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The Myeloma Landscape in 2008

Highlights From the American Society of Hematology 2007 Annual Meeting
Atlanta, Georgia
December 8–11, 2007

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This CME-certified enduring activity is based on information presented at a satellite symposium held on December 8–11, 2007, in Atlanta, Georgia, during the American Society of Hematology (ASH) 49th Annual Meeting.

Activity Overview

The pace of change in myeloma is unprecedented. A review of clinical trials on ClinicalTrials.gov showed over 600 clinical trials in myeloma, of which more than half are actively recruiting. Many of these trials include investigational agents that are not commercially available, but a large number of trials include commercially available agents used in new combinations. Indeed, as the number of approved agents increases, the primary question will be how these agents work together to provide better efficacy and safety. Over the last several years, new strategies including novel agents combined with traditional chemotherapies have showed promising activity in numerous phase II trials, providing a rationale for phase III evaluation.

Educational Needs

Novel agents, often combined with traditional agents, have shown response rates approaching that of transplantation. Although myeloma is still considered incurable, the greater depth of response and longer time to progression, along with a growing array of options for second- and third-line therapy, has caused a re-evaluation of treatment strategies.

Key questions for the treating oncologist in 2008:

1. What are the key measures of efficacy?
2. What is the efficacy and safety profile of these agents?
3. What patient factors (eg, age, renal status, risk factors, comorbidities) affect choice of therapy?
4. Do new combinations result in significant adverse effects not seen with either agent used alone?
5. How do these new combinations affect stem-cell collection?
6. Do new and more potent combinations affect the timing or indications of transplantation?
7. What is the efficacy of these regimens in special populations (eg, the elderly; patients with a history of prior transplantation; patients with risk factors, such as elevated ß2-microglobulin; unfavorable cytogenetics; or impaired renal function)?

Target Audience

This activity has been designed to meet the educational needs of hematologic oncologists.

Learning Objectives

Upon completion of this activity, participants should be able to:

- List phase III trials reported at ASH in newly diagnosed and relapsed/refractory myeloma, and in transplantation
- List the arms of these trials and state primary endpoints
- State primary efficacy findings from these trials
- Describe adverse effects of therapies described in these trials

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There are no fees for participating in this CME activity. To receive credit during the period February 2008 to February 31, 2009, participants must (1) read the learning objectives and disclosure statements, (2) study the educational activity, (3) complete the post-test, and (4) complete the activity evaluation form, including the certificate information section.

To obtain a certificate, you must receive a score of 70% or better on the post-test. The post-test can be accessed at the end of the activity. Please e-mail any questions to: cmeinfo@curatiocme.com.

Medium

The Supplement was selected as the instructional format to accommodate the learning preferences of a significant portion of the target audience.

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Generic Name	Trade Name	Approved Use	Unapproved/ Investigational Use
Bortezomib	Velcade®	Multiple myeloma (MM) patients who have received at least 1 prior therapy	Front-line therapy in combination with melphalan-prednisone, with cyclophosphamide, with thalidomide-dexamethasone, or with lenalidomide-dexamethasone
Lenalidomide	Revlimid®	In combination with dexamethasone in MM patients who have received at least 1 prior therapy	Frontline therapy in combination with dexamethasone or with bortezomib-dexamethasone
Thalidomide	Thalomid®	Frontline therapy in combination with dexamethasone	Frontline therapy in combination with bortezomib

Abbreviations List

ASH (American Society of Hematology)
BCD (bortezomib, cyclophosphamide, dexamethasone)
BTD (bortezomib, thalidomide, dexamethasone)
CI (confidence interval)
CR (complete response)
DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin)
DVT (deep vein thrombosis)
ECOG (Eastern Cooperative Oncology Group
FISH (fluorescence in situ hybridization)
HDAC (histone deacetylase)
ITT (intent to treat)
LCD (lenalidomide, cyclophosphamide, dexamethasone)
LD (lenalidomide and high-dose dexamethasone)
Ld (lenalidomide and low-dose dexamethasone)
MP (melphalan, prednisone)
MR (minor response)
MTD (maximum tolerated dose)
nCR (near CR)
ORR (objective response rate)
OS (overall survival)
PD (progressive disease)
PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatía Maligna)
PFS (progression-free survival)
PR (partial response)
RIC-allo (reduced-intensity conditioning allogeneic transplant)
RR (response rate)
RVD (lenalidomide-bortezomib [Velcade]-dexamethasone)
SD (stable disease)
SWOG (Southwest Oncology Group)
TD (thalidomide, dexamethasone)
TNT (time to next treatment)
TTP (time to progression)
VAD (vincristine, doxorubicin [Adriamycin], dexamethasone)
VD (bortezomib [Velcade], dexamethasone)
VGPR (very good partial response)
VMP (bortezomib [Velcade], melphalan, prednisone)
VTD (bortezomib [Velcade], thalidomide, dexamethasone)

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Recent data at the ASH annual meeting, held in Atlanta, Georgia, in December of 2007, will likely have significant impact on the myeloma landscape in 2008. The most important changes will occur as a result of several large randomized phase III trials that provide guidance on new and better options for the frontline setting. Some of the key findings from these studies in the frontline setting include:

- The use of bortezomib as part of a pretransplant regimen can be considered as a potential new standard
- Results from the VISTA study support bortezomib + MP becoming an important new therapeutic option in the upfront treatment of nontransplant candidates
- A SWOG trial demonstrated lenalidomide plus high-dose dexamethasone was significantly superior in RR and PFS to high-dose dexamethasone, and therefore lenalidomide-based therapy can also be considered an important new option in newly diagnosed patients with myeloma
- An ECOG trial demonstrated that lenalidomide plus low-dose dexamethasone is better tolerated with superior OS but lower RRs than lenalidomide plus high-dose dexamethasone
- Combination strategies augmenting the RR of lenalidomide plus low-dose dexamethasone-based combinations should be explored
- Early clinical trials of bortezomib, lenalidomide, plus low-dose dexamethasone as an example of such an approach show promising activity and encouraging tolerability.

This supplement provides a brief overview of these studies, as well as some highlights from other notable studies in both the transplant and the relapsed/refractory settings.

Frontline Therapy

Nontransplant Regimens

San Miguel (VISTA Trial) Dr. Jesus San Miguel and colleagues[1] reported the VISTA trial. In this phase III trial, 682 newly diagnosed elderly patients were randomized to VMP (n=344) or MP (n=338). The trial was halted early because VMP showed a statistically significant benefit in the TTP (the primary endpoint) and all secondary endpoints (Table 1).

The overall CR (immunofixation negative) rate by M protein was 35% for VMP and 5% for MP

Table 1. VMP versus MP in Patients Ineligible for Transplant[1]

Endpoint	Hazard Ratio (95% CI)*	*P* Value
TTP	0.540 (0.417–0.699)	.000002
PFS	0.609 (0.486–0.763)	.00001
OS	0.607 (0.419–0.880)	.00782
TNT	0.522 (0.390–0.699)	.000009
	Odds Ratio (95% CI)*	
CR	11.2 (6.1–20.6)	<.000001

* All endpoints favor VMP.

(*P*<.000001). VMP was superior to MP regardless of age, renal status, or cytogenetics (t[4;14], t[14;16], 17p deletion). The median TNT, defined as the interval between the start of the study therapy (VMP or MP) and the start of next therapy, has not been reached in the VMP arm; TNT in the MP arm was 20.8 months (*P*=.000009).

VMP had higher rates of grade 3 gastrointestinal toxicities (19% vs 5%), peripheral neuropathy (13% vs 0%), and fatigue (7% vs 2%). Peripheral neuropathy resolved or improved in 75% of cases in a median of 64 days. Grade 4 nonhematologic toxicities were rare in both groups, and treatment-related mortality was low, at 1% in the VMP arm and 2% in the MP arm.

The median age of this population was 71 years. Approximately one third were 75 years or older, had stage III disease, or had a ß2-microglobulin level greater than 5.5 mg/L.

Hulin and Waage: MPT versus MP in the Elderly Dr. Cyrille Hulin and colleagues[2] updated previously reported data (IFM 01/01) showing MPT to be superior to MP in patients 75 years of age or older. Despite a higher rate of withdrawal due to toxicity, MPT was superior to MP in terms of OS, TTP, PFS, and RR. Dr. Anders Waage and colleagues,[3] however, reported a phase III trial conducted by a Nordic study group showing MPT was equivalent to MP in elderly patients in terms of OS. This finding was surprising, as three trials have shown robust superiority of MPT over MP in patients older than 65 years[4,5] and in those older than 75 years.[6] Given that there are three positive studies for MPT, the Waage study likely will not challenge MPT's standing as a standard regimen for newly diagnosed patients who are not eligible for transplant but does suggest that higher doses of thalidomide (eg, >200 mg/day) in this population may be deleterious, primarily as a result of excess toxicity.

Induction Regimens: Phase III Trials

Harousseau (IFM2005/01) Dr. Jean-Luc Harousseau and colleagues[7] reported an updated analysis of IFM2005/01. In this study, 482 newly diagnosed patients were randomized to VD or VAD induction. VD resulted in a statistically significant improvement over VAD in the primary endpoint, CR+nCR rate (ITT analysis; Table 2).

VD was superior to VAD regardless of the presence or absence of adverse risk factors (chromosome 13 deletion, high ß2-microglobulin levels [>3.0 mg/L]). By ITT analysis, posttransplant, patients treated with VD induction had superior CR+nCR rates (35.0% vs 23.6%; *P*=.0056) and VGPR or better rates (61.7% vs 41.7%; *P*<.0001) than patients treated with VAD induction. Importantly, in patients who actually received transplantation, RRs were higher, and DCEP consolidation, which was given prior to the first transplant in a second randomization in both arms, did not appear to add benefit. Furthermore, the need for second transplant was significantly reduced for patients receiving bortezomib-based induction.

Table 2. VD versus VAD as Induction Therapy[7]

Endpoint	VD (n=240)	VAD (n=242)	*P* value
CR	9.6%	2.9%	.0023
CR+nCR	21.3%	8.3%	<.0001
≥VGPR	46.7%	18.6%	<.0001
≥PR	80.0%	62.8%	<.0001
MR+SD	10.0%	23.6%	
PD	4.2%	3.3%	
Death	0.8%	2.9%	
NE	3.8%	7.4%	

Table 3. VTD versus TD as Induction Therapy[8]

Endpoint	VTD	TD	*P* value
CR+nCR	36%	9%	<.001
≥VGPR	60%	27%	<.001
<PR	7%	20%	.003
PD	0	5.5%	.008

In terms of toxicity, VD resulted in a greater incidence of thrombocytopenia (10.1% vs 5% with VAD), herpes zoster infection (8.4% vs 2.1%; patients in this trial were not required to receive acyclovir prophylaxis), fatigue (21.4% vs 16.7%), rash (10.1% vs 5.4%), and peripheral neuropathy (35.3% vs 22.6%), but less anemia (12.2% vs 21.8% with VAD), neutropenia (5% vs 10.9%), infection (5% vs 7.5%), and thrombosis (3.8% vs 8.4%). Rates of grade 3 or 4 peripheral neuropathy were 6.3% with VD and 1.3% with VAD. Moreover, VD had no detrimental impact on stem cell collection.

The median age of the study population was 57 years. Approximately 22% of the patients had stage III disease, approximately 58% had a ß2-microglobulin level of 3 mg/L or higher, and approximately 40% had chromosome 13 deletion (determined by FISH).

Cavo (GIMEMA MMY-3006) Dr. Michele Cavo[8] reported on behalf of his colleagues and the Italian GIMEMA study group the results of MMY-3006. In this trial, 351 newly diagnosed patients were randomized to

Table 4. Lenalidomide Combined With High- or Low-dose Dexamethasone[9]

	Lenalidomide Plus High-dose Dexamethasone (n=196)		Lenalidomide Plus Low-dose Dexamethasone (n=190)	
	Within 4 Cycles	***Best Overall***	***Within 4 Cycles***	***Best Overall***
CR	2%	4%	1%	2%
VGPR	NR	48%	NR	40%
PR	80%	30%	69%	29%
MR	5%	4%	15%	14%
SD	6%	7%	8%	8%
PD	3%	3%	2%	3%
Unevaluable	4%	4%	5%	5%

NR=not reported.

VTD (n=176) or TD (n=175). In this interim analysis, 129 patients in the VTD arm and 127 patients in the TD arm were evaluable for response. VTD resulted in a statistically superior CR+nCR rate. VTD also resulted in a superior rate of patients achieving a VGPR or better (Table 3).

In patients with chromosome 13 deletion, the CR+nCR rate was 43% in patients treated with VTD and 4% in patients treated with TD (*P*<.001). In patients with t(4;14) translocation, the CR+nCR rate was 47% in patients treated with VTD and 8% in patients treated with TD (*P*=.002). Stem cell collection was not impaired by VTD.

A total of 74 patients in the VTD arm and 79 patients in the TD arm went on to transplant. VTD resulted in statistically significant improvement in posttransplant CR+nCR rates (57% vs 28%; *P*<.001) and in posttransplant rates of VGPR or better (77% vs 54%; *P*=.003).

VTD resulted in more peripheral neuropathy (7% vs 2% with TD) and skin rash (6.5% vs 1%), but less DVT (3% vs 6.5%).

In this patient population, approximately half the patients had stage I disease. Median ß2-microglobulin was about 3 mg/L. There were no statistically significant differences in baseline demographics between treatment arms.

Rajkumar (ECOG E4A03) Dr. S. Vincent Rajkumar and colleagues[9] reported updated results from the ECOG E4A03 study. In this trial, 445 newly diagnosed patients were randomized to receive either LD (n=223) or Ld (n=222). In the LD arm, dexamethasone was given at standard doses: 40 mg/day on days 1 through 4, 9 through 12, and 17 through 20 (480 mg per cycle). In the Ld arm, dexamethasone 40 mg/day was given on days 1, 8, 15, and 22 (160 mg per cycle). After 4 cycles, patients achieving a PR or better could elect to go to transplant, and those achieving less than a PR could elect to receive 4 cycles of standard TD.

As reported previously, overall 1-year survival probability was markedly superior in the Ld arm (0.96 vs 0.88 in the LD arm; *P*=.003). However, CR rates, which previously had not been reported, were unexpectedly low in both arms (2% with LD and 1% with Ld; Table 4); this is likely due to incomplete data. Further information on quality of response will be important, as CR rates in excess of 20% would be expected based on the SWOG trial described below and the results of this combination seen in the relapsed setting (with CR/nCR rates of 16% reported). Nonetheless, although ORRs (PR or better) were impressive, they were significantly lower in the Ld arm (70% vs 82% with LD; *P*=.007). Best overall response (including patients proceeding to transplant or TD) was also significantly lower in the Ld arm (71% vs 82% with LD; *P*=.01), but there was no significant difference in CR+VGPR rate (52% for LD vs 42% for Ld; *P*=.06). Similarly, there was no significant difference between the arms in PFS or TTP.

LD was associated with significantly more grade 3 DVT/PE (25% vs 9% with Ld), grade 3 infection/pneumonia (14% vs 7%), and grade 3 nonneuropathic weakness (10% vs 4%), but significantly less grade 3 neutropenia (11.7% vs 18.7%). Of 149 evaluable patients, stem cells were adequately collected from 97%, suggesting that this is not a major difficulty with this regimen.

The patient population in this study had predominantly stage II disease (41%) or stage I disease (~33%). Mean age was approximately 65 years, and approximately

Table 5. LD versus High-dose Dexamethasone[10]

Endpoint	LD	High-dose Dexamethasone
CR	22%	4%
PR	62%	49%
Total	84%	53%

90% had an ECOG performance status of 0 or 1. Average ß2-microglobulin was 3.8 mg/L in the LD arm and 3.5 mg/L in the Ld arm; 65% of patients in the LD arm and 57% of patients in the Ld arm had significant bone disease.

Zonder (SWOG S0232) Dr. Jeffrey Zonder and colleagues[10] reported on SWOG study S0232. In this trial, 198 newly diagnosed patients were randomized to LD (n=100) or standard high-dose dexamethasone alone (n=98). Crossover from the high-dose dexamethasone arm to the LD arm was allowed. This study was terminated early when it was deemed unethical to continue the study given the concerns over LD, which showed a worse OS when compared with Ld. (Please see above.) In patients evaluable for response, LD (n=66) resulted in significantly better overall response and CR rates than high-dose dexamethasone (n=72; Table 5).

The overall RR was 84% with LD and 53% with high-dose dexamethasone (*P*=.001). CR rate was 22% with LD and 4% with high-dose dexamethasone. LD also resulted in a significantly improved PFS (*P*=.002), but not OS. Compared with high-dose dexamethasone, LD was associated with significantly more grade 3 or 4 neutropenia (13.8% vs 2.4% with high-dose dexamethasone; *P*=.010) and grade 3 or 4 infections (51.4% vs 28%; *P*=.003). Including patients who crossed over from high-dose dexamethasone to LD, there were 25 patients with thromboembolic events on LD, compared with 7 on high-dose dexamethasone (*P*=.089). Fourteen cases of thromboembolism also occurred in patients who were receiving aspirin prophylaxis (325 mg/day), suggesting that preventive strategies for DVT need further evaluation and improvement in this setting.

Induction Regimens: Phase II Trials

Three phase II trials of novel agents used in combination with traditional agents were reported. One study assessed BCD followed by BTD,[11] another assessed RVD (Table 6),[12] and the third assessed a lenalidomide-cyclophosphamide-dexamethasone (LCD) regimen.[13] The BCD/BTD[11] and RVD[12] regimens resulted in ORRs between 92% and 98%, with more than half of patients having high-quality response (VGPR or better). The LCD regimen[13] also resulted in a good ORR (84%), with 19% of patients experiencing at least a VGPR/nCR, but no CRs. No unexpected toxicities were seen with these regimens,

Table 6. Phase II Trial of Lenalidomide-Bortezomib-Dexamethasone (Preliminary Results)[12]

	Evaluable Pts	CR	nCR	VGPR	PR	MR
Phase I	31	8 (26%)	3 (10%)	9 (29%)	10 (32%)	1 (3%)
DL 1	3	1	1		1	
DL 2	3	2		1		
DL 3	3	1			2	
DL 4	6	1		3	2	
DL 4M	16	3	2	5	5	1
Phase II (DL 4M)	11	1 (9%)		1 (9%)	9 (82%)	
Total	42	9 (21%)	3 (7%)	10 (24%)	19 (45%)	1 (2%)
		ORR: 98%				

Dose level (DL) 1 = Btz 1.0 mg/m^2, Len 15 mg/day, Dex 40 mg (cycles 1–4) or 20 mg (cycles 5–8)
DL2=Btz 1.3 mg/m^2, Len 15 mg/day, Dex 40 mg (cycles 1–4) or 20 mg (cycles 5–8)
DL3=Btz 1.3 mg/m^2; Len 20 mg/day, Dex 40 mg (cycles 1–4) or 20 mg (cycles 5–8)
DL4=Btz 1.3 mg/m^2; Len 25 mg/day, Dex 40 mg (cycles 1–4) or 20 mg (cycles 5–8)
DL 4M=Btz 1.3 mg/m^2; Len 25 mg/day, Dex 20 mg

though LCD was associated with grade 4 neutropenia (21%) and a relatively high rate of grade 3 or 4 thromboembolism (21%), and stem cell collection failed in 4 patients. Two of these patients had successful stem cell collection after treatment with AMD-3100 (an investigational stem cell mobilization agent; please see below). The high rate of quality responses with BCD/BTD[11] and especially RVD[12] are promising and support further evaluation. Moreover, the excellent tolerability seen with RVD is encouraging and it was noteworthy that although the numbers in this study were small for those going to transplant to date, there were no significant difficulties with stem cell mobilization reported.[12]

Transplantation

In addition to the Harousseau[7] and Cavo[8] trials, three important transplant studies were also reported.

The PETHEMA/GEM group[14] presented results from a randomized trial comparing a second autologous transplant versus RIC-allo. From 1999 to 2004, patients younger than 70 years received induction therapy with VBMCP/VBAD. Responding patients received autologous transplant. Patients who did not achieve at least an nCR with autologous transplant were then given either a second autologous transplant (n=85) or RIC-allo if a sibling donor was not available (n=26). Patients receiving RIC-allo had a significantly higher CR rate (33%, vs 11% with autologous transplantation; *P*=.02) and a trend for higher treatment-related mortality (16% vs 5% with autologous transplant, *P*=.09). Although there was no statistically significant difference in event-free survival or OS between the two groups, at 3 years of follow-up there appeared to be a plateau in the RIC-allo arm. Longer follow-up may reveal superiority of the RIC-allo arm over the autologous transplant arm.

Dr. Christian Straka and colleagues[15] assessed the value of standard (dose-intense) induction chemotherapy versus a less dose-intense induction regimen before tandem transplantation. One group received four cycles of standard induction with VAD or idarubicin/dexamethasone, and one group received only a short course of dexamethasone (40 mg/day on days 1–4 and days 8–11). All patients then proceeded to tandem autologous transplantation using melphalan 140 mg/m^2 as myeloablative therapy before each transplant. This study population was somewhat older, with a median age of 65 years. Patients receiving standard induction therapy, versus patients receiving a short course of dexamethasone induction, had a similar RR after tandem transplantation, so the addition of more intense induction with VAD or VAD-like regimen did not improve response. Furthermore, after 4 years of follow-up, there was no difference in overall survival between the study arms. This study suggests that VAD or VAD-like induction regimens provide little benefit in the tandem transplant setting compared to dexamethasone alone, and further supports the position that induction strategies incorporating novel agents are now the preferred approach.

Effective stem cell mobilization in the transplant setting is an important need, especially in heavily pretreated patients. Plerixafor (AMD3100) is a CXCR4 chemokine antagonist that mobilizes stem cells. Dr. John DiPersio and colleagues[16] reported a randomized, placebo-controlled phase III trial of either plerixafor or placebo added to G-CSF for stem cell mobilization. The primary endpoint was the percentage of patients who achieved at least 6 ɜ 10^6 CD34-positive cells/kg in 2 or fewer apheresis days. Plerixafor met the primary endpoint and resulted in a statistically significant improvement in stem cell mobilization (72% rate of successful mobilization, vs 34% in patients receiving placebo; *P*<.0001). In fact, most patients in the plerixafor group (54%) successfully mobilized after 1 day, compared with 17% of patients receiving placebo. In patients undergoing transplant, time to engraftment and durability of transplant were similar in both groups. Plerixafor tended to result in more gastrointestinal adverse effects and injection-site reactions, both of which proved generally mild and manageable.

Relapsed/Refractory Disease: New Agents

A number of phase I and II trials were reported of new agent in relapsed/refractory myeloma at the meeting. In fact, new product development of small molecules and monoclonal antibodies remains remarkably robust and will hopefully provide even more options for patients with relapsed/refractory disease. This is especially important, as despite the advances made in myeloma therapy over the past several years, there remains no cure and additional new treatments are continuously needed.

New Agents

Perifosine Three early-phase clinical trials assessing perifosine were reported in heavily pretreated populations with relapsed/refractory disease. Perifosine, an orally bioavailable AKT3 inhibitor, appears limited in its efficacy as a single agent in myeloma,[17] but has much better activity when combined with dexamethasone[17] or bortezomib.[18] In a phase I/II trial, the combination of perifosine-bortezomib resulted in a RR (CR + PR + MR) of 56% (n=16).[18] Grade 3/4 toxicities were primarily thrombocytopenia, anemia, and fatigue. No cases of DVT and/or significant peripheral neuropathy were reported. Patients had received

a median of five prior lines of therapy, and all had received prior bortezomib-based therapy, with 83% of patients being relapsed/refractory. The activity of this regimen was notable, with further benefits seen with the addition of dexamethasone. The dose-escalation portion of this trial is complete, and accrual continues at a dose level of perifosine 50 mg/day and bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, given in 21-day cycles.

Tanespimycin Tanespimycin is a heat shock protein 90 (HSP90) inhibitor that has to date been developed in a Cremophor formulation requiring premedication. A new suspension formulation has been developed, and a phase II trial assessing both formulations used in combination with bortezomib was reported at ASH.[19] Patients had received a median of five prior lines of therapy, and most patients had received prior bortezomib. RRs and toxicity were similar with both formulations, though efficacy data in patients treated with the suspension was limited to 9 patients (vs 25 with the Cremophor formulation). RRs in bortezomib-naive and -pretreated patients were nearly the same, at approximately 50%. However, patients with confirmed evidence of being refractory to bortezomib (defined as progression during treatment, or PD within 60 days of being treated with a bortezomib-containing regimen) were less likely to respond to the tanespimycin-bortezomib combination, with a PR or better reported in 3 of 18 (17%) patients, although this group not only was relapsed and refractory but also had advanced disease. Primary toxicities were gastrointestinal (diarrhea), fatigue, elevated liver enzymes, and thrombocytopenia. Interestingly, significant peripheral neuropathy did not occur, potentially as a result of upregulation of heat shock protein 70 by tanespimycin, which may be neuroprotective, an observation that was then confirmed in a rat model.[19]

HDAC Inhibitors Early-phase clinical studies of three HDAC inhibitors given to patients with relapsed/refractory myeloma were reported at ASH, including vorinostat, romidepsin, and ITF2357. Vorinostat and romidepsin were assessed in combination with other drugs, whereas ITF2357 was given alone.

Two phase I studies of vorinostat given in combination with bortezomib showed promising activity in approximately half the patients treated.[20,21] In the study performed by Badros and colleagues,[20] most dose levels used bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, with escalating doses of vorinostat given twice or once daily on days 4 through 11 (100–200 mg bid, for a total of 200–500 mg daily). Patients were heavily pretreated, with a median of six prior lines of therapy, and the majority of patients had received a median of two prior bortezomib-based regimens. In the study by Weber et al,[21] four dose levels of bortezomib ranging from 0.7 to 1.3 mg/m^2 were studied in combination with vorinostat 200 or 400 mg/day. Cycles were 21 days, with vorinostat given on days 1 through 14 and bortezomib on days 1, 4, 8, and 11. The median number of prior therapies was three, and relatively few patients had received prior bortezomib treatment. Interestingly, more activity was seen in the Badros study. This population had received more prior therapies and more prior bortezomib-based treatment, though they also received maximal doses of bortezomib (1.3 mg/m^2). Ten of 23 (43%) patients achieved a PR or better. Hematologic toxicity in this study was cumulative, with QTc prolongation, noted in the first cycle, not seen in subsequent cycles. These preliminary data are encouraging and suggest that phase II trials are warranted.

A phase I trial of romidepsin presented by Dr. Miles Prince demonstrated an MTD at romidepsin 10 mg/m^2 on days 1, 8, and 15, bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 and dexamethasone 20 mg/day on the day of and the day after bortezomib administration.[22] ORR of 70% was reported, with 1 CR and 6 PRs in 10 patients. The proportion of patients with refractory disease was not reported. Although the response rates in this trial are promising, it should be noted that this population had relatively few prior regimens (<2), and all patients were bortezomib naive. Given that bortezomib alone results in ORRs (PR or better) of approximately 28% in a heavily pretreated relapsed/refractory population, these promising RRs with this triple-combination regimen need to be confirmed in additional studies.

A phase II trial of patients with relapsed and refractory myeloma treated with ITF2357 was also reported.[23] The first 6 patients initially received 150 mg orally every 12 hours for 4 consecutive days per week. Because of toxicity, the dose was reduced by 33% to 100 mg. The median number of prior therapies was 3 and of 16 evaluable patients, there was one PR, and 5 patients had stable disease. The primary toxicity was thrombocytopenia, and no grade 4 neutropenia was noted. Although activity was modest, it should be kept in mind that this agent was given alone. For comparison, vorinostat showed 1 MR and SD in 9 patients when given as a single agent in a phase I myeloma trial of 13 patients (also reported as a poster presentation at ASH), but when combined with bortezomib showed better activity, as described above.

Carfilzomib (PR-171) Two phase I trials of the novel and potent proteasome inhibitor carfilzomib were reported.[24,25] A trial employing a 4-week cycle in which carfilzomib is given on days 1, 2, 8, 9, 15, and 16, with 12 days' rest[24] showed better tolerability and more activity than a regimen given on days 1 through 5 in a 14-day cycle.[25] Carfilzomib was generally well tolerated. Carfilzo-

mib was associated with a transient increase in serum creatinine in cycle 1, one episode of renal failure, and mild to moderate peripheral neuropathy as well as thrombocytopenia. This study included both myeloma and lymphoma patients, and neuropathy appeared to be more common in myeloma patients. Encouragingly, responses in patients who were refractory to bortezomib were seen, and this molecule is currently being further evaluated in phase II trials.

Monoclonal Antibodies Although monoclonal antibodies typically have not played a substantial role in the treatment of myeloma, that may change in the future. Several phase I trials have shown that monoclonal antibodies against insulin-like growth factor receptor (CP-751,871 and AVE1642),[26,27] CD56 receptor (hu901-DM1),[28] and CS1 (HuLuc63)[29] can be safely administered. Although responses have been rare to date, disease stabilization with single-agent treatment has occurred in many of these trials, suggesting that further development of monoclonal antibodies in combination is likely. One phase II trial of an anti-IL-6 monoclonal antibody (CNTO 328) was reported.[30] CNTO 328 was administered at a dose of 6 mg/kg IV every 2 weeks in combination with bortezomib. Of 21 evaluable patients, 1 patient achieved a CR and 5 achieved a PR. All patients were bortezomib-naive. Patients were eligible if they had documented PD after at least 1 prior therapy, although the number of prior therapies was not described.

In summary, although there were no new randomized, controlled trials presented at the 2007 annual meeting of ASH that will substantially change the management of advanced myeloma, many early clinical studies with small molecules and monoclonal antibodies were reported. In general, these studies demonstrated that there are a number of promising new agents in clinical development that, when combined with established platforms of bortezomib-, lenalidomide-, and thalidomide-based therapies, may provide additional treatment options for patients with relapsed/refractory disease.

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Notes

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CME Post-Test: *Circle only one answer per question.*

1. In the VISTA trial reported by San Miguel and colleagues, the CR rates for VMP versus MP were:

   a. 5% for VMP and 5% for MP
   b. 15% for VMP and 10% for MP
   c. 25% for VMP and 5% for MP
   d. 35% for VMP and 5% for MP

2. Compared with MP, VMP resulted in statistically superior:

   a. OS
   b. PFS
   c. TTP
   d. All of the above

3. In the trial reported by Harousseau and colleagues comparing VD versus VAD as induction therapy, CR rates with VD were shown to be:

   a. Superior to VAD
   b. Inferior to VAD
   c. Similar to VAD

4. Cavo and colleagues compared VTD versus TD alone. In this trial, CR+nCR rates with VTD were shown to be:

   a. Superior to TD
   b. Inferior to TD
   c. Similar to TD

5. In the ECOG trial reported by Rajkumar and colleagues, Ld was compared with LD. This trial showed that Ld, compared with LD, resulted in:

   a. Superior OS and higher RRs
   b. Superior OS but lower RRs
   c. Worse OS and RRs
   d. Similar efficacy but worse toxicity

6. In the SWOG trial reported by Zonder and colleagues, LD was compared with high-dose dexamethasone alone. In this trial, LD was shown to:

   a. Have superior efficacy, as determined by RRs and PFS
   b. Have worse efficacy, as determined by RRs
   c. Superior OS
   d. None of the above

7. Bladé and colleagues, on behalf of the PETHEMA/GEM study group, reported a randomized trial comparing a second autologous transplant versus RIC-allo in patients responding to a first autologous transplant. Compared with patients receiving a second autologous transplant, patients receiving a RIC-allo had:

   a. Higher treatment-related mortality
   b. Better CR rates
   c. Both A and B
   d. None of the above

8. In patients receiving tandem transplants, Straka and colleagues compared the value of standard VAD or VAD-like induction regimens versus a less dose-intense dexamethasone-only induction. These investigators found that:

   a. VAD or VAD-like induction regimens resulted in significantly superior posttransplant CR rates
   b. Dexamethasone-only induction resulted in significant superior posttransplant CR rates
   c. There was no statistically significant difference between the two induction regimens in terms of RR or OS
   d. None of the above

9. DiPersio and colleagues reported that plerixafor plus G-CSF, compared with placebo+G-CSF, resulted in:

   a. A statistically significant improvement in stem cell mobilization
   b. No significant improvement in stem cell mobilization
   c. A statistically significant reduction in successful stem cell engraftment posttransplant
   d. None of the above

10. In a phase I/II trial reported by Richardson et al., the combination of perifosine-bortezomib, resulted in a CR+PR+MR rate of:

    a. 56%
    b. 66%
    c. 76%
    d. 86%

Program Evaluation

1. Please rate the following supplement entitled "The Myeloma Landscape in 2008: Highlights From the American Society of Hematology 2007 Annual Meeting"

	Poor				*Excellent*
• Content of presentation	1	2	3	4	5
• Subject matter was presented clearly	1	2	3	4	5
• Content was fair, balanced, and free of commercial bias	1	2	3	4	5

2. Please rate how well the following learning objectives were achieved.

Participants should be able to:	*Poor*				*Excellent*
• List phase III trials reported at ASH in newly diagnosed and relapsed/refractory myeloma, and in transplantation	1	2	3	4	5
• List the arms of these trials and state primary endpoints	1	2	3	4	5
• State primary efficacy findings from these trials	1	2	3	4	5
• Describe adverse effects of therapies described in these trials	1	2	3	4	5

3. This activity was fair, balanced, and free of commercial bias.

Strongly Disagree				*Strongly Agree*
1	2	3	4	5

4. Overall comments: _____

5. What questions do you still have? _____

6. Suggested topics and/or speakers you would like for future activities: _____

7. This educational activity has contributed to my professional effectiveness and improved my ability to do the following:

	Strongly Disagree				*Strongly Agree*
• Identify patients for treatment	1	2	3	4	5
• Treat/manage patients	1	2	3	4	5
• Improve standard of care	1	2	3	4	5

8. After participating in this activity, will you make any changes in your practice? ✹ Yes ✹ No
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