiple studies have evaluated different risk factors and concluded that the risk for SPM development is multifactorial in etiology, likely due to a combination of intrinsic (e.g., sex, age, race/ethnicity, comorbidities, and genetic predispositions) and extrinsic (e.g., treatment regimens; lifestyle) risk factors.[169] Due to significant improvement in survival, the risks of SPM in MM are becoming increasingly relevant.

The effect of alkylators, such as melphalan and cyclophosphamide, on the development of SPMs has been extensively investigated, and studies consistently show that prolonged alkylator treatment further increases the risk of hematologic malignancies, specifically acute leukemia.[170,171] Melphalan appears to be the most leukemogenic, particularly when given in high cumulative doses over long periods of time.

ASCT is associated with a potential increase in hematologic and some solid tumours;[172,173] however, multiple studies suggest that the increased risk of SPM is primarily due to alkylator therapy as opposed to ASCT itself. Clinical trials using IMIDs have found higher than expected rates of SPMs, especially hematologic malignancies, including myelodysplastic syndrome (MDS), acute leukemias and lymphomas. These were noted to be higher in patients treated with lenalidomide compared to those not treated with lenalidomide.[174,175] Several RCTs with long-term follow-up suggest an increased risk of hematologic and solid tumor SPMs with lenalidomide post ASCT[8,132,149,176–178] and a meta-analysis reported the cumulative incidence of all SPMs at 5 years to be 6.9% with lenalidomide maintenance versus 4.8% without.[179] On the other hand, a retrospective analysis of the California Cancer Registry that involved over 16,000 patients found lower post ASCT SPM development rates than what has been reported in RCTs.[180] The 5-year and 10-year cumulative rates of any SPM were 4.8% (3.9%-5.9%) and 9.1% (7.7%-10.7%), respectively. The 10-year cumulative incidence rate was 5.7% for solid tumor SPM and 0.9% for hematologic malignancies. The 10-year cumulative incidence of developing any SPM was similar among ASCT recipients (9.1% [7.7–10.7%]) and nonrecipients (7.5% [6.5%-8.6%]; $P = 0.26$), and there was no difference in solid-tumor SPMs ($P = 0.98$). However, considering the noncontrolled nature of the study and limitations associated with real-world retrospective analyses, the study could not assess the contribution of post ASCT lenalidomide maintenance to SPM development. The low incidence of post ASCT SPM is confirmed by the prospective observational CALM study that, at 72 months of follow-up, demonstrated the cumulative incidence of known hematologic and solid malignancies to be 1.4% and 3.6%, respectively.[181]

Furthermore, by improving OS, lenalidomide maintenance is associated with more benefit than harm. Although RCTs consistently show no increased SPM risk with the addition of PIs and/or monoclonal antibodies, robust long-term follow-up has not been reported.[137,182,183] The development of SPM or second hematological malignancy is associated with poor survival[184] and continued vigilance is essential for their early identification.

In summary, while the relative risk of SPM in patients with MM is increased with lenalidomide maintenance post ASCT, the absolute overall risk of SPM development remains low. Therefore, given the significant improvement in myeloma-related outcomes including survival with lenalidomide maintenance therapy, the strong consensus was that the risk of SPM should be discussed with patients but that lenalidomide maintenance should still be the standard of care.

Consensus Recommendations: Management of Key Adverse Events of ASCT	Type of Recommendation (Strength of Recommendation)
Consider antibiotic prophylaxis during induction therapy and pre-engraftment. The risks and benefits of fluoroquinolone prophylaxis should be weighed in the context of local bacterial epidemiology and other risk factors for infection-related mortality.	Evidence-based (Weak)
Provide antiviral prophylaxis during induction therapy, especially for PI and anti-CD38 based induction, as well as for a minimum of 6 months post ASCT.	Evidence-based (Strong)

(*continued on next page*)

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Consensus Recommendations: Management of Key Adverse Events of ASCT	Type of Recommendation (Strength of Recommendation)
ASCT recipients should undergo recommended inactivated vaccination 6-12 months post ASCT.	Evidence-based (Strong)
There is a need for awareness and a low threshold for suspicion for SPM post ASCT. Long-term MM survivors should continue to receive age-appropriate cancer screening that is recommended for the general population.	Consensus (Strong)

Abbreviations: ASCT = autologous stem cell transplantation; PI = proteasome inhibitor; VZV = varicella zoster virus; MM = multiple myeloma;

ESAs = erythropoietin-stimulating agents; QoL = quality of life; SPM = second primary malignancy; IVIG = intravenous immunoglobulin.

Assessment of Treatment Response and Evaluation of Relapse

Categorization of Disease Response and Progression

In most patients with MM, the neoplastic plasma cells secrete a monoclonal protein (MCP, also termed a paraprotein, m-protein, m-spike) that can be monitored as a surrogate marker of tumor burden. Up to 97% of patients with MM have secretory disease, in that the monoclonal protein is detectable in the serum or urine.[185] The International Myeloma Working Group (IMWG) 2016 criteria (summarized in Table 4) provide guidance on assessing disease response.[186]

Assessment of disease response requires the incorporation of tumor markers (serum or urine MCP assessments), imaging to evaluate the presence of plasmacytomas or bone lesions, and bone marrow plasma cell assessments. Practical considerations when applying the IMWG 2016 response criteria include following the appropriate tumor marker; serum FLC levels should only be used to assess response when the serum and urine MCPs are unmeasurable on electrophoresis**.** Measurable disease is defined as a baseline serum monoclonal protein (MCP) $\geq$ 10 g/L, a urine MCP $\geq$200 mg per 24 h, or an abnormal free light chain (FLC) ratio with an involved FLC $\geq$ 100 mg/L (measuring using the Freelite assay by The Binding Site Inc., San Diego, CA). Furthermore, given that IgA and IgD MCPs can comigrate with normal proteins on electrophoresis, the quantitative immunoglobulins values should be used in place of the serum MCP when determining disease response (the same percentage changes apply). With the routine incorporation of monoclonal antibody (mAbs) therapeutics in the treatment of MM, clinicians should be aware that mAbs with the same isotype as the patient's MCP may result in false positive testing on immunofixation, thereby complicating response assessment. Techniques to overcome this include the use of anti-idiotype antibodies that selectively bind to the infused mAb drug and alter its electrophoretic migration pattern, thereby allowing the patient's endogenous MCP to be identified.[187] The development of mass spectrometry-based assays to identify and quantitate MCPs will also allow for specific identification of a patient's MCP,[188] though these assays are not yet routinely incorporated into clinical practice. When evaluating bone marrow biopsies, the highest plasma cell enumeration on the aspirate or trephine biopsy sample should be used to estimate the bone marrow plasma cell burden.

All laboratory measures of response require 2 tests to confirm the response, however the first testing date should be used when assessing time to event outcomes. Clinicians should only evaluate radiated plasmacytomas for progression, as these lesions are not suitable for response assessment. Lastly, patients should be classified at the deepest confirmed response category until there is confirmation of progression or improvement in disease control to a higher response status; patients cannot move to a lower response category (i.e. if a patient is in a VGPR and then has an increase in the MCP, they should remain classified as in a VGPR status until meeting criteria for progression, not be re-classified as a PR or MR in the interim).

The criteria for progressive disease are highlighted in Table 4. Patients are defined as relapsed and refractory if they achieve a minimal response (MR) or better and then become nonresponsive to therapy or meeting criteria for progressive disease within 60 days of last therapy.[189] In contrast, patients with primary refractory MM never achieve a MR or better response prior to disease progression.[189] Clinicians should be aware that emergence of a new isotype MCP post treatment (particularly following ASCT) may be related to oligoclonal reconstitution of the immune system, which is a benign finding that has been associated with improved clinical outcomes. These oligoclonal bands should not be confused with disease relapse, as these bands typically resolve over time.[190–192]

Monitoring Response During Treatment

Patients should undergo laboratory testing at the beginning of each cycle to monitor response. Routine laboratory tests should include a hemoglobin, serum calcium, serum creatinine, quantitative immunoglobulins, serum FLC assay, and serum protein electrophoresis. If a FLC assay is unavailable, 24-hour urine collections for UPEP should be routinely done instead. For nonsecretory patients, where the disease markers are not present in the blood or urine, more frequent bone marrow biopsies might be used to monitor the disease. However, guidelines suggest that repeating bone marrow biopsies should be based on specific clinical indications rather than a fixed schedule.[193]

In patients suspected of achieving a complete response based on the absence of an MCP on SPEP and normalization of the FLCr (Table 4), a 24-hour urine collection for urine protein electrophoresis and immunofixation should be completed, as well as a bone marrow evaluation to confirm response. Though achieving a minimal residual disease (MRD) negative status by either next generation flow or VDJ sequencing has been associated with improvements in PFS and OS,[194,195] to date there is no consensus on how MRD testing should be incorporated into clinical practice. Therefore, given the limited accessibility in the publicly-funded Canadian healthcare context, cost, and lack of evidence-

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Table 4 Summary of the Standard IMWG Response Criteria.[186] Adapted From *Lancet Oncol*. 2016;17(8):e328-e346, With Permission From Elsevier

Response category	Definition
Stringent complete response (sCR)	CR (as defined below), and normal FLCr (between 0.26 and 1.65)[a] and no clonal BM PC (based on IHC)
Complete response (CR)	Negative serum and urine IFE, and disappearance of soft tissue plasmacytomas, and < 5% BM PC
Very good partial response (VGPR)	One of: • Serum MCP decreased by ≥ 90% • MCP unquantifiable on electrophoresis but present on immunofixation • Urine MCP < 100 mg/24h
Partial response (PR)	If measurable serum (≥10 g/L) or urine (≥ 200 mg/24 h) MCP: • ≥ 50% reduction in serum MCP **and** either ≥90% reduction in urine MCP or urine MCP < 200 mg/24 h • If unmeasurable serum or urine, but iFLC measurable (≥ 100 mg/L and FLCr abnormal) at baseline: • ≥ 50% reduction in dFLC • If serum, urine, and FLC unmeasurable at baseline: • ≥ 50% reduction in BM PC (if baseline BM PC ≥30%) **and** ≥50% reduction in SPD size of baseline soft tissue plasmacytomas (if present)
Minimal response (MR)	25%-49% reduction in serum MCP **and** 50%-89% reduction in urine MCP **and** ≥50% reduction in SPD size of baseline soft tissue plasmacytomas (if present)
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or PD
Progressive disease (PD)	Any one of: • ≥ 25% increase in serum MCP compared to the lowest confirmed response value (and absolute increase ≥ 5 g/L, or ≥ 10 g/L if the nadir MCP was ≥ 5 g/L) • ≥ 25% increase in urine MCP (absolute increase ≥200 mg/24 h) • If unmeasurable serum and urine MCP at baseline, an ≥25% increase in the dFLC (absolute increase >100 mg/L) • If unmeasurable serum and urine MCP and FLC at baseline, *a* ≥ 25% in BM PC (absolute increase must be ≥10%) • A new lesion, or *a* ≥ 50% increase from the nadir SPD of >1 lesion, or *a* ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis • ≥50% increase in circulating plasma cells (minimum of 200 cells/microL) if this is the only measure of disease
Clinical relapse	Increasing end organ dysfunction (CRAB features) directly related to the plasma-cell proliferative disorder and not attributable to therapy or non-MM related conditions. CRAB features are defined as hypercalcemia (serum calcium >2.75 mmol/L), decrease in hemoglobin ≥ 20 g/L, rise in creatinine by ≥ 177 μmol/L, or hyperviscosity related to the serum MCP.

[a] The FLC ratio normal ranges are based on the Freelite assay (manufactured by The Binding Site Inc., Birmingham, UK)Abbreviations: IFE, immunofixation; MCP, M-protein; FLCr, free light chain ratio; iFLC, involved free light chain; dFLC, difference in the involved and uninvolved free light chain; BM PC, bone marrow plasma cell; SPD, sum of the maximal perpendicular diameter.

based support on how MRD status should alter clinical management, we do not recommend that MRD testing be performed routinely in clinical practice.

X-ray skeletal surveys are not sufficient for baseline assessment of MM bone disease due to their limited sensitivity. Therefore, the IMWG 2019 guidelines recommend that newly diagnosed patients with newly diagnosed MM undergo a whole-body low dose CT scan (WBLDCT) or a 18f fluorodeoxyglucose (FDG) PET/CT scan to evaluate baseline osteolytic lesions.[196] Ideally, patients should be followed using the same imaging modality, to allow for sequential tests to be more readily compared. In patients with baseline FDG-avid disease on PET/CT scan, we recommend that a PET/CT scan be repeated when patients achieve a plateau/nadir in their disease response post ASCT. Those patients that continue to have FDG-avid disease should be monitored annually with cross-sectional imaging given the risk of early progression.[196] Given variation in accessibility to cross-sectional imaging across Canada, serial imaging post-transplant will be center dependent. However, at minimum, patients with clinical evidence of bone progression should be re-imaged.

Consensus Recommendations: Assessment of Treatment Response and Evaluation of Relapse	Type of Recommendation (Strength of Recommendation)
Following a treatment, response assessment involves a multiparametric approach and should include: • Evaluation of serum and urine MM paraprotein with serum and urine protein electrophoresis and immunofixation in addition to sFLC assay • Evaluation of bone marrow plasma cells • Imaging for known soft tissue plasmacytoma and oligo-/nonsecretory MM	Evidence-based (strong)
MRD evaluation should not yet be used in clinical practice to guide treatment outside of the research setting, but could be used for its prognostic value.	Consensus (Strong)

Abbreviations: MM = multiple myeloma; IMWG = International Myeloma Working Group; MRD = minimal residual disease; sFLC = serum free light chain.

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Conclusion

Advances in the treatment and management of MM have led the CGC to develop this set of best-practice recommendations specific to the first line treatment of TEMM. More effective induction therapy options incorporating an anti-CD38 monoclonal antibody prior to ASCT holds promise for enhancing both QoL and survival outcomes across a broad spectrum of individuals with newly diagnosed TEMM. These recommendations are intended to serve as a valuable resource for clinicians, offering guidance on optimal treatment strategies to improve patient outcomes and enhance the quality of care provided to TEMM patients. Treating physicians should seek assistance from MM specialists whenever concerns about patient safety or questions about clinical care arise.

Reviewers

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CRediT authorship contribution statement

Sahar Khan: Writing – review & editing, Writing – original draft. **Debra J. Bergstrom:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Julie Côté:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Rami Kotb:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Richard LeBlanc:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Martha L. Louzada:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Hira S. Mian:** Writing – review & editing, Writing – original draft. **Ibraheem Othman:** Writing – review & editing, Writing – original draft. **Gabriele Colasurdo:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Alissa Visram:** Writing – review & editing, Writing – original draft.

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Appendix

Appendix 1. Types of Recommendation.[197]

Reused with permission from *American Society of Clinical Oncology*

Type of Recommendation	Definitions
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement.
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Appendix 2. Strength of Recommendation.[197]

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Strength of Recommendation	Definitions
Strong	High confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of authors' agreement.
Moderate	Moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of authors' agreement.
Weak	Some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (eg, benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of authors' agreement.

References

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med*. 1996;335(2):91–97. doi:10.1056/NEJM199607113350204.
2. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348(19):1875–1883. doi:10.1056/NEJMoa022340.
3. Blade J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106:3755–3759.
4. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321 [published correction appears. *J Clin Oncol*. 2006;24(17):2687 Moore, Dennis F Jr [added]]. *J Clin Oncol*. 2006;24(6):929-936. doi:10.1200/JCO.2005.04.5807.
5. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. [published correction appears in Lancet Haematol. 2020 Jun;7(6):e443] [published correction appears in Lancet Haematol. 2020 Nov;7(11):e785]. *Lancet Haematol*. 2020;7(6):e456–e468. doi:10.1016/S2352-3026(20)30099-5.
6. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood*. 2012;120(8):1589–1596. doi:10.1182/blood-2012-02-408922.
7. Gay F, Musto P, Rota-Scalabrini D, 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):1705–1720. doi:10.1016/S1470-2045(21)00535-0.
8. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med*. 2017;376(14):1311–1320. doi:10.1056/NEJMoa1611750.
9. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. *N Engl J Med*. 2022;387(2):132–147. doi:10.1056/NEJMoa2204925.
10. Dhakal B, Szabo A, Chhabra S, et al. Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: a Systematic Review and Meta-analysis. *JAMA Oncol*. 2018;4(3):343–350. doi:10.1001/jamaoncol.2017.4600.
11. Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood*. 2018;132(23):2456–2464. doi:10.1182/blood-2018-06-858613.
12. Mina R, Musto P, Rota-Scalabrini D, 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 [published correction appears in Lancet Oncol. 2023;24(2):e72]. *Lancet Oncol*.. 2023;24(1):64–76. doi:10.1016/S1470-2045(22)00693-3.
13. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120(5):1067–1076. doi:10.1182/blood-2012-01-405985.
14. Dunavin NC, Wei L, Elder P, et al. Early versus delayed autologous stem cell transplant in patients receiving novel therapies for multiple myeloma. *Leuk Lymphoma*. 2013;54(8):1658–1664. doi:10.3109/10428194.2012.751528.
15. Kumar SK, Lacy MQ, Dispenzieri A, et al. Early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. *Cancer*. 2012;118(6):1585–1592. doi:10.1002/cncr.26422.
16. Remenyi P, Varga G, Mikala G, et al. Early Versus Delayed Autologous Stem Cell Transplantation and Interferon Maintenance in Multiple Myeloma: single-Center Experience of 18 Years. *Transplant Proc*. 2016;48(1):177–184. doi:10.1016/j.transproceed.2015.12.031.
17. Munshi PN, Vesole D, Jurczyszyn A, et al. Age no bar: a CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma. [published correction appears in Cancer. 2021;127(20):3904]. *Cancer*. 2020;126(23):5077–5087. doi:10.1002/cncr.33171.
18. Swan D, Hayden PJ, Eikema DJ, et al. Trends in autologous stem cell transplantation for newly diagnosed multiple myeloma: changing demographics and outcomes in European Society for Blood and Marrow Transplantation centres from 1995 to 2019. *Br J Haematol*. 2022;197(1):82–96. doi:10.1111/bjh.18025.
19. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet*. 2007;370(9594):1209–1218. doi:10.1016/S0140-6736(07)61537-2.

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20. Pawlyn C, Cairns D, Menzies T, et al. Autologous stem cell transplantation is safe and effective for fit older myeloma patients: exploratory results from the Myeloma XI trial. *Haematologica*. 2022;107(1):231–242. doi:10.3324/haematol.2020.262360.
21. Muchtar E, Dingli D, Kumar S, et al. Autologous stem cell transplant for multiple myeloma patients 70 years or older. *Bone Marrow Transplant*. 2016;51(11):1449–1455. doi:10.1038/bmt.2016.174.
22. Merz M, Neben K, Raab MS, et al. Autologous stem cell transplantation for elderly patients with newly diagnosed multiple myeloma in the era of novel agents. *Ann Oncol*. 2014;25(1):189–195. doi:10.1093/annonc/mdt509.
23. Marini C, Maia T, Bergantim R, et al. Real-life data on safety and efficacy of autologous stem cell transplantation in elderly patients with multiple myeloma. *Ann Hematol*. 2019;98(2):369–379. doi:10.1007/s00277-018-3528-x.
24. Mian H, Mian OS, Rochwerg B, Foley R, Wildes TM. Autologous stem cell transplant in older patients (age ≥ 65) with newly diagnosed multiple myeloma: a systematic review and meta-analysis. *J Geriatr Oncol*. 2020;11(1):93–99. doi:10.1016/j.jgo.2019.05.014.
25. Dimopoulos MA, Richardson PG, Schlag R, et al. VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *J Clin Oncol*. 2009;27(36):6086–6093. doi:10.1200/JCO.2009.22.2232.
26. Ludwig H, Adam Z, Hajek R, et al. Light chain-induced acute renal failure can be reversed by bortezomib-doxorubicin-dexamethasone in multiple myeloma: results of a phase II study. *J Clin Oncol*. 2010;28(30):4635–4641. doi:10.1200/JCO.2010.28.1238.
27. Morabito F, Gentile M, Ciolli S, et al. Safety and efficacy of bortezomib-based regimens for multiple myeloma patients with renal impairment: a retrospective study of Italian Myeloma Network GIMEMA. *Eur J Haematol*. 2010;84(3):223–228. doi:10.1111/j.1600-0609.2009.01385.x.
28. Augeul-Meunier K, Chretien ML, Stoppa AM, et al. Extending autologous transplantation as first line therapy in multiple myeloma patients with severe renal impairment: a retrospective study by the SFGM-TC. *Bone Marrow Transplant*. 2018;53(6):749–755. doi:10.1038/s41409-018-0122-8.
29. Parikh GC, Amjad AI, Saliba RM, et al. Autologous hematopoietic stem cell transplantation may reverse renal failure in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2009;15(7):812–816. doi:10.1016/j.bbmt.2009.03.021.
30. Balsam L, Saad C, Arsene C, Fogel J. Impact of Autologous Stem Cell Transplantation on Blood Pressure and Renal Function in Multiple Myeloma Patients. *J Natl Med Assoc*. 2017;109(3):182–191. doi:10.1016/j.jnma.2017.02.010.
31. Carlson K. Melphalan 200 mg/m2 with blood stem cell support as first-line myeloma therapy: impact of glomerular filtration rate on engraftment, transplantation-related toxicity and survival. *Bone Marrow Transplant*. 2005;35(10):985–990. doi:10.1038/sj.bmt.1704948.
32. Mahindra A, Hari P, Fraser R, et al. Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a center for international blood and marrow transplant research analysis. *Bone Marrow Transplant*. 2017;52(12):1616–1622. doi:10.1038/bmt.2017.198.
33. San Miguel JF, Lahuerta JJ, García-Sanz R, et al. Are myeloma patients with renal failure candidates for autologous stem cell transplantation? *Hematol J*. 2000;1(1):28–36. doi:10.1038/sj.thj.6200003.
34. Sorror ML, Logan BR, Zhu X, et al. Prospective Validation of the Predictive Power of the Hematopoietic Cell Transplantation Comorbidity Index: a Center for International Blood and Marrow Transplant Research Study. *Biol Blood Marrow Transplant*. 2015;21(8):1479–1487. doi:10.1016/j.bbmt.2015.04.004.
35. Berro M, Arbelbide JA, Rivas MM, et al. Hematopoietic Cell Transplantation-Specific Comorbidity Index Predicts Morbidity and Mortality in Autologous Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2017;23(10):1646–1650. doi:10.1016/j.bbmt.2017.06.014.
36. Saad A, Mahindra A, Zhang MJ, et al. Hematopoietic cell transplant comorbidity index is predictive of survival after autologous hematopoietic cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2014;20(3):402–408.e1. doi:10.1016/j.bbmt.2013.12.557.
37. Labonté L, Iqbal T, Zaidi MA, et al. Utility of comorbidity assessment in predicting transplantation-related toxicity following autologous hematopoietic stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2008;14(9):1039–1044. doi:10.1016/j.bbmt.2008.06.019.
38. Côté J, Kotb R, Bergstrom DJ, et al. First Line Treatment of Newly Diagnosed Transplant Ineligible Multiple Myeloma: recommendations from the Canadian Myeloma Research Group Consensus Guideline Consortium. *Clin Lymphoma Myeloma Leuk*. 2023;23(5):340–354. doi:10.1016/j.clml.2023.01.016.
39. Engelhardt M, Domm AS, Dold SM, et al. A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. *Haematologica*. 2017;102(5):910–921. doi:10.3324/haematol.2016.162693.
40. Facon T, Cook G, Usmani SZ, et al. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. *Leukemia*. 2022;36(4):1066–1077. doi:10.1038/s41375-021-01488-8.
41. Rosiñol L, García-Sanz R, Lahuerta JJ, et al. Benefit from autologous stem cell transplantation in primary refractory myeloma? Different outcomes in progressive versus stable disease. *Haematologica*. 2012;97(4):616–621. doi:10.3324/haematol.2011.051441.
42. Gertz MA, Kumar S, Lacy MQ, et al. Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction. *Blood*. 2010;115(12):2348–2560. doi:10.1182/blood-2009-07-235531.
43. Shah N, Bashir Q, Parmar S, et al. Increased bone marrow plasma cell infiltration pre-transplant is associated with worse outcomes in patients undergoing high dose chemotherapy and autologous stem cell transplantation for multiple myeloma. *Blood*. 2011;118:4135. doi:10.1182/blood.V118.21.4135.413.
44. Farhan S, Lin H, Baladandayuthapani V, et al. Response before autologous hematopoietic stem cell transplantation is an important predictor of outcome in multiple myeloma. *Blood*. 2011;118:4119. doi:10.1182/blood.V118.21.4119.4119.
45. Jackson GH, Davies FE, Pawlyn C, et al. Response-adapted intensification with cyclophosphamide, bortezomib, and dexamethasone versus no intensification in patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2019;6(12):e616–e629. doi:10.1016/S2352-3026(19)30167-X.
46. Mateos MV, Martínez BP, González-Calle V. High-risk multiple myeloma: how to treat at diagnosis and relapse? *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):30–36. doi:10.1182/hematology.2021000229.
47. Kaiser M. Depth of response and MRD status in ultra high-risk myeloma and plasma cell leukemia treated with Dara-CVRd and augmented autologous transplant: results of the risk-stratified UK OPTIMUM/MUKnine trial. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324589/martin.kaiser.depth.of.response.and.mrd.status.in.ultra.high-risk.myeloma.and.html. Accessed October 30, 2023.
48. Brown S, Sherratt D, Hinsley S, 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. doi:10.1136/bmjopen-2020-046225.
49. Leypoldt LB, Tichy D, Besemer B, et al. Isatuximab, carfilzomib, lenalidomide, and dexamethasone for the treatment of high-risk newly diagnosed multiple myeloma. *J Clin Oncol*. 2024;42(1):26–37. doi:10.1200/JCO.23.01696.
50. Usmani SZ, Hoering A, Ailawadhi S, 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. doi:10.1016/S2352-3026(20)30354-9.
51. van de Donk NWCJ, Minnema MC, van der Holt B, et al. Treatment of primary plasma cell leukaemia with carfilzomib and lenalidomide-based therapy (EMN12/HOVON-129): final analysis of a non-randomised, multicentre, phase 2 study. *Lancet Oncol*. 2023;24(10):1119–1133. doi:10.1016/S1470-2045(23)00405-9.
52. Moreau P, Attal M, Hulin C, 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 [published correction appears. *Lancet*. 2019;394(10192):29–38. doi:10.1016/S0140-6736(19)31240-1.
53. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301–313. doi:10.1056/NEJMoa2312054.
54. Perrot A, Lauwers-Cances V, Tournay E, et al. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. *J Clin Oncol*. 2019;37(19):1657–1665. doi:10.1200/JCO.18.00776.
55. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863–2869. doi:10.1200/JCO.2015.61.2267.
56. Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia*. 2019;33(1):159–170. doi:10.1038/s41375-018-0196-8.
57. Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood*. 2006;108(5):1724–1732. doi:10.1182/blood-2006-03-009910.
58. Walker BA, Leone PE, Chiecchio L, et al. A compendium of myeloma-associated chromosomal copy number abnormalities and their prognostic value. *Blood*. 2010;116(15):e56–e65. doi:10.1182/blood-2010-04-279596.
59. Schmidt TM, Barwick BG, Joseph N, et al. Gain of Chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. *Blood Cancer J*. 2019;9(12):94. doi:10.1038/s41408-019-0254-0.
60. Duggan P, Reece DE, Song K, et al. Is tandem ASCT needed in MM patients with high risk cytogenetics in the era of maintenance therapy? Results from the Canadian Myeloma Research Group (CMRG) database. *Blood*. 2020;136(Supplement 1):18–19. doi:10.1182/blood-2020-139689.
61. Gonsalves WI, Rajkumar SV, Go RS, et al. Trends in survival of patients with primary plasma cell leukemia: a population-based analysis. *Blood*. 2014;124(6):907–912. doi:10.1182/blood-2014-03-565051.

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62. García-Sanz R, Orfão A, González M, et al. Primary plasma cell leukemia: clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics. *Blood*. 1999;93(3):1032–1037. doi:10.1182/blood.V93.3.1032.
63. Fernández de Larrea C, Kyle RA, Durie BG, et al. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. *Leukemia*. 2013;27(4):780–791. doi:10.1038/leu.2012.336.
64. Bertamini L, Grasso M, D'Agostino M, et al. Poor prognosis of multiple myeloma predicted by high levels of circulating plasma cells is independent from other high-risk features but is modulated by the achievement of minimal residual disease negativity. *Blood*. 2020;136(suppl 1):12–13. doi:10.1182/blood-2020-137075.
65. Granell M, Calvo X, Garcia-Guiñón A, et al. Prognostic impact of circulating plasma cells in patients with multiple myeloma: implications for plasma cell leukemia definition. *Haematologica*. 2017;102(6):1099–1104. doi:10.3324/haematol.2016.158303.
66. Ravi P, Kumar SK, Cerhan JR, et al. Defining cure in multiple myeloma: a comparative study of outcomes of young individuals with myeloma and curable hematologic malignancies. *Blood Cancer J*. 2018;8(3):26. doi:10.1038/s41408-018-0065-8.
67. Usmani SZ, Heuck C, Mitchell A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. *Haematologica*. 2012;97(11):1761–1767. doi:10.3324/haematol.2012.065698.
68. Lawless S, Iacobelli S, Knelange NS, et al. Comparison of autologous and allogeneic hematopoietic cell transplantation strategies in patients with primary plasma cell leukemia, with dynamic prediction modeling. *Haematologica*. 2023;108(4):1105–1114. doi:10.3324/haematol.2021.280568.
69. Dhakal B, Patel S, Girnius S, et al. Hematopoietic cell transplantation utilization and outcomes for primary plasma cell leukemia in the current era. *Leukemia*. 2021;35(6):1828 [published correction appears in Leukemia. 2021 Jul;35(7):2141]. Leukemia. 2020;34(12):3338–3347. doi:10.1038/s41375-020-0830-0.
70. Musto P, Simeon V, Martorelli MC, et al. Lenalidomide and low-dose dexamethasone for newly diagnosed primary plasma cell leukemia. *Leukemia*. 2014;28(1):222–225. doi:10.1038/leu.2013.241.
71. Royer B, Minvielle S, Diouf M, et al. Bortezomib, doxorubicin, cyclophosphamide, dexamethasone induction followed by stem cell transplantation for primary plasma cell leukemia: a prospective phase II study of the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2016;34(18):2125–2132. doi:10.1200/JCO.2015.63.1929.
72. Moreau P, Avet-Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood*. 2011;118(22):5752–5982. doi:10.1182/blood-2011-05-355081.
73. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood*. 2012;120(1):9–19. doi:10.1182/blood-2012-02-408898.
74. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016;127(21):2569–2574. doi:10.1182/blood-2016-01-693580.
75. Gay FM, Scalabrini DR, Belotti A, et al. Carfilzomib-lenalidomide-dexamethasone (KRd) vs carfilzomib-cyclophosphamide-dexamethasone (KCd) induction: planned interim analysis of the randomized FORTE trial in newly diagnosed multiple myeloma (NDMM). *J Clin Oncol*. 2020;35(15_suppl):8003. doi:10.1200/JCO.2017.35.15_suppl.8003.
76. Dachs LR, Hebraud B, Oriol A, et al. Integrated analysis of randomized controlled trials evaluating bortezomib + lenalidomide + dexamethasone or bortezomib + thalidomide + dexamethasone induction in transplant-eligible newly diagnosed multiple myeloma. *Blood*. 2018;132(suppl_1):3245. doi:10.1182/blood-2018-99-112659.
77. Voorhees PM, Sborov DW, Laubach J, et al. Addition of daratumumab to lenalidomide, bortezomib, and dexamethasone for transplantation-eligible patients with newly diagnosed multiple myeloma (GRIFFIN): final analysis of an open-label, randomised, phase 2 trial. *Lancet Haematol*. 2023;10(10):e825–e837. doi:10.1016/S2352-3026(23)00217-X.
78. Gay F, Roeloffzen W, Dimopoulos MA, et al. Results of the phase III randomized IsKia Trial: isatuximab-carfilzomib-lenalidomide-dexamethasone vs carfilzomib-lenalidomide-dexamethasone as pre-transplant induction and post-transplant consolidation in newly diagnosed multiple myeloma patients. *Blood*. 2023;142(Supplement 1):4. doi:10.1182/blood-2023-177546.
79. Kotb R, Gul E, Reece DE. A phase 2 multi-center, open label study of Isatuximab added to standard Cybord induction and lenalidomide maintenance treatments in newly diagnosed, transplant eligible multiple myeloma. *Blood*. 2021;138(suppl_1):4767. doi:10.1182/blood-2021-153632.
80. Kotb R, White D, Bhella S, et al. Efficacy and tolerance of isatuximab, cyclophosphamide, bortezomib, and dexamethasone (Isa-CBD) induction chemotherapy in newly diagnosed, transplant eligible multiple myeloma: report of the phase 2 Multi-Centre, Open Label Canadian Myeloma Research Group (CMRG)-008 Prospective Clinical Trial. *Blood*. 2023;142(suppl_1):4751. doi:10.1182/blood-2023-190168.
81. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med*. 1984;310(21):1353–1356. doi:10.1056/NEJM198405243102104.
82. Chakraborty R, Muchtar E, Kumar SK, et al. Impact of duration of induction therapy on survival in newly diagnosed multiple myeloma patients undergoing upfront autologous stem cell transplantation. *Br J Haematol*. 2018;182(1):71–77. doi:10.1111/bjh.15244.
83. Vij R, Kumar S, Zhang MJ, et al. Impact of pretransplant therapy and depth of disease response before autologous transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21(2):335–341. doi:10.1016/j.bbmt.2014.10.023.
84. Côté J, LeBlanc R, Mian H, et al. Real-world results of autologous stem cell transplantation in newly diagnosed multiple myeloma: a report from the Canadian Myeloma Research Group database. *Blood Cancer J*. 2023;13(1):137. doi:10.1038/s41408-023-00905-8.
85. Cottler-Fox MH, Lapidot T, Petit I, et al. Stem cell mobilization. *Hematology Am Soc Hematol Educ Program*. 2003:419–437. doi:10.1182/asheducation-2003.1.419.
86. Bensinger W, Appelbaum F, Rowley S, et al. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. *J Clin Oncol*. 1995;13(10):2547–2555. doi:10.1200/JCO.1995.13.10.2547.
87. Giralt S, Stadtmauer EA, Harousseau JL, et al. International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100). *Leukemia*. 2009;23(10):1904–1912. doi:10.1038/leu.2009.127.
88. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transplant*. 2014;20(3):295–308. doi:10.1016/j.bbmt.2013.10.013.
89. Kumar S, Giralt S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. *Blood*. 2009;114(9):1729–1735. doi:10.1182/blood-2009-04-205013.
90. Wang L, Xiang H, Yan Y, et al. Comparison of the efficiency, safety, and survival outcomes in two stem cell mobilization regimens with cyclophosphamide plus G-CSF or G-CSF alone in multiple myeloma: a meta-analysis. *Ann Hematol*. 2021;100(2):563–573. doi:10.1007/s00277-020-04376-w.
91. Zannetti BA, Saraceni F, Cellini C, et al. Low-dose cyclophosphamide versus intermediate-high-dose cyclophosphamide versus granulocyte colony-stimulating factor alone for stem cell mobilization in multiple myeloma in the era of novel agents: a multicenter Retrospective Study. *Transplant Cell Ther*. 2021;27(3):244.e1–244.e8. doi:10.1016/j.jtct.2020.12.009.
92. DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood*. 2009;113(23):5720–5726. doi:10.1182/blood-2008-08-174946.
93. Crees ZD, Rettig MP, Jayasinghe RG, et al. Motixafortide and G-CSF to mobilize hematopoietic stem cells for autologous transplantation in multiple myeloma: a randomized phase 3 trial. *Nat Med*. 2023;29(4):869–879. doi:10.1038/s41591-023-02273-z.
94. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. *Leukemia*. 2007;21(9):2035–2042. doi:10.1038/sj.leu.2404801.
95. Bhutani D, Zonder J, Valent J, et al. Evaluating the effects of lenalidomide induction therapy on peripheral stem cells collection in patients undergoing autologous stem cell transplant for multiple myeloma. *Support Care Cancer*. 2013;21(9):2437–2442. doi:10.1007/s00520-013-1808-5.
96. Shah EE, Young RP, Wong SW, et al. Impact of plerixafor use at different peripheral blood cd34+ thresholds on autologous stem cell collection in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2020;26(5):876–883. doi:10.1016/j.bbmt.2019.11.024.
97. Cavallo F, Bringhen S, Milone G, et al. Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy. *Leukemia*. 2011;25(10):1627–1631. doi:10.1038/leu.2011.131.
98. Popat U, Saliba R, Thandi R, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2009;15(6):718–723. doi:10.1016/j.bbmt.2009.02.011.
99. Costa LJ, Abbas J, Hogan KR, et al. Growth factor plus preemptive ('just-in-time') plerixafor successfully mobilizes hematopoietic stem cells in multiple myeloma patients despite prior lenalidomide exposure. *Bone Marrow Transplant*. 2012;47(11):1403–1408. doi:10.1038/bmt.2012.60.
100. Rybinski B, Rapoport AP, Badros AZ, Hardy N, Kocoglu M. Prolonged lenalidomide induction does not significantly impair stem cell collection in multiple myeloma patients mobilized with cyclophosphamide or plerixafor: a report from the covid era. *Clin Lymphoma Myeloma Leuk*. 2022;22(8):e716–e729. doi:10.1016/j.clml.2022.03.013.
101. Hulin C, Offner F, Moreau P, et al. Stem cell yield and transplantation in transplant-eligible newly diagnosed multiple myeloma patients receiving daratumumab + bortezomib/thalidomide/dexamethasone in the phase 3 CASSIOPEIA study. *Haematologica*. 2021;106(8):2257–2260. doi:10.3324/haematol.2020.261842.

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102. Chhabra S, Callander N, Watts NL, et al. Stem cell mobilization yields with daratumumab- and lenalidomide-containing quadruplet induction therapy in newly diagnosed multiple myeloma: findings from the MASTER and GRIFFIN Trials. *Transplant Cell Ther*. 2023;29(3):174.e1–174.e10. doi:10.1016/j.jtct.2022.11.029.
103. Morris CL, Siegel E, Barlogie B, et al. Mobilization of CD34+ cells in elderly patients (>/= 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. *Br J Haematol*. 2003;120(3):413–423. doi:10.1046/j.1365-2141.2003.04107.x.
104. Boccadoro M, Palumbo A, Bringhen S, et al. Oral melphalan at diagnosis hampers adequate collection of peripheral blood progenitor cells in multiple myeloma. *Haematologica*. 2002;87(8):846–850.
105. Dhakal B, Shah N, Kansagra A, et al. ASTCT clinical practice recommendations for transplantation and cellular therapies in multiple myeloma. *Transplant Cell Ther*. 2022;28(6):284–293. doi:10.1016/j.jtct.2022.03.019.
106. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol*. 2005;23(36):9227–9233. doi:10.1200/JCO.2005.03.0551.
107. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*. 2002;99(3):731–735. doi:10.1182/blood.v99.3.731.
108. Goldschmidt H, Hegenbart U, Wallmeier M, et al. Peripheral blood progenitor cell transplantation in multiple myeloma following high-dose melphalan-based therapy. *Recent Results Cancer Res*. 1998;144:27–35. doi:10.1007/978-3-642-46836-0_4.
109. Brioli A, Felix Vom H, Mügge L-O, et al. Full dose or reduced dose melphalan (MEL) for autologous stem cell transplantation (ASCT) in multiple myeloma (MM): a single center analysis on 187 consecutive patients. *Blood*. 2018;132:4625. doi:10.1182/blood-2018-99-112045.
110. Palumbo A, Bringhen S, Bruno B, et al. Melphalan 200 mg/m^2 versus melphalan 100 mg/m^2 in newly diagnosed myeloma patients: a prospective, multicenter phase 3 study. *Blood*. 2010;115:1873–1879. doi:10.1182/blood-2009-09-241737.
111. Gao F, Lin MS, You JS, et al. Long-term outcomes of busulfan plus melphalan-based versus melphalan 200 mg/m2 conditioning regimens for autologous hematopoietic stem cell transplantation in patients with multiple myeloma: a systematic review and meta-analysis. *Cancer Cell Int*. 2021;21(1):601. doi:10.1186/s12935-021-02313-z.
112. Rodriguez TE, Hari P, Stiff PJ, Smith SE, Sterrenberg D, Vesole DH. Busulfan, melphalan, and bortezomib versus high-dose melphalan as a conditioning regimen for autologous hematopoietic stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22(8):1391–1396. doi:10.1016/j.bbmt.2016.03.021.
113. Roussel M, Lauwers-Cances V, Macro M, et al. Bortezomib and high-dose melphalan conditioning regimen in frontline multiple myeloma: an IFM randomized phase 3 study. [published correction appears in Blood. 2023 Mar 9;141(10):1234]. *Blood*. 2022;139(18):2747–2757. doi:10.1182/blood.2021014635.
114. Farag S, Bacher U, Jeker B, et al. Adding bendamustine to melphalan before ASCT improves CR rate in myeloma vs. melphalan alone: a randomized phase-2 trial. *Bone Marrow Transplant*. 2022;57(6):990–997. doi:10.1038/s41409-022-01681-y.
115. Ladetto M, Pagliano G, Ferrero S, et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol*. 2010;28(12):2077–2084. doi:10.1200/JCO.2009.23.7172.
116. Zamagni E, Barbato S, Cavo M. How I treat high-risk multiple myeloma. *Blood*. 2022;139(19):2889–2903. doi:10.1182/blood.2020008733.
117. Nadeem O, Ghobrial IM. Intensification and consolidation therapy in multiple myeloma in the current era. *Lancet Haematol*. 2020;7(6):e427–e429. doi:10.1016/S2352-3026(20)30110-1.
118. Sonneveld P, Dimopoulos MA, Beksac M, et al. Consolidation and maintenance in newly diagnosed multiple myeloma. *J Clin Oncol*. 2021;39(32):3613–3622. doi:10.1200/JCO.21.01045.
119. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 Trial. *J Clin Oncol*. 2019;37(7):589–597. doi:10.1200/JCO.18.00685.
120. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. [published correction appears in Hemasphere. 2021 Mar 31;5(4):e567] [published correction appears in Hemasphere. 2021 Nov 29;5(12):e659]. *Hemasphere*. 2021;5(2):e528. doi:10.1097/HS9.0000000000000528.
121. Perrot A. How I treat frontline transplantation-eligible multiple myeloma. *Blood*. 2022;139(19):2882–2888. doi:10.1182/blood.2020008735.
122. Hari P, Pasquini M, Stadtmauer E, et al. Long-term follow-up of BMT CTN 0702 (STa- MINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM) [abstract]. *J Clin Oncol*. 2020;38(suppl 15):8506. doi:10.1200/JCO.2020.38.15_suppl.8506.
123. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The chemotherapy of plasma-cell myeloma and the incidence of acute leukemia. *N Engl J Med*. 1979;301(14):743–748. doi:10.1056/NEJM197910043011402.
124. Belch A, Shelley W, Bergsagel D, et al. A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. *Br J Cancer*. 1988;57(1):94–99. doi:10.1038/bjc.1988.17.
125. Shustik C, Belch A, Robinson S, et al. A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. *Br J Haematol*. 2007;136(2):203–211. doi:10.1111/j.1365-2141.2006.06405.x.
126. Browman GP, Bergsagel D, Sicheri D, et al. Randomized trial of interferon maintenance in multiple myeloma: a study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1995;13(9):2354–2360. doi:10.1200/JCO.1995.13.9.2354.
127. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. *Blood*. 2013;121(9):1517–1523. doi:10.1182/blood-2012-09-451872.
128. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. [published correction appears in Lancet Oncol. 2010 Jan;11(1):14]. *Lancet Oncol*. 2010;11(1):29–37. doi:10.1016/S1470-2045(09)70284-0.
129. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med*. 2014;371(10):906–917. doi:10.1056/NEJMoa1402551.
130. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357(21):2133–2142. doi:10.1056/NEJMoa070596.
131. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. [published correction appears in N Engl J Med. 2009 Jul 30;361(5):544]. *N Engl J Med*. 2007;357(21):2123–2132. doi:10.1056/NEJMoa070594.
132. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: a Meta-Analysis. *J Clin Oncol*. 2017;35(29):3279–3289. doi:10.1200/JCO.2017.72.6679.
133. Gay F, Jackson G, Rosiñol L, et al. Maintenance Treatment and Survival in Patients With Myeloma: a Systematic Review and Network Meta-analysis. *JAMA Oncol*. 2018;4(10):1389–1397. doi:10.1001/jamaoncol.2018.2961.
134. Sonneveld P, Schmidt-Wolf IG, van der Holt B, 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. [published correction appears in J Clin Oncol. 2012 Oct 10;30(29):3654]. *J Clin Oncol*. 2012;30(24):2946–2955. doi:10.1200/JCO.2011.39.6820.
135. Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. *Leukemia*. 2018;32(2):383–390. doi:10.1038/leu.2017.211.
136. Neben K, Lokhorst HM, Jauch A, 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):940–948. doi:10.1182/blood-2011-09-379164.
137. Dimopoulos MA, Gay F, Schjesvold F, 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):253–264. doi:10.1016/S0140-6736(18)33003-4.
138. Slade M, Martin TG, Nathwani N, 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):2917–2921. doi:10.1038/s41375-022-01691-1.
139. Dytfeld D, Wróbel T, Jamroziak K, 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):139–150. doi:10.1016/S1470-2045(22)00738-0.
140. Moreau P, Hulin C, Perrot A, 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):1378–1390. doi:10.1016/S1470-2045(21)00428-9.
141. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. *Leukemia*. 2014;28(3):690–693. doi:10.1038/leu.2013.335.
142. Pasvolsky O, Milton DR, Rauf M, 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. doi:10.1016/j.jtct.2022.07.028.

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143. Panopoulou A, Cairns DA, Holroyd A, 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):1666–1674. doi:10.1182/blood.2022018339.
144. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. *Leukemia*. 2014;28(3):690–693. doi:10.1038/leu.2013.335.
145. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1770–1781. doi:10.1056/NEJMoa1114083.
146. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895–905. doi:10.1056/NEJMoa1402888.
147. Pawlyn C, Menzies T, Davies FE, 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):1371–1372. doi:10.1182/blood-2022-165376.
148. Rosiñol L, Oriol A, Ríos R, et al. Lenalidomide and dexamethasone maintenance with or without ixazomib, tailored by residual disease status in myeloma. *Blood*. 2023;142(18):1518–1528. doi:10.1182/blood.2022019531.
149. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366(19):1782–1791. doi:10.1056/NEJMoa1114138.
150. Jackson GH, Davies FE, Pawlyn 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. doi:10.1016/S1470-2045(18)30687-9.
151. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide before and after autologous stem cell transplantation for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial. *Haematologica*. 2021;106(7):1957–1967. doi:10.3324/haematol.2020.247130.
152. Rath C, Yoo C, Cheplowitz H, et al. Predictors of lenalidomide maintenance duration after autologous stem cell transplant in patients with multiple myeloma. *J Oncol Pharm Pract*. 2023;29(7):1715–1724. doi:10.1177/10781552221150935.
153. LeBlanc R, Bergstrom DJ, Côté J, Kotb R, Louzada ML, Sutherland HJ. Management of myeloma manifestations and complications: the Cornerstone of Supportive Care: recommendation of the Canadian Myeloma Research Group (formerly Myeloma Canada Research Network) Consensus Guideline Consortium. *Clin Lymphoma Myeloma Leuk*. 2022;22(1):e41–e56. doi:10.1016/j.clml.2021.07.028.
154. Teh BW, Reynolds G, Slavin MA, et al. Executive summary of consensus clinical practice guidelines for the prevention of infection in patients with multiple myeloma. *Intern Med J*. 2023;53(8):1469–1477. doi:10.1111/imj.16100.
155. Raje NS, Anaissie E, Kumar SK, et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. *Lancet Haematol*. 2022;9(2):e143–e161. doi:10.1016/S2352-3026(21)00283-0.
156. Girmenia C, Cavo M, Offidani M, et al. Management of infectious complications in multiple myeloma patients: expert panel consensus-based recommendations. *Blood Rev*. 2019;34:84–94. doi:10.1016/j.blre.2019.01.001.
157. Christopeit M, Schmidt-Hieber M, Sprute R, et al. Prophylaxis, diagnosis and therapy of infections in patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation. 2020 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2021;100(2):321–336. doi:10.1007/s00277-020-04297-8.
158. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002–Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*. 2005;23(36):9219–9226. doi:10.1200/JCO.2005.03.2086.
159. Drayson MT, Bowcock S, Planche T, et al. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet Oncol*. 2019;20(12):1760–1772. doi:10.1016/S1470-2045(19)30506-6.
160. Maakaron JE, Liscynesky C, Boghdadly ZE, et al. Fluoroquinolone Prophylaxis in Autologous Stem Cell Transplantation: worthy of a Second Look. *Biol Blood Marrow Transplant*. 2020;26(8):e198–e201. doi:10.1016/j.bbmt.2020.03.027.
161. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002–Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*. 2005;23(36):9219–9226. doi:10.1200/JCO.2005.03.2086.
162. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med*. 1992;326(13):845–851. doi:10.1056/NEJM199203263261301.
163. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004;39(10):1407–1416. doi:10.1086/422312.
164. Teh BW, Harrison SJ, Worth LJ, Slavin MA. Antiviral prophylaxis for varicella zoster virus infections in patients with myeloma in the era of novel therapies. *Leuk Lymphoma*. 2016;57(7):1719–1722. doi:10.3109/10428194.2015.1106538.
165. Ljungman P, Cordonnier C, Einsele H, et al. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2009;44(8):521–526. doi:10.1038/bmt.2009.263.
166. Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. *Blood*. 2016;127(23):2824–2832. doi:10.1182/blood-2015-12-550475.
167. Hill JA, Martens MJ, Young JH, et al. SARS-CoV-2 vaccination in the first year after allogeneic hematopoietic cell transplant: a prospective, multicentre, observational study. *EClinicalMedicine*. 2023;59:101983. doi:10.1016/j.eclinm.2023.101983.
168. Bhatia S, Dai C, Landier W, et al. Trends in late mortality and life expectancy after autologous blood or marrow transplantation over three decades: a BMTSS Report. *J Clin Oncol*. 2022;40(18):1991–2003. doi:10.1200/JCO.21.02372.
169. Usmani SZ, Sawyer J, Rosenthal A, et al. Risk factors for MDS and acute leukemia following total therapy 2 and 3 for multiple myeloma. *Blood*. 2013;121(23):4753–4757. doi:10.1182/blood-2012-11-466961.
170. Mailankody S, Pfeiffer RM, Kristinsson SY, et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). *Blood*. 2011;118(15):4086–4092. doi:10.1182/blood-2011-05-355743.
171. Youlden DR, Baade PD. The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. *BMC Cancer*. 2011;11:83. doi:10.1186/1471-2407-11-83.
172. Mahindra A, Raval G, Mehta P, et al. New cancers after autotransplantations for multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21(4):738–745. doi:10.1016/j.bbmt.2014.12.028.
173. Radivoyevitch T, Dean RM, Shaw BE, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome after autotransplants for lymphomas and plasma cell myeloma. *Leuk Res*. 2018;74:130–136. doi:10.1016/j.leukres.2018.07.016.
174. Landgren O, Mailankody S. Update on second primary malignancies in multiple myeloma: a focused review. *Leukemia*. 2014;28(7):1423–1426. doi:10.1038/leu.2014.22.
175. Yang J, Terebelo HR, Zonder JA. Secondary primary malignancies in multiple myeloma: an old NEMESIS revisited. *Adv Hematol*. 2012;2012:801495. doi:10.1155/2012/801495.
176. Straka C, Schaefer-Eckart K, Hertenstein B, et al. Long-term outcome of a prospective randomized trial comparing continuous lenalidomide/dexamethasone with lenalidomide/dexamethasone induction, MEL140 with autologous blood stem cell transplantation and single agent lenalidomide maintenance in patients of age 60-75 years with newly diagnosed multiple myeloma. *Blood*. 2022;140(suppl_1):287–288. doi:10.1182/blood-2022-159357.
177. Holstein SA, Suman VJ, McCarthy PL. Update on the role of lenalidomide in patients with multiple myeloma. *Ther Adv Hematol*. 2018;9(7):175–190. doi:10.1177/2040620718775629.
178. Holstein SA, Jung SH, Richardson PG, 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. [published correction appears in Lancet Haematol. 2018 Aug;5(8):e332] [published correction appears in Lancet Haematol. 2018 Dec;5(12):e608]. *Lancet Haematol*. 2017;4(9):e431–e442. doi:10.1016/S2352-3026(17)30140-0.
179. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol*. 2014;15(3):333–342. doi:10.1016/S1470-2045(13)70609-0.
180. Rosenberg AS, Brunson A, Tuscano J, et al. Effect of autologous hematopoietic stem cell transplant on the development of second primary malignancies in multiple myeloma patients. *Blood Cancer J*. 2021;11(1):5. doi:10.1038/s41408-020-00400-4.
181. Sahebi F, Iacobelli S, Sbianchi G, et al. Incidence of Second Primary Malignancies after Autologous Transplantation for Multiple Myeloma in the Era of Novel Agents. *Biol Blood Marrow Transplant*. 2018;24(5):930–936. doi:10.1016/j.bbmt.2018.01.006.
182. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol*. 2013;31(4):448–455. doi:10.1200/JCO.2012.41.6180.
183. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. [published correction appears in Lancet Oncol. 2017 Oct;18(10):e562]. *Lancet Oncol*. 2017;18(10):1327–1337. doi:10.1016/S1470-2045(17)30578-8.
184. Ragon BK, Shah MV, D'Souza A, et al. Impact of second primary malignancy post-autologous transplantation on outcomes of multiple myeloma: a CIBMTR analysis. *Blood Adv*. 2023;7(12):2746–2757. doi:10.1182/bloodadvances.2022009138.
185. Chawla SS, Kumar SK, Dispenzieri A, et al. Clinical course and prognosis of non-secretory multiple myeloma. *Eur J Haematol*. 2015;95(1):57–64. doi:10.1111/ejh.12478.
186. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328–e346. doi:10.1016/S1470-2045(16)30206-6.

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187. Kirchhoff DC, Murata K, Thoren KL. Use of a daratumumab-specific immunofixation assay to assess possible immunotherapy interference at a major cancer center: our experience and recommendations. *J Appl Lab Med*. 2021;6(6):1476–1483. doi:10.1093/jalm/jfab055.
188. Murray DL, Puig N, Kristinsson S, et al. Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report. *Blood Cancer J*. 2021;11(2):24. doi:10.1038/s41408-021-00408-4.
189. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691–4695. doi:10.1182/blood-2010-10-299487.
190. Ye R, Kundrapu S, Gerson SL, et al. Immune signatures associated with clonal isotype switch after autologous stem cell transplantation for multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2019;19(5):e213–e220. doi:10.1016/j.clml.2018.12.022.
191. Schmitz MF, Otten HG, Franssen LE, et al. Secondary monoclonal gammopathy of undetermined significance after allogeneic stem cell transplantation in multiple myeloma. *Haematologica*. 2014;99(12):1846–1853. doi:10.3324/haematol.2014.111104.
192. Tovar N, de Larrea CF, Aróstegui JI, et al. Natural history and prognostic impact of oligoclonal humoral response in patients with multiple myeloma after autologous stem cell transplantation: long-term results from a single institution. *Haematologica*. 2013;98(7):1142–1146. doi:10.3324/haematol.2013.084350.
193. Tschautscher MA, Jevremovic D, Buadi FK, et al. Utility of repeating bone marrow biopsy for confirmation of complete response in multiple myeloma. *Blood Cancer J*. 2020;10(10):95. doi:10.1038/s41408-020-00363-6.
194. Cavo M, San-Miguel J, Usmani SZ, et al. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. *Blood*. 2022;139(6):835–844. doi:10.1182/blood.2021011101.
195. Munshi NC, Avet-Loiseau H, Anderson KC, 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):5988–5999. doi:10.1182/bloodadvances.2020002827.
196. Hillengass J, Usmani S, Rajkumar SV, et al. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. [published correction appears in Lancet Oncol. 2019 Jul;20(7):e346]. *Lancet Oncol*. 2019;20(6):e302–e312. doi:10.1016/S1470-2045(19)30309-2.
197. American Society of Clinical Oncology (ASCO). ASCO Guidelines Methodology Manual. Available at: https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2019-Guidelines-Methodology-Manual.pdf. Accessed April 29, 2023.

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