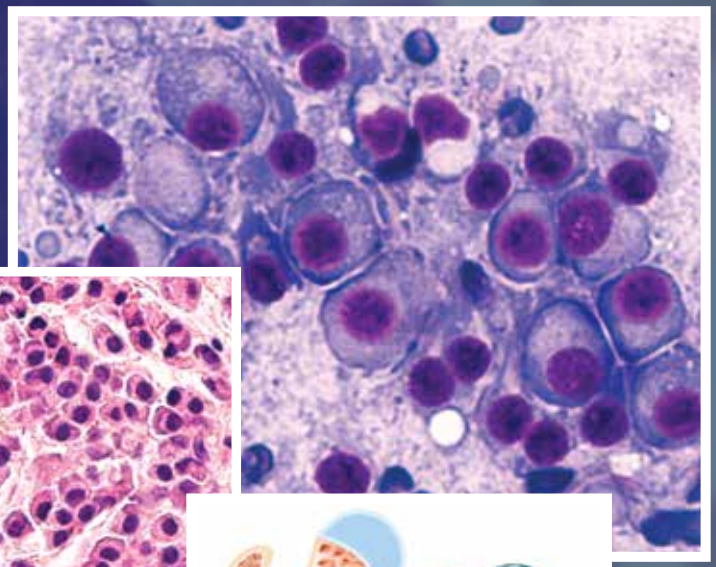
A CME SUPPLEMENT TO FEDERAL PRACTITIONER

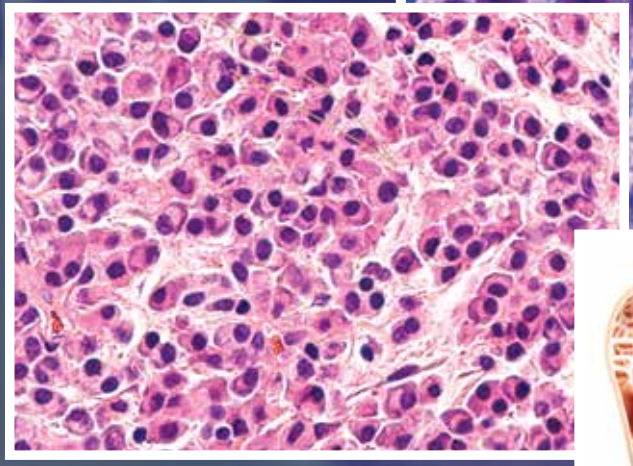
FREE 1.0 CME/CE CREDIT

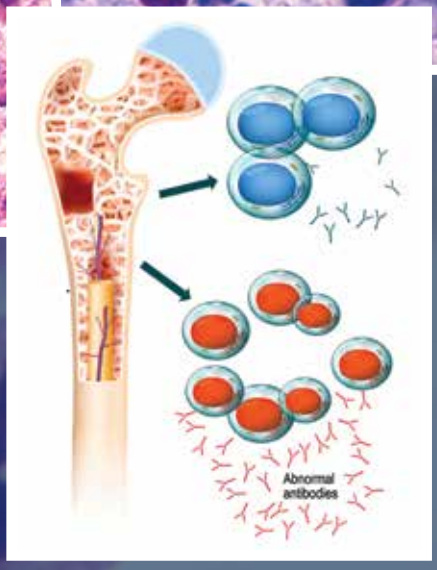
Current Trends in Multiple Myeloma

Customizing Treatment Strategies and Optimizing Outcomes

Thomas R. Chauncey, MD, PhD
Associate Professor of Medicine and Oncology
University of Washington
Associate Member
Fred Hutchinson Cancer Research Center
Director, Marrow Transplant Unit
VA Puget Sound Health Care System
Seattle, WA







This activity is supported by an educational grant from Celgene and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

This activity is supported by an educational grant from Celgene and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC.

This activity is co-provided by Rush University, the Association of VA Hematology/Oncology, Federal Practitioner, and PleXus Communications.

PleXus Communications

Continuing Medical Education (CME/CE) credit is awarded upon completion of the posttest and evaluation. https://www.surveymonkey.com/r/RBTMY3H

ACCREDITATION INFORMATION:
In support of improving patient care, Rush University Medical Center is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

This activity is being presented without bias and with commercial support.

Current Trends in Multiple Myeloma Customizing Treatment Strategies and Optimizing Outcomes is eligible for one (1) ONCC/ILNA recertification points in the following categories: Scientific Basis for Practice; Treatment Modalities.

Rush University Medical Center designates this live activity for a maximum of one (1) AMA PRA Category 1 Credit(s)™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Rush University Medical Center designates this live activity for a maximum of one (1) continuing nursing education credit(s).

Rush University Medical Center designates this live activity for a maximum of one (1) continuing education unit(s) in Pharmacy.

AUDIENCE:
This activity was planned for health care providers who manage and treat patients with multiple myeloma

FACULTY/AUTHOR:
Thomas R. Chauncey, MD, PhD
Associate Professor of Medicine and Oncology
University of Washington
Associate Member
Fred Hutchinson Cancer Research Center
Director, Marrow Transplant Unit
VA Puget Sound Health Care System
Seattle, WA

Michaela R. Ryan, PhD

LEARNING OBJECTIVES:
1. Describe the latest clinical data and predictive measures available for determining risk stratification and personalizing patient management
2. Discuss the unique mechanisms of action of promising novel agents in the treatment of multiple myeloma
3. Develop a personalized treatment approach in the frontline setting considering patient characteristics and risk profile
4. Devise optimal evidence-based strategies for individualized treatment of patients that are relapsed/refractory to initial treatment

DATE OF ORIGINAL RELEASE: September 17, 2018
DATE CREDIT EXPIRES: September 16, 2019

DISCLOSURE INFORMATION:
Dr. Chauncey has disclosed having no financial arrangements or affiliations with any commercial interest(s) whose products or services may be mentioned in this activity:

Michaela Ryan has nothing to disclose

A SUPPLEMENT TO
FEDERAL PRACTITIONER

Current Trends in Multiple Myeloma

Customizing Treatment Strategies and Optimizing Outcomes

Thomas R. Chauncey, MD, PhD
Associate Professor of Medicine and Oncology
University of Washington
Associate Member
Fred Hutchinson Cancer Research Center
Director, Marrow Transplant Unit
VA Puget Sound Health Care System
Seattle, WA

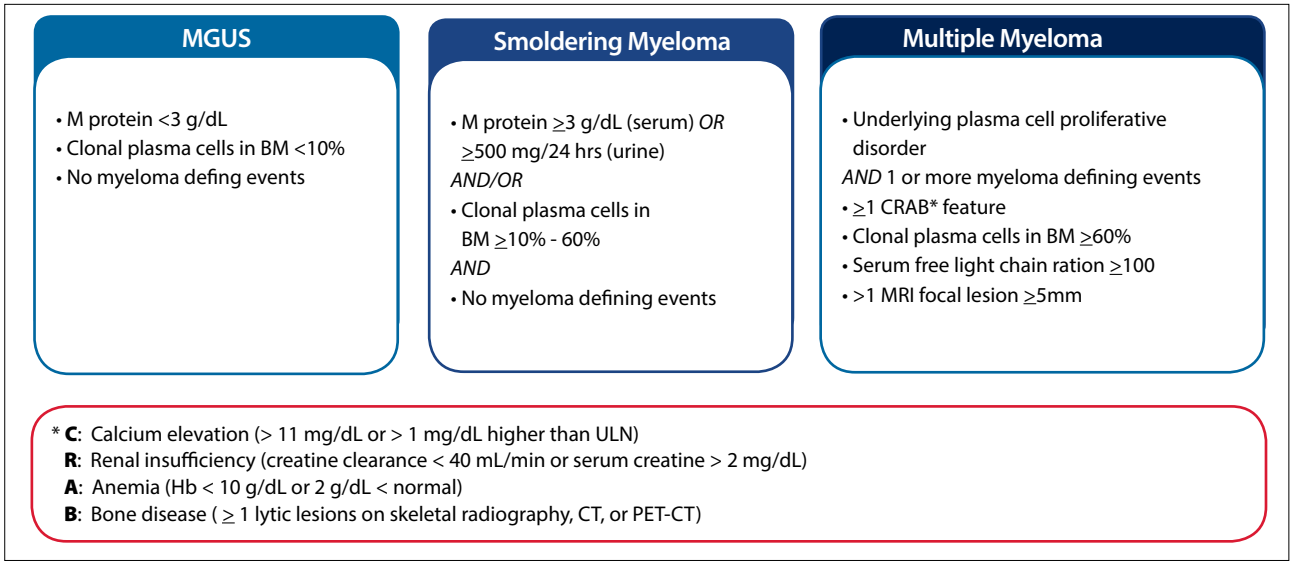
Advances in Diagnosis and Prognosis in Multiple Myeloma

Multiple myeloma (MM) is a hematologic malignancy characterized by malignant plasma cells in the bone marrow (BM) that in turn produce monoclonal immunoglobulin.[1] Ultimately, the process can cause bone damage, anemia, and kidney failure. Approximately 31,000 cases of MM are diagnosed in the United States annually, with the median age of affected individuals close to 70 years of age.[2,3] Recent advances in therapy have greatly improved the prognosis with approximately 50% of patients surviving well in excess of 5 years.[4,5] Disease progression can be relatively slow in many individuals, often involving multiple cycles of response and progression with successive treatments.

Presenting Features

While some patients with MM have no symptoms, many develop painful osteolytic bone lesions, anemia, renal failure, and/or recurrent infections.[6,7] Presenting features include proteinuria (87%), serum M-protein spike (83%), anemia (73%), renal insufficiency (20%), hypercalcemia (13%), and/or neuropathy. Skeletal findings occur in the majority of patients with MM (80%) and these can include bone pain, fractures, and spinal cord compression.

FIGURE 1
Updated IMWG Criteria For Diagnosis[7,8]



Abbreviations: BM, bone marrow; CT, computed tomography, MRI, magnetic resonance imaging; IMWG, International Myeloma Working Group; PET, positron emission tomography; ULN, upper limit of normal.

Diagnostic Evaluation

In the absence of overt presenting features, MM is often diagnosed during routine blood testing or at the time of a pathologic fracture. In 2014, the International Myeloma Working Group (IMWG) guidelines published updated criteria for diagnosing MM.[7] The suggested standard investigative work-up in patients with suspected MM include the following[7,8]:

- **Blood.** Complete blood count with differential; examination of peripheral blood smear; comprehensive metabolic panel (blood urea nitrogen, creatinine, electrolytes, albumin, calcium, serum lactate dehydrogenase [LDH]); beta-2 microglobulin; serum quantitative immunoglobulins), and serum free light chain (FLC)
- **Urine.** 24-hr urine for total protein and creatinine clearance
- **Bone Marrow.** Includes an analysis of unilateral BM aspirate and biopsy, with immunohistochemistry and flow cytometry; metaphase cytogenetics; and plasma cell fluorescence in situ hybridization (FISH) [del 13, del17p13, t(4;14), t(11;14), t(14;16), t(14:20), 1q21 amplifications, 1p abnormality]
- **Imaging.** Though the skeletal survey had been standard for evaluation of MM bone disease, cross sectional imaging with either whole-body low-dose computed tomography (CT), whole-body magnetic resonance imaging (MRI), or whole-body combined fluorine-18-labeled fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is now preferred due to greater sensitivity. The choice among these imaging techniques largely depends on institutional availability, preference, and cost. CT is often preferred due to convenience and cost, while PET is preferred when there is suspicion of extramedullary disease. Those with suspected smoldering MM should have whole body MRI or MRI of the spine and pelvis to confirm the absence of bone lesions, while those with solitary plasmacytoma should have either MRI or PET/CT. For those unable to undergo low-dose whole body CT, MRI, or PET, skeletal surveys can be performed, and should include standard views as well as imaging of any symptomatic areas.

The criteria for distinguishing between monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, and multiple myeloma are summarized in **Figure 1**.[7,8]

TABLE 1
Multiple Myeloma Risk Categories According to Mayo Clinic's mSMART3.0[10-12]

High Risk	Standard Risk

• FISH
  • Del 17p
  • t(4;14)
  • 1q gain
  • t(14;16)
  • t(14;20)
• Revised-ISS Stage 3
• High Plasma Cell S-phase
• GEP: High-risk Signature
	All others including:
	  • Trisomies
	  • t(11;14)
	  • t(6;14)

Abbreviations: FISH, fluorescence in situ hybridization; GEP, gene expression profiling; ISS, International Staging System.

Prognostic Indicators and Risk Stratification

The course of MM can be highly variable, with disease prognosis contingent upon multiple factors including patient-specific factors (age, performance status, co-morbidities) and disease-specific factors (specific genetic characteristics of the malignant plasma cell clone).[8] It is important to note that users of the VA health care system are more likely to have a higher comorbidity burden than the general US population.[9]

TABLE 2
Mutiple Myeloma Staging According to International Staging System and Revised International Staging System[8,15]

Stage	ISS	R-ISS
I	Serum beta-2M <3.5 mg/L *AND* Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH (No high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)]) *AND* Serum LDH ≤ ULN
II	Not ISS stage I or III	Not ISS stage I or III
III	Serum beta-2M ≥5.5 mg/L	ISS stage III *AND EITHER* High-risk chromosomal abnormalities by FISH ([del(17p) and/or t(4;14) and/or t(14;16)]) *OR* Serum LDH > ULN

Abbreviations: CA, chromosomal abnormalities; FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised international staging system; ULN, upper limit of normal.

Following diagnosis, patients should be assessed for standard versus high-risk disease, as this can impact both survival and treatment choice (**Table 1**).[7,10-13] Unfavorable prognostic factors include high-risk cytogenetic abnormalities [del17p, t(4;14), ampl1q, t(14;16), t(14;20)], a high-risk gene expression profile, high serum levels of LDH, a high International Staging System (ISS) stage, presence of extramedullary disease, and presence of circulating plasma cells.[12,14] Patients with high-risk features have significantly reduced overall survival (OS) compared to those with standard-risk features.

Staging: ISS and R-ISS

To assess prognosis, patients should be staged using the Revised International Staging System (R-ISS).[8,15] This system uses 4 features to determine the stage of disease and to define risk: serum albumin, serum beta-2-microglobulin, serum LDH, and specific cytogenetic abnormalities (**Table 2**).[8,15] Patients with R-ISS-stage 1 disease (5-year OS, 82%; 5-year progression-free survival [PFS], 55%) have significantly better anticipated outcomes than patients with R-ISS-stage 3 disease (5-year OS, 40%; 5-year PFS, 24%).[15] Other factors that impact survival include kidney function, age, and concurrent morbidities.

Management of the Newly Diagnosed Patient—Frontline Regimens

MM therapy has seen significant advances over the past 15 years, with a number of new drug approvals over this period. With these successes, MM has been transformed from a disease with few treatment options and a median life expectancy of close to 3 years from diagnosis, to one with many effective therapies used in numerous combinations, often extending median survivals by many years.

In order to optimize patient care, several factors need to be considered when determining an appropriate treatment plan. These include eligibility for transplant, frailty, comorbidities, renal function, steroid tolerance, neuropathy, functional status, oral adherence, convenience of therapy, venous thromboembolism (VTE) risk, financial status, insurance status, and support systems. Supportive care interventions should always be considered (**Table 3**).[8,16]

TABLE 3
Supportive Care Considerations[8,16]

Clinical Manifestation	Considerations/Interventions
Anemia	• Consider erythropoietin for anemic patients (especially those with renal failure) • Type and screen prior to daratumumab

Bone Disease	• All MM patients should receive bisphosphonates (zoledronic acid and pamidronate) or denosumab
	  • Monitor for osteonecrosis of the jaw
	  • Monitor for renal dysfunction with bisphosphonates

Renal Dysfunction	• Avoid NSAIDs • Avoid IV contrast dye (oral contrast dye does not carry the same risk) • Hydration • Monitor for renal dysfunction with chronic bisphosphonate use
Infections	• 15-fold increased risk of infection • Gamma globulin can be administered for recurrent life-threatening infections • Consider Pneumococcal vaccine, influenza vaccine • PJP, herpes, antifungal prophylaxis if high-dose dex • Herpes zoster prophylaxis for patients treated with proteasome inhibitors (ie, bortezomib, carfilzomib, ixazomib) or daratumumab
Coagulation/ Thrombosis	• Recommended full-dose aspirin with IMiDs used in combination induction therapy • Therapeutic anticoagulation for those at high-risk for thrombosis

Abbreviations: dex, dexamethasone; IMiDs immunomodulatory drugs; IV, intravenous; MM, multiple myeloma; NSAID, nonsteroidal anti-inflammatory drug; PJP, pneumocystis jiroveci pneumonia.

TABLE 4

Select Available and Experimental Treatment Options for Multiple Myeloma

Steroids	Conventional Chemo	IMiDs	Proteasome Inhibitors	HDAC inhibitors	Monoclonal antibodies	Novel Mechanisms	Immuno-therapies
Prednisone	Melphalan	Thalidomide	Bortezomib	Panobinostat	Daratumumab (anti-CD38)	Venetoclax	Nivolumab (anti-PDL1) PDL-1/PDL
Dexamethasone	Cyclo-phosphamide	Lenalidomide	Carfilzomib	Ricolinostat	Elotuzumab: (anti CS1/ SLAMF7)	Selinexor	Durvalumab Anti-PDL1)
	Doxil	Pomalidomide	Ixazomib	Citarinostat (ACY 241)	Isatuximab (anti-CD38)	Filanesib	Pembrolizumab (Anti-PD1)
	DCEP/D-PACE	CC-122	Oprozomib	Romidepsin	MOR202 (anti-CD38)		CAR-T
	BCNU	CC-220	Marizomib NPI0052		Denosumab (anti-RANKL)		BiTE
	Bendamustine				Siltuximab (anti-IL6)		Nelfinavir

Abbreviations: BCNU, carmustine, BiTE, bi-specific T-cell engagers; CAR-T, chimeric antigen receptor therapy; DCEP, dexamethasone/cyclophosphamide/etoposide/cisplatin; D-PACE, dexamethasone/cisplatin/doxorubicin/cyclophosphamide/etoposide; IMiDs, immunomodulatory drugs; MM, multiple myeloma; PDL, programmed cell death ligand; SLAM, signaling lymphocyte activation molecule family;

The treatment of patients with MM is complex, with contemporary treatment approaches evolving with the introduction of new therapies and novel classes of drugs (**Table 4**). Therapeutic mechanisms focus on disrupting myeloma—marrow stroma interactions, enhancing the immune response, and specific targeting of clonal myeloma cells. With a significant number of new drug approvals and label-updates in the last 3 to 5 years (ie, carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, and elotuzumab), and multiple new therapies and regimens in the pipeline that include additional proteasome inhibitors (oprozomib, marizomib), histone deacetylase inhibitors (ricolinostat, quisinostat), monoclonal antibodies (isatuximab), immune checkpoint inhibitors (pembrolizumab, nivolumab), Bruton's tyrosine kinase inhibitors (ibrutinib), and small molecule inhibitors (venetoclax, selinexor), the MM treatment landscape is rapidly changing. These novel therapeutic strategies have the potential to substantially affect current treatment and management algorithms (**Figure 2**).[8,17,18]

Smoldering Myeloma

Smoldering multiple myeloma (SMM) is defined as having the paraprotein and/or marrow plasmacytosis criteria necessary for a diagnosis of MM, but without any end-organ CRAB criteria (**Figure 1**).[7,15,20] Though historical series showed that most patients with SMM eventually develop symptomatic MM, the 2014 criteria for diagnosis of myeloma moved an "ultra-high-risk" group of SMM to MM.[7,20] In turn, this reconfigured the demographics for SMM and changed the risks for evolution to MM.

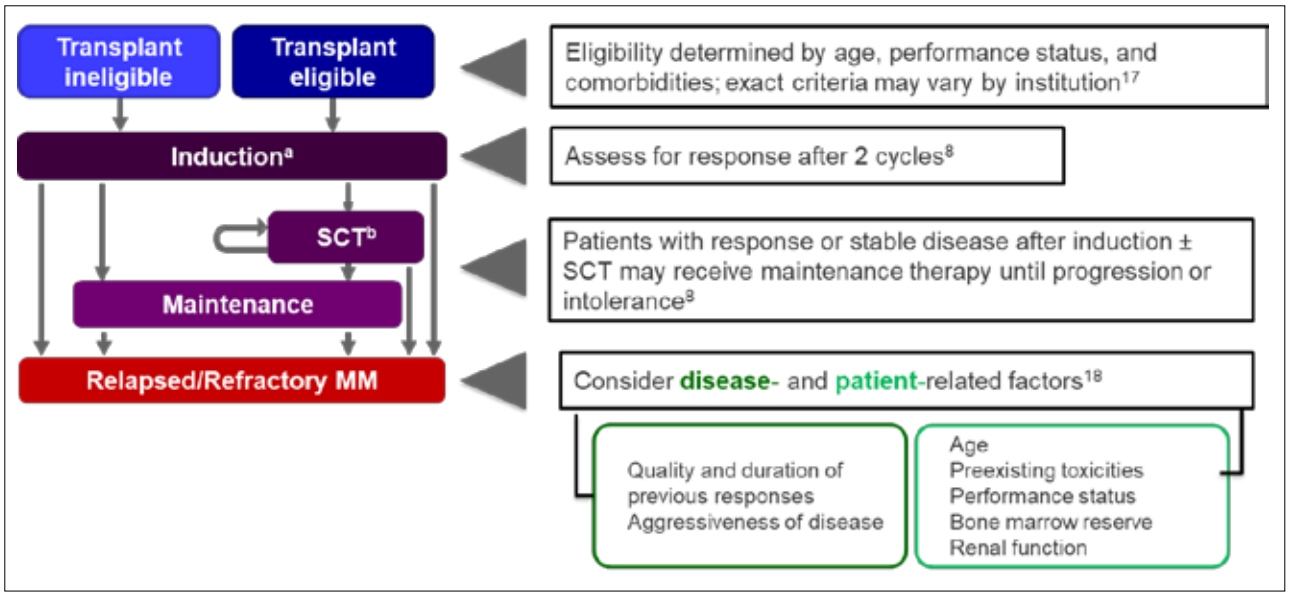
Several studies have examined interventions for SMM to delay progression to MM, and while some have shown that intervention can delay progression and even improve PFS and OS,[19,20] different studies had defined higher risk SMM in different ways. More importantly, the current risk landscape of SMM has now changed. There are current trials underway that look at intervention for SMM with contemporary definitions of SMM,[21] though until those results become available, SMM remains a diagnostic state where expectant monitoring and surveillance is the standard of care. Treatment for smoldering myeloma should only occur within the context of a clinical trial.[8]

Transplant-eligible Newly Diagnosed MM.

Autologous stem cell transplant (ASCT) as part of first line therapy remains the standard of care for patients younger than 65 years with newly diagnosed MM (NDMM), even in the era of novel agents. In transplant-eligible NDMM patients, the standard approach is induction therapy, followed by stem cell harvest and ASCT, often followed by maintenance therapy.[8] Current National Comprehensive Cancer Network (NCCN) recommendations indicate a preference for 3-drug regimens (bortezomib/lenalidomide/dexamethasone, bortezomib/cyclophosphamide/dexamethasone, carfilzomib/lenalidomide/dexamethasone) over 2-drug regimens due to deeper responses (ie, more patients achieving a very good partial response (VGPR) or better).[8] Though less effective, doublet therapy may be better tolerated.

The phase 3 S0777 trial demonstrated that induction with 8 cycles of bortezomib/lenalidomide/dexamethasone (VRd) compared to 6 cycles of lenalidomide/dexamethasone (Rd), followed by maintenance with lenalidomide in both arms, prolonged PFS and OS,[22] in NDMM patients without intent for immediate ASCT. The combination of VRd was generally well tolerated, with both median PFS (43 months *vs* 30 months; stratified hazard

FIGURE 2
Sample Multiple Myeloma Treatment Approach[1,8,17,18]



Abbreviations: MM, multiple myeloma; SCT, stem cell transplant.

ratio [HR], .712) and OS (75 months *vs* 64 months, HR, .709) improved in the VRd group. VRd also showed a higher response rate of 15.7% compared with 8.4% (*P*=.02) for patients in the Rd group. In another study for transplant-ineligible NDMM patients, a modified combination of "VRd-lite" provided patients with an overall response rate (ORR) of partial response (PR) or better of 81.8%.[23]

The phase 3 IFM/DFCI 2009 DETERMINATION trial randomized 700 patients with NDMM to receive induction therapy with 3 cycles of VRd and then consolidation therapy with either 5 additional cycles of VRd (350 patients) or high-dose melphalan plus stem-cell transplantation followed by 2 additional cycles of VRd (350 patients); with both groups of patients receiving lenalidomide maintenance.[24] Response rates (complete response [CR], 59% vs 48%, *P*=.03; ORR, 88% vs 78%), PFS (50 months vs 36 months, adjusted HR for disease progression or death, .65; *P*<.001) and the percentage of patients in whom minimal residual disease (MRD) was not detected (79% vs 65%, *P*<.001) were improved in the transplant arm. Current assessment of OS data was comparable between the groups (4-year OS 81% vs 82%), though this may change as the data continues to mature.

VRd is the current preferred initial therapy for most transplant eligible patients; however, other induction regimens like carfilzomib/lenalidomide/dexamethasone (KRd) show potential for improved efficacy. In a phase 2 study, after 4 cycles of KRd, patients underwent ASCT followed by 4 cycles of lower-dose consolidation; after cycle 8, patients received maintenance KRd for 10 cycles and then single-agent lenalidomide maintenance.[25] At the end of cycle 18, the stringent complete response (sCR) rate was 82% for KRd + ASCT versus 55% in a historical group without ASCT. Other upfront therapies currently under investigation include daratumumab + bortezomib/cyclophosphamide/dexamethasone (CyBorD), durvalumab + Rd,[26] elotuzumab + VRd,[27] KRd versus carfilzomib/cyclophosphamide/dexamethasone (KCd),[28] daratumumab + KRd,[29] and others.

Maintenance Therapy

The goal of maintenance therapy is to extend remission and increase survival, and the most established maintenance option for standard-risk MM is lenalidomide. A meta-analysis of 3 randomized trials (US CALGB 100104 [Alliance], French IFM 2005-02, and Italian GIMEMA-RVMM-PI-209) found that after a median follow-up of 80 months, lenalidomide maintenance decreased risk of death by 23%, with an estimated improvement in OS of 2.5 years (median OS, not evaluable (NE) vs 86; HR, .74; 95% CI, .62-.89; *P*=.001).[30] It should be noted that the risk of developing a second primary malignancy (SPM) post-AHCT was higher in the lenalidomide group (HR, 2.03; 95% CI 1.14-3.61); however, the magnitude of the PFS and OS benefit should be considered when considering these risks. As a result of data from these maintenance trials, the US Food and Drug Administration (FDA) expanded the approved indications for lenalidomide to include maintenance following ASCT.

Bortezomib maintenance therapy may prove more beneficial for those patients with high-risk MM.[31] Though the randomized phase 3 HOVON-65/GMMG-HD4 trial used regimens now only of historical relevance as induction before high-dose melphalan and ASCT, maintenance consisted of thalidomide daily or bortezomib once every 2 weeks for 2 years. The study found that in high-risk patients (increased creatinine more than 2 mg/dL or deletion 17p13), bortezomib significantly improved PFS and OS. Limited data on VRd maintenance after ASCT suggests that this approach may also be efficacious for patients with high-risk MM.[32] A summary of lenalidomide and bortezomib maintenance trials is shown in **Table 5**.[31-36]

TABLE 5
Select Lenalidomide and Bortezomib Maintenance Trials for Newly Diagnosed Multiple Myeloma

Trial	Comparison Arms	Duration	Median Follow-up (months)	PFS (months)	OS
Lenalidomide					
IFM 2005-02[33]	LEN vs PBO	Median of 32 mos	45	41 vs 24 (*P*<.001)	82% vs 81% (*P*=.7)
CALGB-100104[34]	LEN vs PBO	Until progression	48	50 vs 27 (*P*<.001)	NR vs 73% (*P*<.008)
RV-MM-PI-209[35]	LEN vs No maintenance	Until progression	51	42 vs 22 (*P*<.001)	3 years 88% vs 79% (*P*=.14)
Bortezomib					
HOVON 65 MM/ GMMG-HD4[31]	BTZ vs THAL mx	2 yrs	74	36 vs 27 (*P*=.001)	NR vs 84 mos (*P*=.049)
				Pts w/creatinine > 2 mg/dL 30 vs 13 (*P*=.04)	54 vs 21 mos (*P* <.001)
				Pts w/deletion 17p13 22 vs 12 (*P* = .01)	NR vs 24 mos (*P* = .03)
PETHEMA/GEM[36]	VT vs THAL vs Interferon-a	3 yrs	34.9	2 years 78% vs 63% vs 49% (*P*=.01)	NS
VRd Combnation[32]	VRd			32	3-yr OS: 93%

Abbreviations: BTZ, bortezomib; LEN, lenalidomide; NR, not reported; NS, not significant; OS, overall survival; PBO, placebo; PFS, progression-free survival; THAL, thalidomide/dexamethasone; VRd, lenalidomide/bortezomib/dexamethasone; VT bortezomib/thalidomide/dexamethasone.

A number of newer agents and combination regimens are currently under investigation with the goal of further improving post-transplant maintenance therapy.[37] These include the oral second-generation proteasome inhibitor ixazomib; the next-generation irreversible proteasome inhibitor carfilzomib; the monoclonal antibodies elotuzumab and daratumumab; and the histone deacetylase inhibitors vorinostat and panobinostat.

Transplant-Ineligible NDMM

For NDMM patients who are transplant ineligible, NCCN guidelines preferred primary regimens are bortezomib/lenalidomide/dexamethasone, lenalidomide/lowdexamethasone, or bortezomib/cyclophosphamide/dexamethasone.[8]

Similar to the transplant-eligible NDMM patients, ongoing clinical trials are focusing on combination therapies using some of the newer agents (ie, lenalidomide/dexamethasone +/- daratumumab, elotuzumab, ibrutinib, or ixazomib, as well as carfilzomib-based combinations). Recent results from the phase 3 ACYCLONE trial of bortezomib/melphalan/prednisone (VMP) +/- daratumumab (D-VMP) in transplant-ineligible NDMM patients reported that after a median follow-up of 16.5 months, D-VMP reduced the risk of progression or death by 50% compared with VMP alone (PFS at 18 months, 71.6% vs 50.2%; HR, .50; 95% CI, .38-.65; P<.001) across all subgroups.[38,39] In addition, D-VMP induced significantly deeper responses, including a greater than 3-fold higher minimum residual disease (MRD)-negativity rate than VMP. With the positive results from this study, in May 2018 the FDA approved D-VMP for the treatment of patients with NDMM who are ineligible for ASCT.

Assessing treatment response with MRD

Assessment of MRD as depth of response has emerged as an important prognostic target. In several large trials[40,41] and pooled analyses,[42,43] MRD-negative status (below 10-5 to 10-6 thresholds) was strongly associated with prolonged PFS and OS. Based on new criteria from the IMWG, NCCN guidelines now contain criteria for determining MRD negativity based on next-generation flow cytometry (NGF), next-generation sequencing (NGS) on BM aspirate, and imaging. For sustained MRD-negative response, there must be MRD-negativity in the marrow (assessed by NGS, NGF, or both) and by imaging, confirmed by a minimum of 1 year apart.[8] Clinical trials are in progress to determine how these techniques can be best incorporated in MM management algorithms and to further individualize and fine-tune treatment. In the future, MRD status may be used as a predictive indicator for assessing treatment decisions, including the timing and duration of treatment.[44]

Treatment Advances and Current Management Strategies for Relapsed/Refractory Patients

Despite significant improvements in survival, MM is typically not curable and most patients eventually relapse. Patients who experience early progression generally have poorer outcomes.[44] Recurrence can be "primary refractory" (patients who have never achieved a minimal response [MR] or better); "double-refractory" (refractory to both proteasome inhibitors and immunomodulatory drugs [IMiDs]); and/or "relapsed and refractory" (relapse after achieving at least MR, which then becomes nonresponsive while on salvage therapy or progresses within 60 days of last treatment).

According to IMWG guidelines,[49] treatment is indicated if the patient experiences clinical relapse (the appearance

or reappearance of one or more CRAB criteria [**Figure 1**]) as well as >50% increase in size of plasmacytomas and/or or paraprotein relapse (doubling of the M-protein in 2 consecutive measurements separated by ≤2 months; or an increase in the absolute levels of serum M-protein by ≥10 g/L, or urine M-protein increase by ≥500 mg/24 h, or increase of the involved FLC level by ≥200 mg/L [plus an abnormal FLC ratio] in two consecutive measurements separated by ≤ 2 months).[49]

The choice of therapy at relapse depends on disease, patient, and treatment-related considerations. Disease-related considerations include rapid increase in tumor burden, extramedullary disease, cytogenetic risk, high LDH levels, high-risk gene expression profiling, presentation as plasma cell leukemia, and whether there is clinical or paraprotein criteria for relapse. Patient factors include performance status, age, frailty, comorbidities, patient preference, cost, and convenience. Treatment-related considerations include previous stem-cell transplant, type of prior therapy, depth/duration of response to those agents, time since prior treatment, previous tolerability, availability of new treatment options, and clinical trial availability.[48,50]

Selection of treatment for relapsed/refractory MM (RRMM) can be challenging, since the last 3 to 5 years have seen a significant number of approvals of new agents (**Table 4**) and combinations (**Table 6,** previous page).[51-61] At the time of relapse, treatment approaches include doublet or triplet regimens using combinations of novel therapies until development of progressive disease, or participation in clinical trials. Patients not previously treated with a novel agent should be treated with a proteasome inhibitor-based regimen, or an IMiD-based regimen, or a combination of both.[8] If not refractory, retreatment with a prior regimen that had efficacy and tolerability is feasible.[18] Salvage HDT-ASCT can be an option in select transplant-eligible patients.[61-63] Those with IMiD-refractory disease should preferably be treated with a proteasome inhibitor-containing regimen at relapse, and patients with proteasome inhibitor-refractory disease should be treated with an IMiD-containing regimen. Those refractory to both IMiD and proteasome-inhibitor therapy have a very poor event-free survival and OS (5 and 13 months, respectively),[1,64] and clinical trials should be considered.

Recent phase 3 trials with triplet combinations have demonstrated superior response rates and prolonged disease control when compared to doublet regimens for both standard and high-risk patients. Survival and response data from lenalidomide-based triplets are shown in **Table 7** and bortezomib-based triplets are shown in **Table 8**.[51-60] It should be noted that these trials did not include frail patients or those with end-stage renal disease. As such, the benefit of triplet therapy in those patients is less clear and doublet therapies may be preferred in frail, elderly, or physiologically impaired RRMM patients.

TABLE 6
Recent FDA Approved Agents/Combinations for Relapsed/Refractory Multiple Myeloma

Treatment	Number of Lines of Prior Therapy
Daratumumab + either lenalidomide or bortezomib + dex (POLLUX[55] & CASTOR[56,57] trials)	≥1
Ixazomib + lenalidomide + dexamethasone (TOURMALINE-MM1 trial[53])	≥1
Carfilzomib + lenalidomide + dexamethasone (ASPIRE trial[51])	1-3
Carfilzomib (56) mg/m^2, dexamethasone (ENDEAVOR trial[60])	1-3
Elotuzumab + lenalidomide + dexamethasone (ELOQUENT 2 trial[52])	1-3
Pomalidomide + dexamethasone	≥2
Panobinostat + bortezomib + dexamethasone (PANORAMA-1[54])	≥2
Daratumumab + pomalidomide + dexamethasone[58]	≥2
Daratumumab monotherapy (SIRIUS trial[60])	≥3

Abbreviations: FDA, US Food and Drug Administration.

TABLE 7
Lenalidomide-based Regimens for Relapsed/Refractory Multiple Myeloma

Trial	Regimen	PFS (mon)	ORR (%)	VGPR (%)	PFS (HR, 95% CI)	OS (HR, 95% CI)
ASPIRE[51] N=792	Rd + carfilzomib	26.3	87.1	69.9	.69 (.57-.83) *P*=.0001	.79 (.63-.99) *P*=.04
	Rd	17.6	66.7	40.4		
ELOQUENT-2[52] N=646	Rd + elotuzumab	19.4	79	33	.70 (.57-.85) *P*<.01	.78 (.63-.96)
	Rd	14.9	66	28		
TOURMALINE MM-1[53] N=722	Rd + ixazomib	20.6	78.3	48.1	.74 (.59-.74) *P*=.01	NR
	Rd	14.7	71.5	39		
POLLUX[55] N=569	Rd + daratumumab	NR	93	75.8	.37 (.28-.50) *P*<.0001	.63 (.42-.95)
	Rd	18.4	76	44.2		

Abbreviations: HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide/dexamethasone; VGPR, very good partial response.

TABLE 8
Bortezomib-based Regimens for Relapsed/Refractory Multiple Myeloma

Trial	Regimen	PFS (mon)	ORR (%)	VGPR (%)	PFS (HR, 95% CI)	OS (HR, 95% CI)
PANORAMA[54] N=768	Vd + panobinostat	11.99	60.7	28	.63 (.52-.76) *P*<.0001	.87 (.69-1.10) *P*=.26
	Vd	8.08	54.6	16		
ENDEAVOR[55] N=929	Vd + carfilzomib	18.7	76.7	54	.53 (.44-.65) *P*<.0001	.79 (.58-1.08) *P*=.06
	Vd	9.4	62.3	29		
CASTOR[56,57] N=498	Vd + daratumumab	16.7	84	62	.31 (.24-.39) *P*<.0001	.63 (.42-.96)
	Vd	7.1	63	29		

Abbreviations: HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Vd, bortezomib/dexamethasone; VGPR, very good partial response.

TABLE 9
Summary of Adverse Events Associated with Newer Agents[8]

Agent	Major Adverse Events
Pomalidomide	• Most common grade 3/4 toxicities being hematologic (neutropenia, anemia, and pancytopenia) • Thromboembolic events similar to other IMiDs
Carfilzomib	• Most common AE (any grade) – fatigue, nausea, anemia, thrombocytopenia, PN rare (mostly grade 1-2) • Cardiac failure in 7% of patients; dyspnea 35% (5% grade 3)
Panobinostat	• In combination with bortezomib, major AEs are diarrhea (68%, grade 3/4 25%) and asthenia/fatigue (57%, grade 3/4 24%) • 12% arrhythmias (black box warning) – avoid QT prolonging meds
Ixazomib	• Most significant AEs – neutropenia, thrombocytopenia, rash • No significant worsening of PN
Elotuzumab	• Infusion reactions (pyrexia, chills, HTN) 10%, most grade 1/2 • Little additive toxicity to len or bortezomib
Daratumumab	• Infusion reactions (cough, dyspnea, bronchospasm, vomiting) in 45% (5% grade 3); >90% during first infusion • ↑Grade 3/4 hem toxicity

Abbreviations: AE, adverse event; HTN, hypertension; IMiDs, immunomodulatory drugs; PN, peripheral neuropathy.
NCCN. Clinical Practice Guidelines in Oncology: Multiple Myeloma. (NCCN Guidelines®) Version 4.2018.

TABLE 10
Promising Agents in Clinical Trials for Multiple Myeloma

Agent	MoA	Phase in Development
Pembrolizumab	PD-1 antibody	III
Ibrutinib	Tyrosine kinase inhibitor	III
Oprozomib	Proteasome inhibitor	III
Selinexor	XPO1 inhibitor	III
Isatuximab	CD38 antibody	III
Venetoclax	Selective BCL-2 inhibitor	III
Filanesib	Kinesin spindle protein inhibitor	II
MOR202	CD38 antibody	I/II
Indatuximab ravtansine	CD138 antibody–drug conjugate	I/II
Ricolinostat	HDAC inhibitor	I/II
Durvalumab	PD-L1 antibody	I/II

Abbreviations: BCL-2, B-cell lymphoma 2; HDAC, histone deacetylase; PD-1, programmed cell death protein 1; PD-L1, Programmed death-ligand 1; XPO1, exporter protein exportin 1.

In the absence of direct comparisons between all available treatment options for RRMM, the relative value of each new treatment can be difficult to assess. Two recently published meta-analyses have attempted to determine the relative value of available treatment options for RRMM. In a one study, 17 randomized controlled phase 3 trials including 18 treatment options were analyzed.[65] The authors of the study concluded that the combination of daratumumab/lenalidomide/dexamethasone (Dara-Rd) had the most favorable hazard ratio for PFS (.13; 95% CI, .09 - .19). Dara-Rd reduced the risk of progression or death by 87% versus dexamethasone, 81% versus bortezomib plus dexamethasone, and 63% versus lenalidomide plus dexamethasone. According to this meta-analysis, the next

best treatment options were triplet regimens that included KRd, elotuzumab/lenalidomide/dexamethasone (Elo-Rd), daratumumab/bortezomib/dexamethasone (Dara-Vd), and ixazomib/lenalidomide/dexamethasone. Another meta-analysis of 27 randomized-controlled trials determined the relative efficacy of Dara-Rd and Dara-Vd versus other RRMM therapies.[66] Dara-Rd and Dara-Vd had a higher probability of success (probability, .997 and .999, respectively) with the lowest risk of progression or death compared with other approved treatments. There was also significant benefit observed when daratumumab was used after first relapse. While these meta-analyses can be informative, individual studies should be considered within the context of the unique populations being evaluated in each study.

In addition to efficacy, it is important to consider potential toxicities and adverse events associated with newer MM drugs and combinations. For example, bortezomib and thalidomide should be discouraged or used with caution in those patients with a history of neuropathy. There should be close monitoring when using carfilzomib in the presence of cardiomyopathy, daratumumab in the presence of COPD, and IMiDs in patients with a history or increased risk of deep vein thrombosis (DVT)/pulmonary embolism (PE). **Table 9** (previous page) summarizes the toxicities associated with newer MM therapies.[8]

Future Treatment Directions

Though MM remains a largely incurable disease, survival has been continuously improving. Numerous recently approved and emerging pipeline therapies along with combinations of newer agents with established regimens, all set the stage for continued improvement in long-term outcomes. Newer strategies likely to have a therapeutic presence in MM include CAR-T therapy, immune checkpoint inhibitors, as well as novel small molecule targeting agents (**Table 10,** previous page). Outstanding challenges include determining the optimal timing and combinations based on an individual's clinical characteristics and biological profile.

References

1. Kumar, SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia*. 2012;26(1):149-157.
2. American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018.
3. Zullig LL, Sims KJ, McNeil R, et al. Cancer incidence among patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Military Medicine*. 2017;182:e1883–e1891.
4. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111:2516-2520.
5. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;28(5):1122-1128.
6. Roodman GD. Pathogenesis of myeloma bone disease. *Leukemia*. 2009;23(3):435–441.
7. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
8. National Comprehensive Care Network. Clinical Practice Guidelines in Oncology: Multiple Myeloma. (Version 4.2018) https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed June 7, 2018.
9. Agha Z, Lofgren RP, VanRuiswyk JV, et al. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. *Arch Intern Med*. 2000;160(21): 3252–3257.
10. mSMART. Stratification for Myeloma and Risk-adapted Therapy. Available at https://www.msmart.org/home.html. Accessed July 25, 2018.
11. Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc*. 2009;84(12):1095-1110.
12. Mikhael JR, Dingli D, Roy V, et al. 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(4):360-376.
13. Chng WJ, Dispenzieri A, Chim CS , et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;28(2):269-277.
14. Moreau P, Cavo M, Sonneveld P, et al. Combination of international scoring system 3, high lactate dehydrogenase, and t(4;14) and/or del(17p) identifies patients with multiple myeloma (MM) treated with front-line autologous stem-cell transplantation at high risk of early MM progression-related death. *J Clin Oncol*. 2014;32(20):2173–2180.
15. 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.
16. International Myeloma Foundation. Supportive Care: Myeloma.org. Available at: https://www.myeloma.org/understanding/10-steps/supportive-care. Accessed July 25, 2018.
17. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011; 364(11):1046-1060.
18. Mohty B, El-Cheikh J, Yakoub-Agha I, Avet-Loiseau H, Moreau P, Mohty M. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequencing and 'retreatment' approaches in the era of novel agents. *Leukemia*. 2012;26(1):73-85.
19. Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk shouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2016;17(8):1127-36.
20. Rajkumar SV, Landgren O, Mateos MV, et al. Smoldering multiple myeloma. *Blood*. 2015;125(20):3069-3075.
21. Zonder JA. The difficult business of assessing new therapies for smouldering multiple myeloma [published online ahead of print May 16, 2018]. *Br J Haematol*. 2018.16.
22. Durie BG, Hoering A2, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527.
23. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase II study of modified lenalidomide, bortezomib, and dexamethasone (RVD-lite) for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2014;124:3454.
24. 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.
25. Zimmerman T, Raje NS, Vij R, et al. Final results of a phase 2 trial of extended treatment (tx) with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (KRd) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). *Blood*. 2016;128(22):675.
26. Lonial S, Oriol A, Mateos MV, et al. A phase 1/2 study of durvalumab (DURVA) in combination with lenalidomide (LEN) with or without dexamethasone (DEX) in patients (pts) with newly diagnosed multiple myeloma (NDMM). *J Clin Oncol*. 2017;35(15_suppl):doi: 10.1200/JCO.2017.35.15_suppl.TPS8055.
27. Laubach J, Nooka AK, Cole C, O'Donnell E, Vij R, Usmani SZ. An open-label, single arm, phase IIa study of bortezomib, lenalidomide, dexamethasone, and elotuzumab in newly diagnosed multiple myeloma. *J Clin Oncol*. 2017;35(15_suppl): 8002.
28. 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*. 2017;35(15_suppl):8003.
29. Jakubowiak A, Chari A, Lonial S, et al. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients (pts) with newly diagnosed multiple myeloma (MMY1001): an

open-label, phase 1b study. *J Clin Oncol.* 2017; 35(15_suppl):8000-8000.
30. 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.
31. 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. *J Clin Oncol.* 2012;30(24):2946-2955.
32. 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.
33. 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.
34. 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.
35. 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.
36. Rosiñol L, Oriol A, Teruel AI,et al; Programa para el studio y la Terapéutica de las Hemopatías Malignas/Grupo Español de Mieloma (PETHEMA/GEM) group . 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.
37. Sengsayadeth S, Malard F, Savani BN, Garderet L, Mohty M. Posttransplant maintenance therapy in multiple myeloma: the changing landscape. *Blood Cancer Journal.* 2017;7(3):e545.
38. Mateos MV, Meletios AD, Cavo M, et al. LBA-4: Phase III ALCYONE clinical trial: daratumumab plus bortezomib, melphalan, and prednisone (D-VMP) in NDMM patients ineligible for transplant. Presented at 59th ASH Annual Meeting and Exposition; December 9-12, 2017;Atlanta, Georgia.
39. Mateo MV, Meletios AD, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated mMyeloma. *N Engl J Med.* 2018;378:518-528
40. Avet-Loiseau H, Lauwers-Cances V, Corre J, et al. Minimal residual disease in multiple myeloma: final analysis of the IFM2009 Trial. *Blood.* 2017;130(Suppl 1):435.
41. 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
42. Lahuerta JJ, Paiva B, Vidriales MB, et al. Depth of response in multiple myeloma: a pooled analysis of three PETHEMA/GEM Clinical Trials. *J Clin Oncol.* 2017;35(25):2900-2910.
43. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: a meta-analysis. *JAMA Oncol.* 2017;3(1):28-35.
44. Anderson KC, Auclair D, Kelloff GJ, et al. The role of minimal residual disease testing in myeloma treatment selection and drug development: current value and future applications. *Clin Cancer Res.* 2017;23(15);3980-3993.
45. Majithia N, Rajkumar SV, Lacy MQ, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. *Leukemia.* 2016;30(11):2208-2213.
46. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia.* 2006;20(9):1467-1473.
47. Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson P; ASH/FDA Panel on Clinical Endpoints in Multiple Myeloma. Clinically relevant end points and new drug approvals for myeloma. *Leukemia.* 2008;22(2):231-239.
48. Nijhof IS, van de Donk NWCJ, Zweegman S, Lokhorst HM. Current and new therapeutic strategies for relapsed and refractory multiple myeloma: an update. *Drugs.* 2018;78(1):19-37.
49. 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.
50. Ludwig H, Sonneveld P, Davies F, et al. European perspective on multiple myeloma treatment strategies in 2014. *Oncologist.* 2014;19(8):829-844.
51. Stewart K, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2015;372(2):142-152.
52. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373(7):621-631.
53. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med.* 2016; 374(17):1621-1634.
54. San-Miguel, Hungria VT, Yoon SS, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. *Lancet Haematol.* 2016;3(11):e506-e515.
55. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med.* 2016;375(14):1319-1331.
56. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med.* 2016;375(8):754-766.
57. Lentzsch S, Weisel KC, Mateos MV, et al. Daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): efficacy and safety update (CASTOR). *J Clin Oncol.* 2017;35(15 suppl):8036-8036.
58. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood.* 2017;130(8):974-981.
59. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol.* 2016;17(1):27-38.
60. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet.* 2016; 387(10027):1551-1560.
61. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia.* 2016;30(5):1005-1017.
62. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol.* 2016;3(7):e340–e351.
63. Giralt S, Garderet L, Durie B, et al. American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma. *Biol Blood Marrow Transpl.* 2015;21(12):2039-2051.
64. Weinhold N, Ashby C, Rasche L, et al. Clonal selection and double-hit events involving tumor suppressor genes underlie relapse in myeloma. *Blood.* 2016;128(13):1735-1744.
65. van Beurden-Tan CHY, Franken MG, Blommestein HM, Uyl-de Groot CA, Sonneveld P. Systematic Literature Review and Network Meta-Analysis of Treatment Outcomes in Relapsed and/or Refractory Multiple Myeloma. *J Clin Oncol.* 2017;35(12):1312-1319.
66. Maiese EM, Ainsworth C, Le Moine JG, Ahdesmäki O, Bell J, Hawe E. Comparative efficacy of treatments for previously treated multiple myeloma: a systematic literature review and network meta-analysis. *Clin Ther.* 2018;40(3):480-494.e23.