Moving Beyond Autologous Transplantation in Multiple Myeloma: Consolidation, Maintenance, Allogeneic Transplant, and Immune Therapy

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OVERVIEW

For multiple myeloma, introduction of novel agents as part of the front-line treatment followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) induces deep responses in a majority of patients with this disease. However, disease relapse is inevitable, and, with each relapse, the remission duration becomes shorter, ultimately leading to a refractory disease. Consolidation and maintenance strategy after ASCT is one route to provide sustained disease control and prevent repeated relapses. Though the consolidation strategy remains largely confined to clinical trials, significant data support the efficacy of consolidation in improving the depth of response and outcomes. There are also increasing rates of minimal residual disease–negativity with additional consolidation therapy. On the other hand, maintenance with novel agents post-transplant is well established and has been shown to improve both progression-free and overall survival. Evolving paradigms in maintenance include the use of newer proteasome inhibitors, immunotherapy maintenance, and patient-specific maintenance—a concept that utilizes minimal residual disease as the primary driver of decisions regarding starting or continuing maintenance therapy. The other approach to overcome residual disease is immune therapeutic strategies. The demonstration of myeloma-specific alloimmunity from allogeneic transplantation is well established. More sophisticated and promising immune approaches include adoptive cellular therapies, tumor vaccines, and immune checkpoint manipulations. In the future, personalized minimal residual disease–driven treatment strategies following ASCT will help overcome the residual disease, restore multiple myeloma–specific immunity, and achieve sustained disease control while minimizing the risk of overtreatment.

Autologous hematopoietic cell transplantation with high-dose chemotherapy and autologous cell rescue is a mainstay of therapy for patients with multiple myeloma and induces a response in a large proportion of patients. However, relapse is near universal as a result of either measurable disease or minimal residual disease (MRD) after ASCT, and multiple myeloma remains incurable.[1] Effective therapies for sustained disease control after ASCT and prevention of repeated relapses in high-risk subgroups are unmet needs. Consolidation and maintenance after ASCT is one route to overcome residual disease, whereas immune approaches such as allogeneic transplantation (allo-HCT), adoptive cellular therapies, vaccines, or antibody-based immune manipulations represent another approach. Allo-HCT, despite its toxicities, has been known to cure a minority of patients by establishing myeloma-specific alloimmunity.[2-4] Herein, potential treatments beyond ASCT (planned consolidation or maintenance), allo-HCT, and emerging immune therapies, are discussed.

CONSOLIDATION THERAPY IN MULTIPLE MYELOMA

Consolidation therapy following ASCT for multiple myeloma implies a short period of intensive treatment with a single-agent or a combination of agents. Depth of response is widely accepted as prognostic for outcomes with multiple myeloma, and this strategy further reduces disease burden following ASCT.[5,6] Yet, compared with lower-dose long-term maintenance, consolidation mostly remains confined to clinical trials. Historically, efforts of post-transplant consolidation have ranged from aggressive attempts to eradicate disease with tandem autologous transplantation and consolidation cytotoxic chemotherapy, to modern novel agent–based approaches[6,7]

TABLE 1. Lenalidomide and Bortezomib Monotherapy Consolidation

Study	Consolidation Regimen	Induction Regimen	Comparison Arm	Duration	Before Consolidation	After Consolidation	PFS	OS
Attal et al[11] (614 patients)	Lenalidomide	VAD (46%) VD (46%)	None (all treated)	2 cycles	≥ VGPR: 58%	≥ VGPR: 69% (p < .001)	4-year: 43% vs. 22%	4-year : 73% vs. 75%
Uy et al[13] (40 patients)	Bortezomib	Bortezomib-naive	None	6 cycles	CR + VGPR: 43%	CR + VGPR: 43%	NR	3-year: 63.1%
Mellqvist et al[14] (187 patients)	Bortezomib	Bortezomib-naive	Placebo	6 cycles	≥ nCR: 20.1% ≥ VGPR: 39.7%	≥ nCR: 45.1% ≥ VGPR: 70.9%	27 vs. 20 months	3-year: 80% vs. 80%

Abbreviations: PFS, progression-free survival; OS, overall survival; VAD, vincristine/doxorubicin/dexamethasone; VD, bortezomib/dexamethasone; VGPR, very good partial response; nCR, near CR; NR, not reported.

TANDEM TRANSPLANTATION AND CYTOTOXIC CHEMOTHERAPY

Initial efforts of post-ASCT consolidation therapy evolved from the University of Arkansas Total Therapy trials and mirrored prolonged treatment regimens in pediatric acute lymphocytic leukemia. Total Therapy 1 (TT1) (which did not include consolidation) used aggressive induction chemotherapy and tandem ASCT combined with maintenance interferon (IFN) to produce results superior to contemporary standard therapy in a SWOG cooperative group trial.[8] Total Therapy 2 (TT2), which expanded on TT1, evaluated aggressive induction chemotherapy, tandem ASCT followed by four cycles of dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DPACE) consolidation chemotherapy; patients were then randomly assigned to receive maintenance therapy with IFN with or without thalidomide.[9] Total Therapy 3 (TT3A) included the addition of bortezomib-based chemotherapy induction, tandem ASCT followed by DPACE plus thalidomide and bortezomib (V-DTPACE) consolidation and then maintenance.[10] The role of maintenance in these trials was evaluated in a nonrandomized fashion, making its individual contribution difficult to discern; however, they spawned further interest for improved post-ASCT strategies.

KEY POINTS

- **Induction with novel agent combinations followed by high-dose chemotherapy ASCT is the standard of care in patients with multiple myeloma who are eligible for transplant.**
- **Relapse is inevitable in the majority of the patients despite recent improvements in progression-free survival.**
- **Effective strategies to overcome residual disease and prevent relapse is an unmet need.**
- **Post-transplant consolidation and minimal residual disease–directed maintenance are promising new avenues.**
- **Emerging post-ASCT immunotherapy to establish myeloma-specific immunity and allotransplant are tools for long-term disease control, especially for young high-risk patients.**

IMMUNOMODULATORY AGENT CONSOLIDATION THERAPY

Novel agents such as proteasome inhibitors and immunomodulatory agents (IMIDs) have advanced all aspects of multiple myeloma treatment. Evaluation of consolidation therapy with IMID monotherapy was undertaken in a phase III study by Intergroupe Francophone du Myelome (IFM 05-02; Table 1).[11] Newly diagnosed patients with multiple myeloma who underwent post-ASCT consolidation therapy with lenalidomide were randomly assigned to receive maintenance lenalidomide versus placebo. Two cycles of lenalidomide (25 mg daily) improved the rate of complete response (CR) or very good partial responses (PR) from 58% to 69% (p < .001), respectively, among all participants, but maintenance was not associated with improvement of overall survival (OS). A similarly designed phase III U.S. study (CALGB 100104) lacked the lenalidomide consolidation phase, but randomly assigned patients to receive maintenance lenalidomide versus placebo and reported an OS benefit in the maintenance arm.[12] One of the possible explanations for the lack of OS benefit in the former study is that a short period of consolidation given to all subjects in IFM 0502 may have abrogated the survival benefit for protracted maintenance therapy.

PROTEASOME INHIBITOR–BASED CONSOLIDATION

Bortezomib

Uy et al[13] evaluated pre- and post-ASCT bortezomib consolidation in a phase II study with 40 patients (all newly diagnosed with multiple myeloma) who received two cycles of intravenous bortezomib followed by ASCT, and six cycles of intravenous bortezomib after ASCT. Only 28 patients received post-ASCT bortezomib, with two upgraded responses—one from very good PR to CR and one from PR to very good PR. The 3-year OS and disease-free survival (DFS) were 63.1% and 38.2%, respectively.[13]

The NORDIC Myeloma Study Group randomly assigned bortezomib-naive patients post-ASCT to receive either no further treatment or bortezomib consolidation for six cycles. With a median follow-up of 38 months, PFS for the bortezomib-treatment group was 27 months compared with 20 months for the control group (p = .05), and no difference in OS. Patients who experienced at least a very good PR

TABLE 2. Bortezomib and Immunomodulatory Combination Consolidation Therapy

Study	Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	PFS	OS
Cavo et al[72]	VTD (160 patients)	VTD x 3	TD (161 patients)	2 cycles	CR: 48.7% ≥ VGPR: 86.2%	CR: 60.6% ≥ VGPR: 91.9% p = NS (VGPR)	3-year: 60%	3-year: 90%
Cavo et al[72]	TD (161 patients)	TD x 3	VTD (160 patients)	2 cycles	CR: 40.4% ≥ VGPR: 81.4%	CR: 46.6% ≥ VGPR: 88.2% p = NS (VGPR)	3-year: 48%	3-year: 88%
Leleu et al[17]	VTD (121 patients)	VTD	No consolidation (96 patients)	2 cycles	CR: 33% ≥ VGPR: 43%	CR: 52% ≥ VGPR: 31% p < .001 (CR)	NR	3-year: NR vs. 22 months
Roussel et al[73]	RVD (31 patients)	RVD	None	2 cycles	CR: 47% ≥ VGPR: 70%	CR: 50% ≥ VGPR: 87%	3-year: 77%	3-year: 100%
Nooka et al[18]	RVD	RVD	None	3 years	sCR approx. 20% ≥ VGPR approx. 85%	sCR: 51% ≥ VGPR: 96%	32 months	3-year: 93%
Moreau et al[19]	RVD	RVD	No transplant	2 cycles	≥ VGPR:73%	≥ VGPR: 81%	34 vs. 43 months	4-year: 81% vs. 83%

Abbreviations: PFS, progression-free survival; OS, overall survival; CR, complete response; NR, not reported; NS, not significant; RVD, lenalidomide/bortezomib/dexamethasone; TD, thalidomide/dexamethasone; VGPR, very good partial response; VTD, bortezomib/thalidomide/dexamethasone.

demonstrated a prolonged PFS irrespective of bortezomib consolidation. The beneficial effect of bortezomib consolidation was confined to patients who did not have at least a very good PR following ASCT. More importantly, PFS among patients whose disease had a very good PR to therapy at randomization was similar to patients whose disease response improved to the very good PR category or better during consolidation. These results provide substantial support to the role of post-transplant consolidation to further deepen disease response.[14]

Combination Therapy Bortezomib and Immunomodulatory Agents

In a phase III trial, Cavo et al[15] assessed the efficacy of consolidation with thalidomide and dexamethasone (TD) compared with bortezomib, thalidomide, and dexamethasone (VTD; Table 2). The patients were randomly assigned at diagnosis to induction therapy with either VTD or TD, and all underwent tandem ASCT followed by two 35-day consolidation cycles with the same regimen as their induction therapy (VTD vs. TD). CR rates after second ASCT was 48.7% for the VTD group and 40.4% for the TD group, improving to 60.6% and 46.6%, respectively, following consolidation. PFS was superior for the VTD group compared with the TD group (60% vs. 48% at 3 years; p = .042).[15] Notably, rates of CR and at least very good PR favored VTD treatment, but were not significant. The isolated impact of consolidation is difficult to determine from this study.

Roussel et al[16] investigated lenalidomide, bortezomib, and dexamethasone (RVD) induction and consolidation therapy in 31 patients with newly diagnosed multiple myeloma who received three RVD induction cycles, followed by ASCT and two RVD consolidation cycles with subsequent lenalidomide maintenance for 1 year. The estimated 3-year PFS and OS were 77% and 100%, respectively, and CR rates were 47% following ASCT and 50% after RVD consolidation. Therapy was tolerable, with no treatment-related mortality (TRM), and 97% completed the planned sequence.[16] Leleu et al[17] retrospectively analyzed 121 patients with newly diagnosed multiple myeloma across nine IFM centers who had received three cycles of VTD induction, followed by ASCT and two cycles of VTD consolidation. Complete response rates increased from 33% after induction and ASCT to 52% following consolidation. Compared with 96 similar patients treated with VTD induction and ASCT without consolidation, CR rates were superior and relapse risk were lower in the consolidation arm.[17]

Nooka et al[18] evaluated prolonged therapy with RVD in 45 patients with high-risk multiple myeloma (p53 deletion, 1p deletion, immunoglobulin heavy chain gene translocations, or plasma cell leukemia). Patients received RVD as consolidation/maintenance therapy post-ASCT for up to 3 years, followed by single-agent lenalidomide maintenance thereafter. RVD consolidation/maintenance achieved at least very good PR status in 96% of patients, and a stringent CR (sCR) in 51%. Median PFS was 32 months with a 3-year OS of 93%—a promising improvement in PFS and OS in this high-risk group. Despite its length and intensity, therapy was well tolerated overall.[18]

More recently, the second interim analysis of the IFM 2009 trial was reported.[19] In this trial, RVD was administered for eight cycles followed by 12 months of lenalidomide maintenance or RVD induction with RVD consolidation post-ASCT followed by lenalidomide maintenance. Response to treatment continued to deepen with progressive therapy, and at least very good PR rates improved from 73% to 81% after RVD consolidation. This study also showed an improvement in PFS (median of 34 vs. 43 months) in the ASCT arm.

TABLE 3. Carfilzomib-Based Consolidation Therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation	PFS	OS
KTd (Sonneveld et al[20]; 91 patients)	KTd	None	4 cycles	CR: 33%	CR: 63%	3-year: 60%	3-year: 90%
				≥ VGPR: 76%	≥ VGPR: 89%		
KRd (Jakubowiak et al[21]; 71 patients)	KRd	None	4 cycles	≥ CR: 27%	≥ CR: 77%	11 months: 99%	11 months: 100%
				≥ sCR: 22%	≥ sCR: 70%		

Abbreviations: PFS, progression-free survival; OS, overall survival; KTd, carfilzomib/thalidomide/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; CR, complete response; VGPR, very good partial response; sCR, stringent complete response.

Carfilzomib

In a multicenter phase II study from the European Myeloma Network, the carfilzomib, thalidomide, and dexamethasone (KTd) combination was investigated as induction and consolidation therapy in patients with multiple myeloma who were previously untreated (Table 3). KTd was given in 28-day cycles for up to four cycles and followed by ASCT. After ASCT patients received four cycles of KTd consolidation therapy. The at least very good PR rate increased from 68% after induction to 76% after ASCT, and finally to 89% after four cycles of consolidation. Progression-free survival at 36 months was 72%, and only 5% of patients discontinued therapy.[20] Pre- and post-transplant carfilzomib, lenalidomide, and dexamethasone (KRd) was studied in a phase II trial. After KRd induction, ASCT and KRd consolidation (four cycles) were administered followed by KRd maintenance for nine cycles, and then lenalidomide maintenance off-protocol. Rates of CR increased from 27% following ASCT to 77% after consolidation. At the conclusion of KRd treatment, 90% of patients demonstrated an at least CR with a 3-year PFS and OS of 79% and 100%.[21]

CONSOLIDATION THERAPY AND MINIMAL RESIDUAL DISEASE

The role of MRD evaluation in prediction of outcomes and duration of therapy is increasing. Ladetto et al[22] enrolled patients whose disease had a very good PR following ASCT and monitored MRD after four cycles of VTD consolidation using polymerase chain reaction–based techniques (Table 4).[22] Molecular remission rates were 3% after ASCT compared with 18% after VTD consolidation. Achievement of MRD-negative response was significantly associated with improved median PFS (68 months vs. 23 months, p < .0001).

In the study by Roussel et al,[16] the outcomes of patients who were MRD-negative (evaluated by marrow flow cytometry) were impressive with a 3-year PFS of 100%.[16] MRD negativity rates steadily increased through induction to the completion of consolidation. Jakubowiak et al[21] assessed MRD in a subset of patients whose disease had a CR using 10-color flow cytometry and noted substantial improvements in MRD negativity rates with consolidation therapy.[21]

CONSOLIDATION VERSUS MAINTENANCE

Current evidence does not enable a clear recommendation of consolidation therapy for all patients after they have undergone ASCT. Substantial data support its efficacy in improving depth of response of multiple myeloma, which has historically translated into improvements of survival outcomes. The awaited results of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 STAMINA trial (NCT 1109004), compares three competing post-ASCT strategies after initial ASCT: patients will be randomly assigned to receive a second (tandem) ASCT, RVD consolidation, or immediate initiation of lenalidomide maintenance (Fig. 1). All arms will ultimately receive lenalidomide maintenance based on the paradigm that continuous therapy or maintenance is sufficient to control residual disease. Additionally, an ongoing multicenter study (NCT02253316) is evaluating the role of ixazomib-based consolidation therapy followed by maintenance with MRD post-ASCT (Fig. 2).

TABLE 4. Minimal Residual Disease With Consolidation Therapy

Consolidation Regimen	Induction Regimen	Comparator Arm	Duration	Before Consolidation	After Consolidation
VTD (Ladetto et al[22]; 39 patients)	VAD	None	4 cycles	CR: 15%	CR: 49%
				MRD: 4.15–log reduction*	MRD: 10.09–log reduction*
VRD (Roussel et al[16]; 26 patients)	VRD	None	2 cycles	MRD: 54% negative	MRD: 58% negative
KRd (Jakubowiak et al[21]; 71 patients)	KRd	None	4 cycles	MRD: 79% negative	MRD: 90% negative

*Reduction from baseline levels.
Abbreviations: VTD, bortezomib/thalidomide/dexamethasone; VAD, vincristine/doxorubicin/dexamethasone; CR, complete response; MRD, minimal residual disease; KRd, carfilzomib/lenalidomide/dexamethasone.

FIGURE 1. CTN 0702 Study (STAMINA) Schema
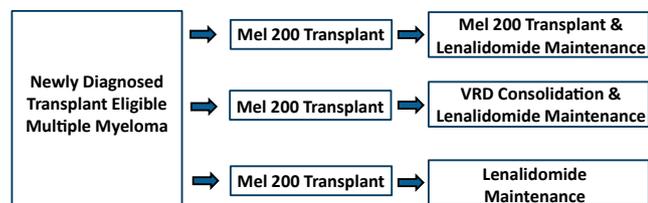
MAINTENANCE THERAPY AFTER TRANSPLANTATION: THE PAST AND THE FUTURE

The concept of sustained low intensity post-ASCT therapy (or maintenance) for patients with multiple myeloma dates back to IFN, which was associated with improved PFS and OS in several trials.[23] The advent of novel agents with improved efficacy and toxicity supplanted IFN. Given emerging immuno-oncologic approaches, this may also have been prescient in harnessing the immune system as the major mechanism to maintain control against residual disease.

Maintenance Agents: Immunomodulatory Agents

Thalidomide. Probably the largest body of clinical trial experience has been with thalidomide maintenance therapy, although these trials differed with some having used thalidomide as part of induction continuing through maintenance, whereas others used it in conjunction with steroids, and with major variation in thalidomide doses chosen. Table 5 outlines the major trials of thalidomide maintenance following ASCT. All studies of thalidomide maintenance suggest improved PFS, but toxicity and tolerability remain issues. In the IFM 99 trial, 39% of patients discontinued thalidomide mainly due to neuropathy.[24] In the MRC IX trial with thalidomide maintenance after intensive (transplant) or nonintensive (chemotherapy only) pathways, 52% stopped therapy due to side effects, and thalidomide maintenance did not prolong PFS or OS in those with adverse cytogenetics.

FIGURE 2. Design of NCT02253316: Ixazomib, Lenalidomide, and Dexamethasone Consolidation Therapy and Minimal Residual Disease
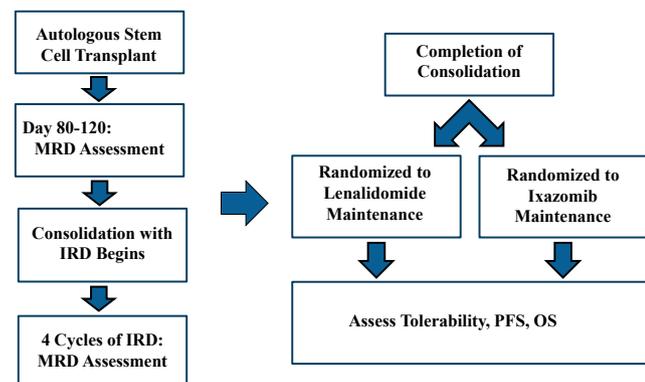
Abbreviations: MRD, minimal residual disease; IRD, ixazomib, lenalidomide, and dexamethasone; PFS, progression-free survival; OS, overall survival.

In the United States, therefore, interest shifted to lenalidomide as a better-tolerated IMID maintenance strategy.[25]

Lenalidomide. Three published phase III trials explored lenalidomide maintenance after ASCT (Table 6). The CALGB 100104 Intergroup trial randomly assigned patients to receive lenalidomide (10 mg daily escalated to 15 mg) or observation after ASCT. The median time-to-progression (TTP) was 46 months in the lenalidomide arm compared with 27 months with placebo, which translated into an improved OS (88% vs. 80% at 3 years).[12] A recently updated analysis showed a median TTP of 53 months compared with 27 months as well as continued OS advantage.[26] The phase III IFM 05-02 trial, as noted previously, had the subtle, but important, difference that all patients received lenalidomide consolidation followed by lenalidomide maintenance or placebo.[11] In this trial, although median TTP was superior for the lenalidomide arm (41 months vs. 23 months $p < .001$), there was no difference in OS. The lack of OS benefit may in part be attributed to lenalidomide consolidation and or an imbalance of high-risk patients between arms. An Italian trial (GIMEMA RV-MM-PI209) assigned patients to melphalan, prednisone, and lenalidomide (MPR) or ASCT followed by second random assignment to maintenance lenalidomide or no maintenance. The maintenance lenalidomide cohort in both the MPR and ASCT groups had superior PFS (but not OS).[27] In all trials, the lenalidomide cohorts had a higher incidence of neutropenia. Even more important was the higher incidence of second primary malignancies (SPM) at around 8% in the IFM and CALGB trials compared with 3% to 4% in the placebo arm. Strategies to minimize SPM risk without losing the benefit of maintenance are areas of study, such as limiting the duration of maintenance, pre-assessing SPM risk, and MRD-based discontinuation.

A comparison of the recently reported IFM DFCI 2009 trial with the ongoing DFCI (Dana-Farber Cancer Institute) BMT CTN Determination trial is expected to shed light on the duration of maintenance lenalidomide and the impact of MRD. As described previously, the IFM version of this phase III trial incorporated 1 year of lenalidomide maintenance.[19] In contrast, the DFCI version (DFCI10-106; NCT1208662) follows the same overall schema, but lenalidomide maintenance continues until disease progression. The incidence of SPM as well as sequential evaluation of MRD by flow cytometry and next-generation sequencing is being evaluated in both trials.[28]

Maintenance Agents: Proteasome Inhibitors

Bortezomib. Although there is a large body of evidence surrounding bortezomib maintenance (Table 5), most protocols used bortezomib administered intravenously, which renders the toxicity data less relevant in the era of subcutaneous dosing. A large Dutch-German trial randomly assigned patients to receive bortezomib, doxorubicin, and dexamethasone (PAD) or vincristine, doxorubicin, and dexamethasone (VAD)[29] induction followed by ASCT. The PAD induction arm subsequently received bortezomib

TABLE 5. Thalidomide and Bortezomib Maintenance Studies

Schedule	Control	CR	PFS/EFS/TTP	Reference
PAM + Thal 400 mg/day	PAM or OBS	NR	52% (3-year)	Attal et al[24]
Thal 400 mg/day	None	50%	72% (6-year)	Barlogie et al[74]
Thal 200 mg/day + PSE 50 mg QOD	PSE	NR	42% (3-year)	Spencer et al[75]
Thal 50 mg/day	IFN	31%	50% (34-month)	Lokhorst et al[76]
Thal 100 mg/day	OBS	NR	50% (30-month)	Morgan et al[25]
Thal 200 mg/day + PSE 50 mg QOD	OBS	NR	32% (4-year)	Stewart et al[77]
Bort 1.3 mg/m^2 Q2 weeks	Thal	NR	50% (35-month)	Sonneveld et al[29]
Bort + Thal	Thal or IFN	19%	50% (45-month)	Rosinol et al[31]

Abbreviations: CR, complete response; PFS, progression-free survival; EFS, event-free survival; TTP, time-to-progression; PAM, pamidronate; Thal, thalidomide; OBS, observation, NR, not reported; PSE, prednisone; QOD, every other day; IFN, interferon; Bort, bortezomib; Q2, every two.

maintenance for 2 years, whereas the VAD arm received thalidomide maintenance. Median PFS was 35 months in the bortezomib-treated arm compared with 28 months in the VAD/thalidomide-treated arm. A landmark analysis suggested an OS benefit, although it is not clear if the benefit was derived solely from the bortezomib maintenance or induction, or from the higher discontinuation rates with thalidomide maintenance. There was particular improvement in the high-risk subgroup with 17p deletion that received bortezomib (PFS of 26 months vs. 12 months in the thalidomide arm).[30] Another three-arm Spanish trial compared bortezomib plus thalidomide, thalidomide, or IFN as maintenance with a planned duration of 3 years. PFS was superior with the bortezomib/thalidomide combination, but there was no OS benefit.[31]

Carfilzomib and ixazomib. Other proteasome inhibitors could offer the potential advantages of minimizing neuropathy with possibly higher potency. Carfilzomib-based combinations with lenalidomide have been described previously, whereas ixazomib maintenance is another attractive option, given its oral administration and lower neuropathy risk. As shown in Fig. 2, a current trial (NCT02253316) is evaluating ixazomib, lenalidomide, and dexamethasone consolidation followed by random assignment to ixazomib or lenalidomide maintenance until disease progression. Although not powered to show a benefit with either of the maintenance arms, the tolerability and feasibility of ixazomib maintenance and ongoing MRD assessments will be

valuable. In another phase II trial using ixazomib and lenalidomide combination maintenance,[32] ixazomib dose was reduced to 3 mg or less (from the standard 4 mg) in some patients because of the development of neuropathy. Overall, the combination was well-tolerated, with the majority of patients still receiving treatment at 30-plus cycles with an estimated 2-year PFS of 83%.

In the allogeneic setting, the BMT CTN 1302 phase II trial for patients with protocol-defined high-risk multiple myeloma (NCT02440464) randomly assigned patients to receive ixazomib maintenance or placebo starting at 60- to 120-days after allo-HCT. Because bortezomib has been shown to reduce graft-versus-host disease (GVHD), the effects of ixazomib on GVHD and relapse rates are being evaluated.

Immunotherapy

Immunotherapy for multiple myeloma encompasses approved myeloma-directed passive antibody or active approaches that enhance tumor-specific immune responses. The post-ASCT maintenance setting is the ideal platform for immunotherapy, given low disease burden as well as a favorable immune milieu. Multiple immunotherapy options are being evaluated in trials designed to elicit antitumor immune responses, as well as augment T-cell function (Table 7).

Daratumumab,[33] the newly approved anti-CD38–directed antibody, has a half-life of 21 days, which makes it an attractive maintenance option. An ongoing IFM phase III trial (NCT02541383) for front-line therapy randomly assigns patients to receive daratumumab maintenance for 2 years

TABLE 6. Lenalidomide Maintenance Studies

Maintenance Study	Comparison	Planned Length of Maintenance	Outcome	
			PFS	OS
McCarthy et al[12] (CALGB 100104)	Lenalidomide vs. placebo	Until progression	Median PFS (46 vs. 27 months; p < .001)	3-year OS (88% vs. 80%; p = .03)
Attal et al[75] (IFM 0502)	Lenalidomide vs. placebo after 2 months lenalidomide consolidation	Until progression, but terminated early for SPM	Median PFS (41 vs. 23 months; p < .001)	4-year OS (73% vs. 75%; p = NS)
Palumbo et al[27]	MPR vs. tandem ASCT followed by lenalidomide vs. placebo	Until progression	Median PFS 41.9 vs. 21.6 months; (p < .001)	3-year OS (88% vs. 79.2%; p = .14)

Abbreviations: PFS, progression-free survival; OS, overall survival; SPM, secondary primary malignancies; NS, not significant; MPR, melphalan/prednisone/lenalidomide; ASCT, autologous hematopoietic cell transplantation.

TABLE 7. Comparison of Immunotherapy Maintenance Strategies

Therapy	Advantage	Disadvantage
Vaccine	Ease of administration Low toxicity	Patient-specific (manufacturing)
T-cell–based (Including CAR)	Cytolytic trafficking to extramedullary sites	Toxicity manufacturing
Antibodies	Long half-life Commercially available	Infusional toxicity Cytopenias
Checkpoint Blockade	Commercially available	Low single-agent response rates in MM

Abbreviations: CAR, chimeric antigen receptor; MM multiple myeloma.

after ASCT. Elotuzumab, a natural killer (NK) cell–directed antibody requires lenalidomide to augment its activity. An ongoing phase II trial (NCT 02420860) explores the combination of elotuzumab with lenalidomide following ASCT.

Emerging Paradigms in Maintenance

Patient-specific maintenance is a concept that utilizes MRD as the primary driver of decisions regarding starting or continuing maintenance therapy. Most ongoing phase III and phase II trials are collecting MRD data at various points in time, although the optimal method for MRD assessment is debated (multicolor flow cytometry vs. sequencing). To a smaller extent, decisions regarding choice of maintenance drug are also patient- and disease-specific (e.g., bortezomib for patients with t[4,14] or 17p deletion). Further refinement of this concept with more targeted therapy based on genetic sequencing is key. Lastly, augmenting immune function through a variety of methods including adoptive cell therapy, vaccines, checkpoint blockade, and myeloma-specific antibodies will likely become the backbone of post-ASCT interventions.

IMMUNOTHERAPY FOR MULTIPLE MYELOMA: ALLOGENEIC TRANSPLANTATION AND BEYOND

Allogeneic transplantation is a well-established immunotherapy strategy for multiple myeloma with evidence of the existence of a potent and often sustained graft-versus-myeloma effect.[4] Conventional myeloablative regimens resulted in prohibitive TRM (40% to 60%), but apparent plateaus in transplant survival curves indicated long-term disease control. The allogeneic arm of U.S. intergroup trial (S93-21) was prematurely closed as a result of high early TRM (53%), but showed long relapse-free survivorship of 39% at 7 years.[34] Development of nonmyeloablative and reduced-intensity conditioning regimens has decreased TRM,[35,36] but the lower TRM was negated by an increase in relapse risk during later years.[37] The risks of chronic GVHD and the need for long-term immunosuppression remain major challenges. The success of allo-HCT as a relapse prevention strategy resides in the ability of donor-derived alloreactive T cells to eliminate or suppress multiple myeloma propagating residual cells. Several lines of evidence point to this, including the correlation of chronic GVHD with protection from relapse,[2,4] the ability of donor derived lymphocytes to eliminate residual or relapsing disease,[38] and lower relapse rates observed in recipients of T-cell replete allografts compared with recipients of T-cell depleted or syngeneic grafts.

Modern Randomized Trials of Allo-HCT

After promising phase II data, a series of randomized, prospective studies explored the concept of decoupling myeloablation and immune therapy by a tandem approach involving an initial autologous myeloablative transplant followed (within 3 to 6 months) by an allogeneic non-myeloablative transplant from a matched sibling or unrelated donor. The results of this strategy have been discordant in the front-line treatment of multiple myeloma. Two major European studies[39,40] reported favorable long-term OS.[41,42] In these studies, compared with tandem autologous transplantation, a second (tandem) allo-HCT from an HLA-matched donor (after a prior autograft) results in superior PFS and OS despite an increase in early TRM. This is in contrast to the U.S. study led by the BMT CTN in which no survival or progression benefit was seen in the allo-HCT group.[2] Interestingly, in the larger European Group on Blood and Marrow Transplantation (EBMT) study, in addition to relapse risk being lower in the allograft arm, post-relapse survival was also superior for the allo-HCT cohort compared with tandem autograft recipients.[42] This latter phenomenon has been attributed to a synergy between novel agents and the immune benefits of an allo-HCT.

As discussed in the maintenance section, more recent studies incorporated maintenance agents (lenalidomide, bortezomib, and others) in the post allo-HCT setting. These results were discordant with the HOVON group,[43] reporting substantial GVHD that threatened the feasibility of planned lenalidomide maintenance. In contrast, a multicenter U.S. study,[44] in a predominantly high-risk population, indicated promising PFS and OS of 63% and 78%, respectively, at 18 months. A current multicenter U.S. study (BMT CTN 1302; NCT02440464) uses the newly approved agent ixazomib in maintenance after an allogeneic transplant in patients with genetically defined high-risk multiple myeloma, plasma cell leukemia, or early relapse after an ASCT.

On a practical basis, if allo-HCT is considered part of the therapeutic armamentarium, clinicians are faced with two major questions: (1) identifying the patients who benefit the most from allo-HCT and (2) identifying the optimal time point for referral for allo-HCT.

Who Should Be Considered for Allo-HCT for Multiple Myeloma

In practical terms, this boils down to the identification of patients who are at such high clinical or biologic risk that the TRM risk of allo-HCT is balanced by the intrinsic negative prognosis. Biologically, high-risk myeloma is defined by the presence of chromosomal abnormalities t(4:14), t(14:16), +1q21, 17p by fluorescence in situ hybridization (FISH); 13q deletion by karyotyping or high-risk gene expression profiling (GEP).[45,46] Based on the recently developed *R*-ISS staging system that incorporates disease burden and biology, the highest risk subgroup (stage III) had a predicted 5-year OS and PFS of 40% and 24%, respectively.[47] Similarly, relapse within 18 months of ASCT is an extremely negative prognostic marker.[48] Effective treatment that establishes long-term disease control in these high-risk patient populations is an unmet need, and allo-HCT becomes a consideration. Both prospective and retrospective studies have explored the role of allo-HCT in patients with high-risk multiple myeloma with variable outcomes. The EBMT NMAM 2000 study reported a 21% PFS at the 8-year follow-up in patients with the higher risk deletion 13 (by FISH) who underwent allo-HCT versus 5% in the tandem ASCT group.[42] Knop et al showed that in the highest risk subgroup with del(17p) and del(13q) abnormality,[49] median PFS (p = .002) and OS (p = .011) were superior compared with tandem ASCT. In younger eligible patients with well-defined high-risk features, it is reasonable to consider allo-HCT, especially within a clinical trial and early in the clinical course (front-line or first relapse). The mortality and morbidity in general has steadily declined in recent years, making the short-term risks lower than in published studies from a decade or more ago.[37] In contrast, after repeated relapses, allo-HCT itself is associated with very poor survival, making this modality a very poor late salvage option.[50] In the United States, overall allogeneic transplant activity has declined for patients with multiple myeloma and more transplants, unfortunately, are now suboptimally performed later in the disease course.

Timing of Allo-HCT for Relapsed Multiple Myeloma

Prospective data that demonstrated a benefit for allo-HCT are all derived from the up-front setting after an initial ASCT. Understandably in the modern era, patients and physicians are still hesitant regarding a treatment with high immediate TRM risk. In patients whose disease relapsed after an ASCT, the benefit of allo-HCT was found to be highest when this modality was used earlier in the disease course and when used as a strategy for consolidation of remission induced by salvage therapy.[51,52] A donor versus no donor analysis considered 169 consecutive patients who had relapsed after an ASCT and underwent HLA-typing immediately after relapse. The 2-year PFS was higher in the allo-HCT group (with donors) at 42% compared with 18% in the no donor group (p = .0001) with similar OS, although TRM was 22% versus 1% in the allo-HCT and ASCT groups, respectively.[53] In another prospective phase II multicenter EBMT trial, 49 patients who had relapsed after a previous ASCT received allo-HCT from

related or unrelated donors with an overall response rate of 90%, including a CR rate of 40%. Cumulative incidence of 1-year TRM was 25% and was significantly lower in transplants from fully HLA-matched donors compared with mismatched donors (10% vs. 53%, p = .001). After a median follow-up of 43 months, the 5-year PFS and OS were 20% and 26%, respectively, and were greater in patients who demonstrated post-transplant CR.[54] In light of the above data, it is reasonable to consider allo-HCT in high-risk patients who have relapsed and who demonstrated a deep remission to salvage regimens prior to allo-HCT.

Conditioning Regimen Intensity

The optimal intensity of conditioning regimens for allo-HCT is still controversial for patients with multiple myeloma. Fully myeloablative regimens have been largely abandoned, whereas nonmyeloablative stem cell transplant regimens (e.g., total body irradiation of 2 Gy) without anti-multiple myeloma activity have been associated with lower TRM risk but increased relapse.[37] The pendulum of regimen intensity has now swung back to reduced-intensity conditioning with regimens that incorporate intermediate doses of active anti-multiple myeloma therapy. The most popular approach in the United States is a combination of fludarabine and melphalan at a dose of 140 mg/m^2 (CIBMTR data). The addition of proteasome inhibitors to conditioning is being explored as an additional strategy to increase the antineoplastic potential without incurring additional toxicity.

IMMUNE-BASED THERAPIES BEYOND ALLO-HCT

A variety of novel post-ASCT or allo-HCT immunotherapeutic strategies are now being explored for patients with multiple myeloma (Table 7). These include cellular approaches such as myeloma-specific T cells (via T-cell expansion), marrow infiltrating lymphocytes and redirected T cells with chimeric antigen receptors (CAR T), and tumor-based vaccines to induce myeloma-specific immunity in the context of enhanced antigen presentation. HCT provides an ideal platform for additional immune-based therapies. The recovery phase from ASCT (or other lymphodepleting therapy) represents a favorable platform for adoptive cellular therapy. The homeostatic lymphocyte proliferation following lymphopenia is a context in which immune checkpoint blockers may also be able to reverse multiple myeloma-associated T-cell exhaustion. Additionally, lymphopenia resulting from ASCT eliminates tolerogenic antigen-presenting cells and induces cytokine release that generates a more favorable environment for adoptive T-cell therapy. Indirect evidence suggests that the immune system can contribute to the clinical benefits of ASCT. For example, patients with early lymphoid recovery after ASCT have superior long-term outcomes.[55]

Donor Lymphocyte Infusion

Donor lymphocyte infusions have been used upon relapse after allo-HCT and even to preempt relapse, but exacerbation of GVHD is a major risk. Disease control is generally superior in patients in whom GVHD develops.[38]

Donor lymphocyte infusions have been combined with IMIDs or bortezomib.[56] Preemptive donor lymphocyte infusions at a defined time period has been used to enhance reconstitution of donor T cells and antitumor immunity.[57] Emergence of WT1-specific cytotoxic T lymphocytes (WT1-CTL) has been correlated with better PFS after allo-HCT. Infusion of donor-derived T cells directed against specific myeloma antigens such as WT1 or cancer testis antigens[58,59] is another promising area of adoptive T-cell therapy using the allo-HCT platform.

Myeloma Infiltrating T Lymphocytes

Marrow lymphocytes in patients with multiple myeloma are enriched for T cells with myeloma-specific antigen specificity. Noonan et al[60] described adoptive transfer of such autologous marrow-derived, ex vivo activated and expanded T cells on day 3 after ASCT.[60] They demonstrated measurable myeloma-specific activity for the ex vivo expanded product and persistence of myeloma-specific immunity even at 1 year.

CAR T-Cell Therapy

CAR T-cell therapy involves transducing activated T cells with genes encoding T-cell receptors specific to the antigen of interest. Although multiple myeloma is not a classic CD19-positive malignancy, deep sustained response to anti-CD19 CAR T cells in conjunction with second salvage ASCT for patients with relapsed/refractory multiple myeloma was recently reported.[61] Several promising antigenic targets have been identified for the development of anti-multiple myeloma CARs (40) such as B–cell maturation antigen (BCMA), CD138, kappa light chains, and CS-1. Notably, allogeneic CD19-directed CAR T cells (derived from donor lymphocytes) have induced remissions without induction of GVHD in patients who relapsed after allo-HCT.[61,62] Thus, the allo-HCT or ASCT platform could be adapted to subsequent CAR T technology.

Natural Killer–Cell Therapy

Natural killer cells have innate cytotoxicity against multiple myeloma cells, while multiple myeloma exhibits specific immune-evasive strategies to circumvent and attenuate NK-cell function.[63] Modulation of NK activity using anti-KIR Ab IPH2101 (monoclonal antibody against inhibitory KIR on NK cells) is being explored as a means to establish multiple myeloma–specific immunity.[64] Autologous-, allogeneic-, and cord-derived NK cells have been found to be safe and efficacious for multiple myeloma.[65] In a phase I study, up to 1×10^8 NK cells/kg freshly expanded cord blood NK cells were found to be safe when given before high-dose melphan

along with lenalidomide.[66] Haploidentical allo-HCT followed by planned NK-cell infusion attempts to use donor-recipient KIR ligand mismatch and NK-cell reactivity to facilitate long-term remission (NCT02100891).

Immune Checkpoint Inhibitors

Immune responses against multiple myeloma–specific antigens are minimally protective, although detectable in patients. Inhibitors of PD-1 and PD-L1 interaction are being studied as a means of breaking down multiple myeloma immune tolerance. In patients with multiple myeloma, PD-1 expression was upregulated on T cells concomitant with increased PD-L1 expression on plasma cells.[67,68] The anti–PD-1 agent nivolumab as monotherapy was unimpressive,[69] but promising response rates were observed in combination with lenalidomide, even for patients whose disease was refractory.[70] The anti–PD-1 agent pembrolizumab is being studied in the lymphocyte recovery phase after ASCT (NCT02331368) in combination with lenalidomide.

Vaccines

The vaccine approach holds great promise for patients with multiple myeloma. Patients who received a patient-specific dendritic cell/myeloma fusion vaccine demonstrated the expansion of multiple myeloma–specific T cells, as well as upgrading of response in a subgroup of patients.[71] This concept has been expanded to a intergroup randomized phase II trial (BMT CTN 1401) with ASCT followed by lenalidomide maintenance with or without vaccination using the dendritic cell/myeloma fusion vaccine.

The direct manipulation of T cells by increasing T-cell number, as well as engineering the T cells for augmented anti-multiple myeloma affinity was studied in a phase I/II trial. In this study, autologous T cells were transduced with a lentiviral vector that encoded the affinity-enhanced NY-ESO T-cell receptor. Patients received an infusion of these T cells after ASCT, which was shown to lead to long-term engraftment, infiltration of marrow, and trafficking to other tumor sites.

CONCLUSION

The role of transplant-based approaches as a key step in inducing long-term remissions for patients with multiple myeloma continues to evolve. The next decade of studies will likely establish personalized post-transplant maintenance strategies designed to achieve the trifecta of MRD negativity, restoration of multiple myeloma–specific immunity, and freedom from multiple myeloma clonal evolution.

References

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111: 2516-2520.

2. Krishnan A, Pasquini MC, Logan B, et al; Blood Marrow Transplant Clinical Trials Network (BMT CTN). Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic

stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011;12: 1195-1203.

3. Gahrton G, Tura S, Ljungman P, et al; European Group for Bone Marrow Transplantation. Allogeneic bone marrow transplantation in multiple myeloma. *N Engl J Med*. 1991;325:1267-1273.

4. Tricot G, Vesole DH, Jagannath S, et al. Graft-versus-myeloma effect: proof of principle. *Blood*. 1996;87:1196-1198.

5. Harousseau JL, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. *Blood*. 2009;114:3139-3146.

6. San-Miguel JF, Mateos MV. Can multiple myeloma become a curable disease? *Haematologica*. 2011;1246-1248.

7. Zangari M, van Rhee F, Anaissie E, et al. Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1. *Br J Haematol*. 2008;141:433-444.

8. Vesole DH, Barlogie B, Jagannath S, et al. High-dose therapy for re-fractory multiple myeloma: improved prognosis with better supportive care and double transplants. *Blood*. 1994;84:950-956.

9. Barlogie B, Jagannath S, Desikan KR, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. *Blood*.1999;93: 55-65.

10. Barlogie B, Tricot G, Rasmussen E, et al. Total therapy 2 without tha-lidomide in comparison with total therapy 1: role of intensified in-duction and posttransplantation consolidation therapies. *Blood*. 2006; 107:2633-2638.

11. Attal M, Lauwers-Cances V, Marit G, et al; IFM Investigators. Lenali-domide maintenance after stem-cell transplantation for multiple my-eloma. *N Engl J Med*. 2012;366:1782-1791.

12. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366: 1770-1781.

13. Uy GL, Goyal SD, Fisher NM, et al. Bortezomib administered pre-auto-SCT and as maintenance therapy post transplant for multiple myeloma: a single institution phase II study. *Bone Marrow Transplant*. 2009;43: 793-800.

14. Mellqvist UH, Gimsing P, Hjertner O, et al; Nordic Myeloma Study Group. Bortezomib consolidation after autologous stem cell trans-plantation in multiple myeloma: a Nordic Myeloma Study Group ran-domized phase 3 trial. *Blood*. 2013;121:4647-4654.

15. Cavo M, Pantani L, Petrucci MT, et al; GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hemato-poietic stem cell transplantation in patients with newly diagnosed multiple myeloma. *Blood*. 2012;120:9-19.

16. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line trans-plantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2014;32: 2712-2717.

17. Leleu X, Fouquet G, Hebraud B, et al; Intergroupe Francophone du Myélome (IFM). Consolidation with VTd significantly improves the complete remission rate and time to progression following VTd in-duction and single autologous stem cell transplantation in multiple myeloma. *Leukemia*. 2013;27:2242-2244.

18. 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;28:690-693.

19. Attal M, Lauwers-Cances V, Hulin C, et al. Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial). *Blood*. 2015;126:391-391.

20. Sonneveld P, Asselbergs E, Zweegman S, et al. Phase 2 study of carfilzomib, thalidomide, and dexamethasone as induction/consolidation therapy for newly diagnosed multiple myeloma. *Blood*. 2015;125:449-456.

21. Jakubowiak A, Griffith K, Jasielec J, et al. Post-transplant carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone (KRd) consolida-tion in newly diagnosed multiple myeloma (NDMM): efficacy and toler-ability of extended treatment. *Haematologica*. 2015;100:1-800.

22. 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 mye-loma. *J Clin Oncol*. 2010;28:2077-2084.

23. Björkstrand B, Svensson H, Goldschmidt H, et al. Alpha-interferon maintenance treatment is associated with improved survival after high-dose treatment and autologous stem cell transplantation in pa-tients with multiple myeloma: a retrospective registry study from the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2001;27:511-515.

24. Attal M, Harousseau JL, Leyvraz S, et al; Inter-Groupe Francophone du Myélome (IFM). Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.

25. Morgan GJGW, Gregory WM, Davies FE, et al; National Cancer Research Institute Haematological Oncology Clinical Studies Group. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012;119:7-15.

26. Holstein SA, Owzar K, Richardson PG, et al. Updated analysis of CALGB/ECOG/BMT CTN 100104: lenalidomide maintenance therapy after single autologous stem cell transplant (ASCT) for multiple myeloma. *J Clin Oncol*. 2015;33: (suppl; abstr 8523).

27. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and main-tenance therapy in multiple myeloma. *N Engl J Med*. 2014;371:895-905.

28. Avet-Loiseau H, Corre J, Lauwers-Cances V, et al. Evaluation of minimal residual disease (MRD) By next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial. *Blood*. 2015;126:191-191.

29. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib in-duction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol*. 2012;30:2946-2955.

30. Neben K, Lokhorst HM, Jauch A, et al. Administration of bortezomib before and after autologous stem cell transplantation improves out-come in multiple myeloma patients with deletion 17p. *Blood*. 2012;119: 940-948.

31. Rosinol L OA, Teruel A. Maintenance therapy after stem cell trans-plantation for multiple myeloma with bortezomib/thalidomide vs thalidomide vs alfa 2 b interferon: final results of a phase 3 Pethema/GEM randomized trial. *Blood*. 2012;120: (abstr 334).

32. Shah JJ, Feng L, Weber D, et al. Phase II study of the combination of ixazomib with lenalidomide as maintenance therapy following autol-ogous stem cell transplant in patients with multiple myeloma. *Blood*. 2015;126:3155-3155.

33. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with dar-atumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373: 1207-1219.

34. 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. *J Clin Oncol*. 2006;24: 929-936.

35. Giralt S, Aleman A, Anagnostopoulos A, et al. Fludarabine/melphalan conditioning for allogeneic transplantation in patients with multiple myeloma. *Bone Marrow Transplant*. 2002;30:367-373.

36. Kröger N, Sayer HG, Schwerdtfeger R, et al. Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. *Blood*. 2002;100:3919-3924.

37. Kumar S, Zhang MJ, Li P, et al. Trends in allogeneic stem cell transplantation for multiple myeloma: a CIBMTR analysis. *Blood*. 2011;118:1979-1988.

38. Lokhorst HM, Wu K, Verdonck LF, et al. The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. *Blood*. 2004;103:4362-4364.

39. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356:1110-1120.

40. Björkstrand B, Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. *J Clin Oncol*. 2011;29:3016-3022.

41. Giaccone L, Storer B, Patriarca F, et al. Long-term follow-up of a comparison of nonmyeloablative allografting with autografting for newly diagnosed myeloma. *Blood*. 2011;117:6721-6727.

42. Gahrton G, Iacobelli S, Björkstrand B, et al; EBMT Chronic Malignancies Working Party Plasma Cell Disorders Subcommittee. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. *Blood*. 2013;121:5055-5063.

43. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. *Blood*. 2011;118:2413-2419.

44. Alsina M, Becker PS, Zhong X, et al. Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20:1183-1189.

45. Chng WJ, Dispenzieri A, Chim CS, et al; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;28:269-277.

46. Mikhael JR, Dingli D, Roy V, et al; Mayo Clinic. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88:360-376.

47. 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;33:2863-2869.

48. Kumar S, Mahmood ST, Lacy MQ, et al. Impact of early relapse after auto-SCT for multiple myeloma. *Bone Marrow Transplant*. 2008;42:413-420.

49. Knop S LP, Hebart H, et al. Autologous followed by allogeneic versus tandem-autologous stem cell transplant in newly diagnosed FISH-del13q myeloma. *Blood*. 2014;124:43.

50. Freytes CO, Vesole DH, LeRademacher J, et al. Second transplants for multiple myeloma relapsing after a previous autotransplant-reduced-intensity allogeneic vs autologous transplantation. *Bone Marrow Transplant*. 2014;49:416-421.

51. de Lavallade H, El-Cheikh J, Faucher C, et al. Reduced-intensity conditioning allogeneic SCT as salvage treatment for relapsed multiple myeloma. *Bone Marrow Transplant*. 2008;41:953-960.

52. Michallet M, Sobh M, El-Cheikh J, et al. Evolving strategies with immunomodulating drugs and tandem autologous/allogeneic hematopoietic stem cell transplantation in first line high risk multiple myeloma patients. *Exp Hematol*. 2013;41:1008-1015.

53. Patriarca F, Einsele H, Spina F, et al. Allogeneic stem cell transplantation in multiple myeloma relapsed after autograft: a multicenter retrospective study based on donor availability. *Biol Blood Marrow Transplant*. 2012;18:617-626.

54. Kröger N, Schwerdtfeger R, Kiehl M, et al. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood*. 2002;100:755-760.

55. Porrata LF, Gertz MA, Inwards DJ, et al. Early lymphocyte recovery predicts superior survival after autologous hematopoietic stem cell transplantation in multiple myeloma or non-Hodgkin lymphoma. *Blood*. 2001;98:579-585.

56. Kröger N, Badbaran A, Lioznov M, et al. Post-transplant immunotherapy with donor-lymphocyte infusion and novel agents to upgrade partial into complete and molecular remission in allografted patients with multiple myeloma. *Exp Hematol*. 2009;37:791-798.

57. Bellucci R, Alyea EP, Weller E, et al. Immunologic effects of prophylactic donor lymphocyte infusion after allogeneic marrow transplantation for multiple myeloma. *Blood*. 2002;99:4610-4617.

58. de Carvalho F, Alves VL, Braga WM, et al. MAGE-C1/CT7 and MAGE-C2/CT10 are frequently expressed in multiple myeloma and can be explored in combined immunotherapy for this malignancy. *Cancer Immunol Immunother*. 2013;62:191-195.

59. Tyler EM, Jungbluth AA, O'Reilly RJ, et al. WT1-specific T-cell responses in high-risk multiple myeloma patients undergoing allogeneic T cell-depleted hematopoietic stem cell transplantation and donor lymphocyte infusions. *Blood*. 2013;121:308-317.

60. Noonan KA, Huff CA, Davis J, et al. Adoptive transfer of activated marrow-infiltrating lymphocytes induces measurable antitumor immunity in the bone marrow in multiple myeloma. *Sci Transl Med*. 2015;7:288ra78.

61. Garfall AL, Stadtmauer EA, June CH. Chimeric antigen receptor T cells in myeloma. *N Engl J Med*. 2016;374:194.

62. Garfall AL, Fraietta JA, Maus MV. Immunotherapy with chimeric antigen receptors for multiple myeloma. *Discov Med*. 2014;17:37-46.

63. Childs RW, Carlsten M. Therapeutic approaches to enhance natural killer cell cytotoxicity against cancer: the force awakens. *Nat Rev Drug Discov*. 2015;14:487-498.

64. Benson DM Jr, Hofmeister CC, Padmanabhan S, et al. A phase 1 trial of the anti-KIR antibody IPH2101 in patients with relapsed/refractory multiple myeloma. *Blood*. 2012;120:4324-4333.

65. Szmania S, Lapteva N, Garg T, et al. Ex vivo-expanded natural killer cells demonstrate robust proliferation in vivo in high-risk relapsed multiple myeloma patients. *J Immunother*. 2015;38:24-36.

66. Shah N, Li L, Kaur I, et al. Infusion of ex vivo expanded allogeneic cord blood-derived natural killer cells in combination with autologous stem cell transplantation for multiple myeloma: results of a phase I study. *Blood*. 2015;126:929-929.

67. Benson DM Jr, Bakan CE, Mishra A, et al. The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. *Blood*. 2010;116:2286-2294.

68. Rosenblatt J, Glotzbecker B, Mills H, et al. PD-1 blockade by CT-011, anti-PD-1 antibody, enhances ex vivo T-cell responses to autologous dendritic cell/myeloma fusion vaccine. *J Immunother*. 2011;34:409-418.

69. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a phase I study of nivolumab(BMS-936558) in patients with relapsed or refractory lymphoid malignancies. Paper presented at: 56th ASH Annual Meeting and Exposition; December 2014; San Francisco, CA.

70. San Miguel J, Mateos M-V, Shah JJ, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Keynote-023. *Blood*. 2015;126:505-505.

71. Rosenblatt J, Avivi I, Vasir B, et al. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic

and clinical responses in multiple myeloma patients. *Clin Cancer Res*. 2013;19:3640-3648.

72. Cavo M, Pantani L, Petrucci MT, et al; GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. 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;120:9-19.

73. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2014;32: 2712-2717.

74. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*. 2008;112:3115-3121.

75. Spencer A PH, Roberts AW, et al. Consolidation therapy with low dose thalidomide and prednisolone prolong survival of multiple myeloma patients undergoing a single autologous stem cell transplantation procedure. *J Clin Oncol*. 2009;27:6.

76. Lokhorst HM, van der Holt B, Zweegman S, et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone and high dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood*. 2010;115: 1113-1120.

77. 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; 121:1517-1523.