

**Multiple Myeloma Update**  
*from the 44th Annual Meeting  
of the American Society of Clinical Oncology (ASCO)*



**Multiple Myeloma Update**  
*from the 44th Annual Meeting  
of the American Society of Clinical Oncology (ASCO)*

---

**Moderated By:**  
**Anne Quinn Young, MPH**  
*Multiple Myeloma Research Foundation  
Norwalk, CT*

**Multiple Myeloma Update**  
*from the 44th Annual Meeting  
of the American Society of Clinical Oncology (ASCO)*

---

**Welcome and Introduction**

**Moderated by**  
Anne Quinn Young, MPH

**Featuring**



**Jean-Paul Femand, MD**  
*Hôpital Saint-Louis  
Paris, France*



**Carol Ann Huff, MD**  
*Sidney Kimmel  
Comprehensive Cancer  
Center at Johns  
Hopkins University  
Baltimore, MD*



**S. Vincent Rajkumar, MD**  
*Mayo Clinic  
Rochester, MN*



**Multiple Myeloma Update**  
 from the 44th Annual Meeting  
 of the American Society of Clinical Oncology (ASCO)




**Multiple Myeloma Update**  
 from the 44th Annual Meeting  
 of the American Society of Clinical Oncology (ASCO)

---


**Upfront and Induction Therapy**

**Moderated by**  
 Anne Quinn Young, MPH


**Featuring**




**Jean-Paul Femand, MD**  
*Hôpital Saint-Louis  
 Paris, France*



**Carol Ann Huff, MD**  
*Sidney Kimmel  
 Comprehensive Cancer  
 Center at Johns  
 Hopkins University  
 Baltimore, MD*



**S. Vincent Rajkumar, MD**  
*Mayo Clinic  
 Rochester, MN*




**ECOG E4A03 Lenalidomide Plus High-dose Dexamethasone (RD) vs. Low-dose Dexamethasone (Rd): Primary Study**

---

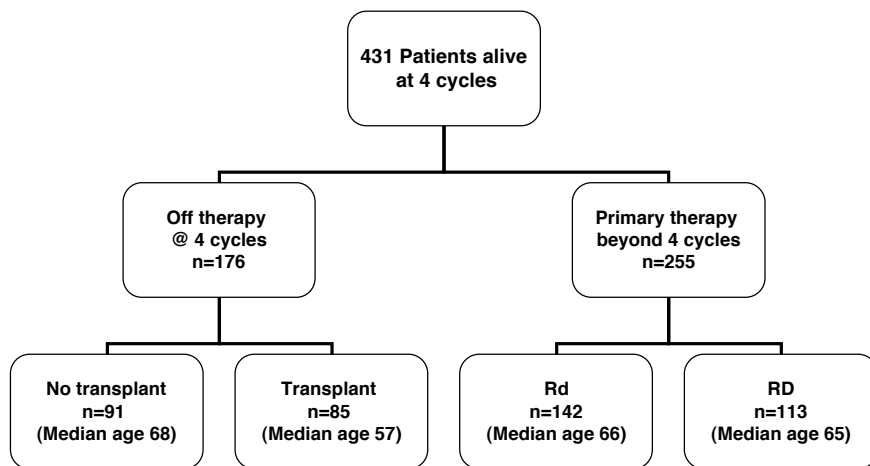
	RD n=214	Rd n=207	Fisher's Exact P Value
<b>Primary Endpoint</b>			
Overall response rate (ORR) at 4 cycles, %	79	69	0.020*
% Successful mobilization (n=163)	96	99	
Overall survival (OS), %			
1 year	88	96	0.005*
2 year	78	88	0.007*

\*Statistically significant.

Rajkumar SV et al. 2008 ASCO. Abstract 8504.



**ECOG E4A03 Lenalidomide Plus High-dose  
 Dexamethasone (RD) vs. Low-dose Dexamethasone (Rd):  
 Landmark Analysis**



Rajkumar SV et al. 2008 ASCO. Abstract 8504.



**ECOG E4A03 Lenalidomide Plus High-dose  
 Dexamethasone (RD) vs. Low-dose Dexamethasone (Rd):  
 2-year Survival Rates After 4 Cycles of Treatment**

	<b>RD</b>	<b>Rd</b>
<b>No transplant</b>	<b>69%</b>	<b>72%</b>
<b>Transplant</b>	<b>94%</b>	<b>92%</b>

Rajkumar SV et al. 2008 ASCO. Abstract 8504.



**ECOG E4A03 Lenalidomide Plus High-dose  
 Dexamethasone (RD) vs. Low-dose Dexamethasone (Rd):  
 Results of Treatment Beyond 4 Months of Rd**

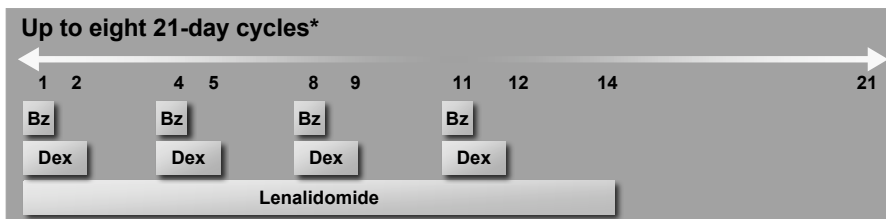
	Primary Rd	All Rd patients except SCT group	SCT group	ITT Rd arm
<b>N</b>	142	181	85	222
<b>Median age, yrs</b>	66	64	59	65
<b>&gt; Partial response (PR) after 4 cycles</b>	86	74	70	69
<b>1-yr survival</b>	99	96	99	96
<b>2-yr survival</b>	93	88	93	88

ITT, intent-to-treat; SCT, stem cell transplant.

Rajkumar SV et al. 2008 ASCO. Abstract 8504.



**Phase I/II Study of Lenalidomide, Bortezomib (Bz),  
 and Dexamethasone (Dex): Study Design**



\*DEX, 40 mg/day days 1, 2, 4, 5, 8, 9, 11, and 12; 20 mg, cycles 5–8; amended to 20 mg/10 mg cycles 1–4/5–8 based on safety data

- Patients with  $\geq$ PR may proceed to autologous stem cell transplant (ASCT) after  $\geq$ 4 cycles
- Maintenance therapy permitted in patients  $\geq$ SD using weekly (days 1 and 8) schedule of Bz and Dex on days 1, 2, 8 and 9
- Antithrombotic therapy with daily aspirin (81 mg or 325 mg)
- Antiviral therapy as prophylaxis against herpes zoster

Richardson PG et al. 2008 ASCO. Abstract 8520.





### **Phase I/II Study of Lenalidomide, Bortezomib, and Dexamethasone: Results**

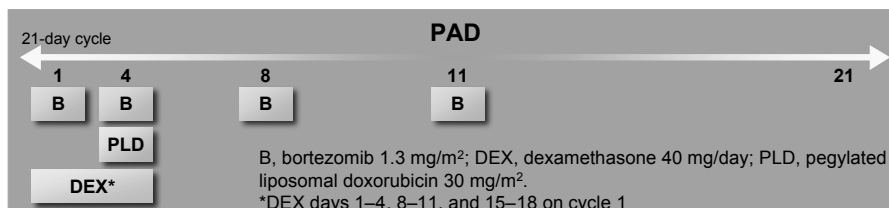
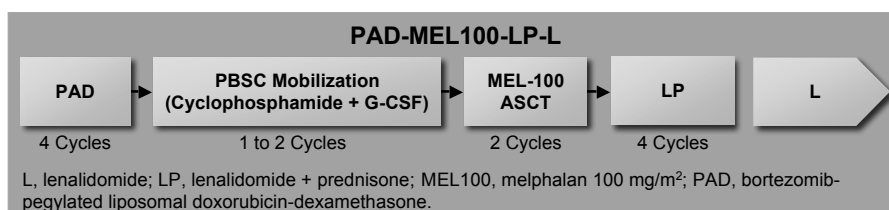
- Maximum tolerated dose: lenalidomide 25 mg/day, bortezomib 1.3 mg/m<sup>2</sup>, dexamethasone 20 mg
- No grade 4 peripheral neuropathy, ≤ grade 3 peripheral neuropathy in 5% of patients

<b>Response</b>	<b>%</b>
<b>ORR</b>	<b>98</b>
<b>Complete response (CR)/near CR (nCR)</b>	<b>36</b>
<b>CR/nCR + very good partial response (VGPR)</b>	<b>71</b>

Richardson PG et al. 2008 ASCO. Abstract 8520.



### **Bortezomib-Pegylated Liposomal Doxorubicin- Dexamethasone (PAD) as Induction Therapy: Treatment Schedule**



Palumbo AP et al. 2008 ASCO. Abstract 8518.



***PAD as Induction Therapy: Results***

Response, %	PAD n=86	PAD/MEL100 n=51	DAV/MEL200* n=124
CR/nCR	21	59	29
VGPR	38	29	7
PR	35	6	45
Minor response (MR)	2	6	11
Stable disease (SD)	2	0	7
Progressive disease (PD)	1	0	1

MEL, melphalan.

\*Historical control.

Palumbo AP et al. 2008 ASCO. Abstract 8518.



***VAD vs. Vel-dex as Induction Therapy: Results***

	VAD n=219	Vel-Dex n=223	P value
CR/nCR	8	19	0.0004*
≥VGPR	19	47	<0.0001*
≥PR	66	83	<0.0001*
Patients needing 2nd transplant, n (%)	87 (47)	55 (28)	
18-month OS rate, %	89	92	0.45
18-month PFS rate, %	85	90	0.38

PFS, progression-free survival; OS, overall survival; VAD, vincristine-adriamycin-dexamethasone; Vel-dex, Velcade® (bortezomib)-dexamethasone.

\*Statistically significant.

Harousseau JL et al. 2008 ASCO. Abstract 8505.



**Multiple Myeloma Update**  
from the 44th Annual Meeting  
of the American Society of Clinical Oncology (ASCO)



**MMRF**  
Multiple Myeloma  
Research Foundation

**Multiple Myeloma Update**  
from the 44th Annual Meeting  
of the American Society of Clinical Oncology (ASCO)

---

**Upfront and Induction Therapy: Discussion**

**Moderated by**  
Anne Quinn Young, MPH

**Featuring**



**Jean-Paul Fermand, MD**  
*Hôpital Saint-Louis  
Paris, France*



**Carol Ann Huff, MD**  
*Sidney Kimmel  
Comprehensive Cancer  
Center at Johns  
Hopkins University  
Baltimore, MD*



**S. Vincent Rajkumar, MD**  
*Mayo Clinic  
Rochester, MN*



**MMRF**  
Multiple Myeloma  
Research Foundation

**Upfront and Induction Therapy: Discussion**

---

- Standards of care
  - Patients who are stem cell transplant candidates
  - Patients who are not stem cell candidates
- The role of transplant
- Collection and mobilization of stem cells



**MMRF**  
Multiple Myeloma  
Research Foundation

**Multiple Myeloma Update**  
*from the 44th Annual Meeting*  
*of the American Society of Clinical Oncology (ASCO)*




**Multiple Myeloma Update**  
*from the 44th Annual Meeting*  
*of the American Society of Clinical Oncology (ASCO)*

---


**Treating Relapsed/Refractory Disease**

**Moderated by**  
 Anne Quinn Young, MPH


**Featuring**




**Jean-Paul Femand, MD**  
*Hôpital Saint-Louis*  
*Paris, France*



**Carol Ann Huff, MD**  
*Sidney Kimmel*  
*Comprehensive Cancer*  
*Center at Johns*  
*Hopkins University*  
*Baltimore, MD*



**S. Vincent Rajkumar, MD**  
*Mayo Clinic*  
*Rochester, MN*




**Final Analysis of MM-014 – Lenalidomide as a Single Agent**

---

	ITT n=222	Evaluable n=183
<b>ORR (CR + PR + MR)</b>	44	51
<b>CR</b>	2	3
<b>PR</b>	24	29
<b>MR</b>	18	20
<b>SD</b>	48	48
<b>PD</b>	4	1
<b>Median duration of response, mos</b>	13	13
<b>Median PFS, mos</b>	4.9	
<b>Median OS, mos</b>	23.2	

ITT, intent-to-treat.

Hussein et al. 2008 ASCO. Abstract 8524.



### ***Long-term Responses With Lenalidomide***

- 15 patients remain on therapy: 11 on lenalidomide 30 mg once daily, 4 on lenalidomide 15 mg twice daily

	<b>n=15</b>
<b>ORR* (CR + PR), n (%)</b>	<b>11 (73)</b>
<b>SD, n (%)</b>	<b>4 (27)</b>
<b>Median response duration, mos</b>	<b>36</b>

\*One patient progressed after 3.7 years.

Jagannath S et al. 2008 ASCO. Abstract 8525.



### ***Safety of Treatment in Patients With Impaired Renal Function***

- Lenalidomide
  - Response rates good in patients with mild to moderate renal impairment<sup>1</sup>
  - Safety in patients with severe renal impairment?
- Bortezomib-pegylated doxorubicin
  - Time-to-progression 3 months longer with combination vs. single-agent bortezomib, even in patients with renal impairment<sup>2</sup>
  - Safety of this combination in patients with severe renal impairment?

1. Weber DM et al. 2008 ASCO. Abstract 8542; 2. Bladé J et al. 2008 ASCO. Abstract 8562.





## **Phase II Study of Lenalidomide, Bortezomib, and Dexamethasone**

- Dose/schedule
  - Lenalidomide 15 mg/day, days 1–14
  - Bortezomib 1.0 mg/m<sup>2</sup> days 1, 4, 8, and 11
  - Dexamethasone 40/20 mg/day (cycles 1–4/5–8) on days of/after bortezomib for up to eight 21-day cycles

<b>Response, %</b>	<b>N=33</b>
<b>≥MR</b>	<b>73</b>
<b>≥PR</b>	<b>55</b>
<b>CR/nCR/VGPR</b>	<b>36</b>

Anderson KC et al. 2008 ASCO. Abstract 8545.



## **Targeting Cdk4/Cdk6**

### **PD 0332991**

- Cdk4/6-specific kinase inhibitor
- Orally bioactive small molecule with low toxicity
- Reversible
- Inhibits phosphorylation of Rb in myeloma cells
- Prevents tumor growth in human myeloma xenograft models and the mouse 5TMM model
- May be best combined with agents that affect cell survival – dexamethasone, bortezomib, NPI-0052

Chen-Kiang S et al. 2008 ASCO. Abstract 8503.





### ***Phase I Study of Vorinostat and Bortezomib***

---

- Vorinostat
  - Histone deacetylase inhibitor
- Combination with bortezomib
  - 23 patients treated
  - 3 patients refractory to bortezomib achieved a partial response with the combination
  - Phase III trial is being developed

Badros A et al. 2008 ASCO. Abstract 8548.



### ***Phase II Study of CNTO 328 and Dexamethasone***

---

- CNTO 328 is a chimeric monoclonal humanized antibody directed against IL-6.
- Combination trial with dexamethasone
  - 14 patients treated
  - Well tolerated
  - No responses to date

Voorhees PM et al. 2008 ASCO. Abstract 8593.





## ***Other Promising New Agents***

---

- Cyclin/cdk inhibitors
- Histone deacetylase (HDAC) inhibitors
- Proteasome inhibitors
  - Carfilzomib (PR-171)
- CC-4047 – analog of lenalidomide and thalidomide



## ***Multiple Myeloma Update*** from the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO)

---

### ***Genetics/Prognostic Factors***

**Moderated by**  
Anne Quinn Young, MPH

**Featuring**



**Jean-Paul Femand, MD**  
*Hôpital Saint-Louis  
Paris, France*



**Carol Ann Huff, MD**  
*Sidney Kimmel  
Comprehensive Cancer  
Center at Johns  
Hopkins University  
Baltimore, MD*



**S. Vincent Rajkumar, MD**  
*Mayo Clinic  
Rochester, MN*





### ***CR as a Surrogate Marker***

---

- CR does not always correlate with OS in clinical trials
- Overemphasis on CR may actually reduce OS
- Need to balance toxicity and efficacy
- Still needs to be investigated further



### ***Prognostic Risk Factors and Biomarkers***

---

- High-risk cytogenetic features
  - t(4;14), t(14;16), 17p-, hypodiploidy or deletion of chromosome 13
  - Bortezomib may be able to overcome some of these.
  - Lenalidomide may also be able to overcome some of these.
- Identification of additional prognostic markers<sup>1</sup>
  - Amplification of chromosome 1?
  - Deletion of 12p
  - Addition of chromosome 5
  - $\beta_2$ -microglobulin levels

1. Avet-Loiseau H et al. 2008 ASCO. Abstract 8522.



**Multiple Myeloma Update**  
*from the 44th Annual Meeting*  
*of the American Society of Clinical Oncology (ASCO)*



**MMRF**  
Multiple Myeloma  
Research Foundation

**Multiple Myeloma Update**  
*from the 44th Annual Meeting*  
*of the American Society of Clinical Oncology (ASCO)*

---

**Closing Remarks**

Moderated by  
Anne Quinn Young, MPH  
Multiple Myeloma Research Foundation  
Norwalk, CT

