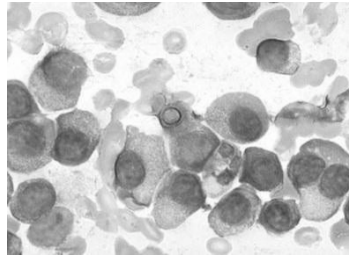


Multiple Myeloma: ASH 2008



Steven Coutre, M.D.
Associate Professor of Medicine
Division of Hematology
Stanford University School of Medicine

About These Slides

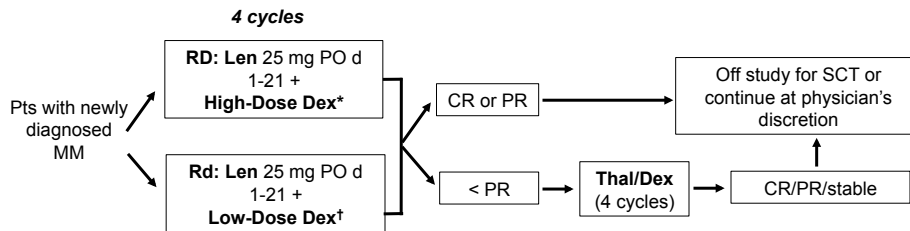
- These slides accompany CCO's comprehensive online Independent Conference Coverage of the American Society of Hematology 2008 Annual Meeting
- Our thanks to the presenters who gave permission to include their original data
- The full program is available on the Clinical Care Options for Hematology/Oncology Web site: clinicaloptions.com/Hematology2008
- Users are encouraged to use these slides in their own noncommercial presentations, but we ask that content and attribution not be changed. Users are asked to honor this intent
- These slides may not be published or posted online without permission from Clinical Care Options

Disclaimer

The materials published on the Clinical Care Options Web site reflect the views of the authors of the CCO material, not those of Clinical Care Options, LLC, the CME providers, or the companies providing educational grants. The materials may discuss uses and dosages for therapeutic products that have not been approved by the United States Food and Drug Administration. A qualified healthcare professional should be consulted before using any therapeutic product discussed. Readers should verify all information and data before treating patients or using any therapies described in these materials.

Myeloma Patients Eligible for Transplantation

E4A03: Len + High-Dose Dex vs Len + Low-Dose Dex in Newly Diagnosed Pts



*Dex given on d 1-4, 9-12, 17-20 for a total of 480 mg.
 †Dex given on d 1, 8, 15, and 22 for a total of 160 mg.

- Primary endpoint: response at 4 mos
- Equivalence: ORR in the Rd arm < 15%

Rajkumar SV, et al. ASCO 2008. Abstract 8504.

E4A03: Updated Follow-up Results— Response, Toxicity

Response, %	RD	Rd	P Value
Response in 4 cycles (\geq PR)	79	68	.008
\geq VGPR within 4 cycles	42	24	< .008
Best overall response (\geq PR)	81	70	.009
\geq VGPR	51	40	.040
CR (IF-)	17	14	.428

- Grade 3 nonhematologic SAEs (RD vs Rd)
 - DVT/PE: 26% vs 12%; $P < .001$
 - Infection/pneumonia: 16% vs 9%; $P = .043$
- Any nonhematologic toxicity (\geq grade 3; RD vs Rd): 66% vs 8%; $P < .001$
- Any type of toxicity (\geq grade 4; RD vs Rd): 21% vs 14%; $P < .001$

Rajkumar SV, et al. ASCO 2008. Abstract 8504.

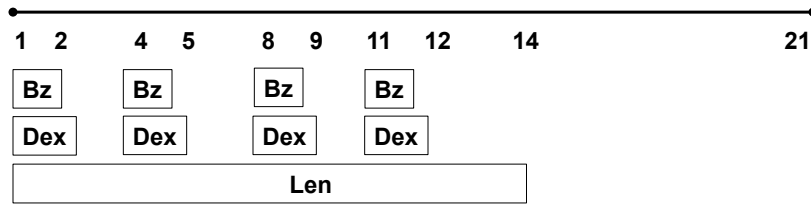
E4A03: Updated Follow-up Results — OS

- 2-yr OS (Rd vs RD): 88% vs 78%; $P = .007$
 - Trial closed as a result of this outcome
- 2-yr OS higher in pts who received SCT vs those who did not
 - Rd: 92% vs 69%, respectively
 - RD: 94% vs 72%, respectively

Rajkumar SV, et al. ASCO 2008. Abstract 8504.

Len/Bz/Dex in Previously Untreated Pts: Ph I/II Study

Up to eight 21-d cycles



- Pts with \geq PR could proceed to ASCT after 4 or more cycles
- After 8 cycles, responding pts could receive maintenance therapy with wkly (d 1, 8) bz and dex d 1, 2, 8, 9
- Daily antithrombotic therapy with aspirin (81 or 325 mg)
- Prophylactic antiviral therapy against herpes zoster

Richardson PG, et al. ASH 2008. Abstract 92.

Len/Bz/Dex in Previously Untreated Pts: Ph I Dose Levels

Dose Level	Len, mg/d	Bz, mg/m ²	Dex, mg
1	15	1.0	40
2	15	1.3	40
3	20	1.3	40
4	25	1.3	40
4M*	25	1.3	20

*Dose level 4M introduced based on safety data; dex 20 mg, cycles 1-4, and dex 10 mg, cycles 5-8. 140 mg, cycles 1-4; 20 mg, cycles 5-8.

- Two dose-limiting toxicities observed at dose level 4
 - Grade 3 hyperlipidemia due to high-dose dex
 - Maximum tolerated dose reached in dose level 4

Richardson PG, et al. ASH 2008. Abstract 92.

Len/Bz/Dex in Previously Untreated Pts: Results

Best Response by EBMT/UC

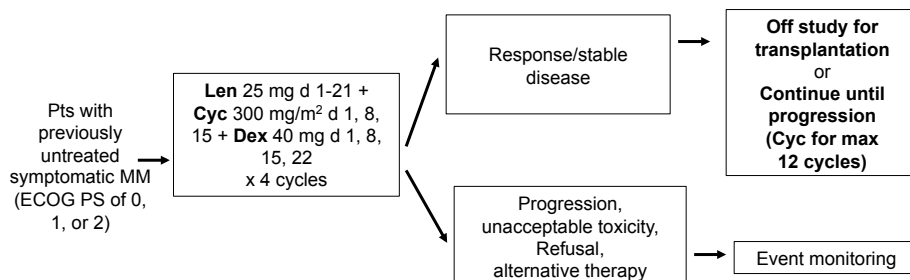
Response, n (%)	Patients (n = 65)
CR	17 (26)
nCR	12 (18)
PR*	36 (55)

*VGPR in 20 pts (30%).

- Median follow-up: 8 mos
 - Median TTP, PFS, and OS not yet reached
- Successful stem cell collection in 21/23 pts
 - Median 6.2×10^6 CD34+ cells following 6 cycles of therapy
 - 15 pts continued to ASCT, with unremarkable transplantation course
- Manageable toxicity profile
 - Grade 3 PN in 2 pts (3%)
 - DVT in 4 pts (4%)

Richardson PG, et al. ASH 2008. Abstract 92.

Len + Cyc/Dex in Newly Diagnosed Pts: Ph II Trial



- Primary endpoint: response at 4 cycles
- Enrollment
 - Cohort 1: 34 patients
 - Cohort 2: 19 patients

Kumar S, et al. ASH 2008. Abstract 91.

Len + Cyc/Dex in Newly Diagnosed Pts: Responses

- Response within 4 cycles
- Best response (ITT population, N = 53): 83%
 - CR: 2%
 - VGPR: 38%
 - PR: 43%
 - < PR: 17%
 - CR + VGPR: 40%
- 6 pts (cohort 1: 5; cohort 2: 1) went off study < 4 cycles

Kumar S, et al. ASH 2008. Abstract 91.

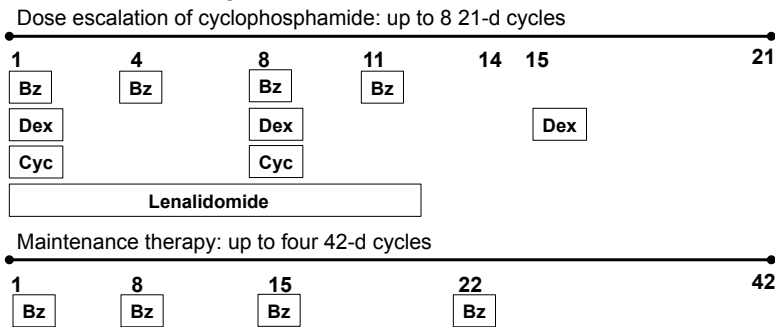
Len + Cyc/Dex in Newly Diagnosed Pts: Safety Data

- 25/53 pts discontinued study treatment
 - 14 completed study protocol
 - 5 had PD
 - 3 had AEs
 - 3 had alternate treatment
- Hematological tox most common grade 4 toxicity (8 pts)
- Nonhematological toxicity: neuropathy, diarrhea, cystitis, thrombosis
- 1 pt died off study (intracranial hemorrhage)

Kumar S, et al. ASH 2008. Abstract 91.

Ph I/II EVOLUTION: VDCR Therapy in Newly Diagnosed Pts: Initial Results

- Phase I trial design



- Prophylactic antibiotics, acyclovir, and anticoagulants permitted
- ASCT permitted in eligible patients after 4 cycles

Kumar S, et al. ASH 2008. Abstract 93.

EVOLUTION: Ph I Results in 25 Pts

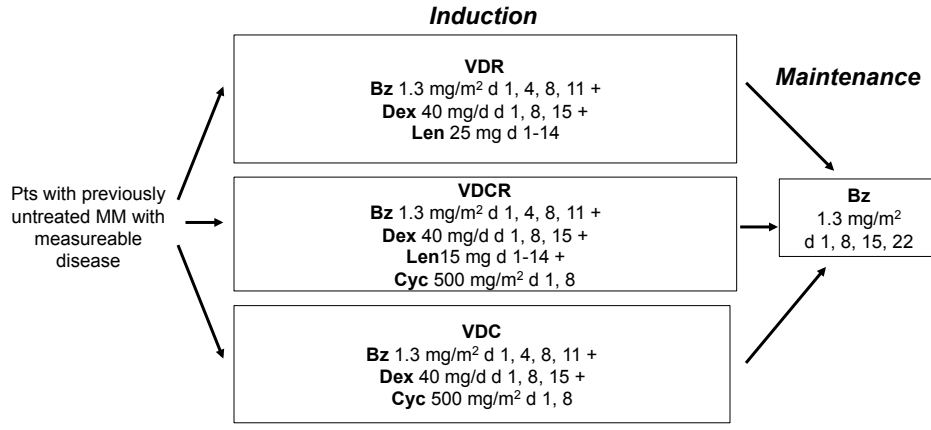
Response, n (%)	Patients (N = 25)
sCR	5 (20)
≥ CR	9 (36)
≥ VGPR	17 (68)
≥ PR	25 (100)

} ORR 100%

- Median treatment duration: 6 cycles (range: 3-12)

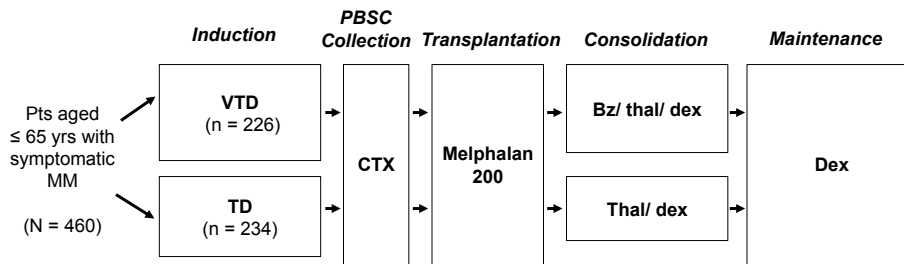
Kumar S, et al. ASH 2008. Abstract 93.

EVOLUTION: Ph II Enrollment Ongoing



- Eligible patients may undergo ASCT after 4 cycles
- Kumar S, et al. ASH 2008. Abstract 93.

GIMEMA: VTD vs TD in Newly Diagnosed Pts



- Induction: three 21-d cycles
 - Bz 1.3 mg/m² on d 1, 4, 8, and 11; thali 100-200 mg/d on d 1-63; dex 320 mg/cycle
- Consolidation: two 35-d cycles
 - Bz 1.3 mg/m² on d 1, 8, 15, and 22; thal 100 mg/d on d 1-70; dex 320 mg/cycle

Cavo M, et al. ASH 2008. Abstract 158.

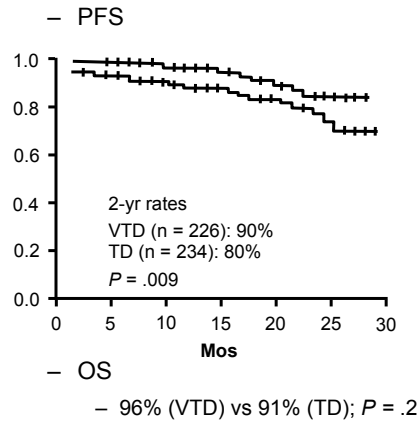
GIMEMA: Results

- Primary endpoint: CR + nCR (VTD vs TD as induction therapy)

Response, %	VTD (n = 226)	TD (n = 234)	P Value
CR + nCR	32	12	< .001
≥ VGPR	62	29	< .001
≥ PR	94	79	< .001
Progression	0	4.7	.001

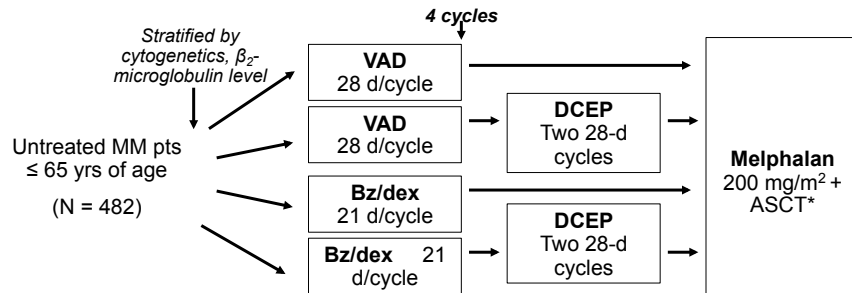
EBMT criteria (added nCR and VGPR categories)

- Secondary endpoints



Cavo M, et al. ASH 2008. Abstract 158.

IFM2005/01 Trial: Bz + Dex vs VAD in Newly Diagnosed Patients



*Second ASCT or reduced-intensity conditioning allogeneic transplantation if < VGPR.

Harousseau JL, et al. ASH 2008. Abstract.

IFM2005/01 Trial: Updated Results

- Preliminary results: higher CR + VGPR rates with bz/dex compared with VAD after induction and after ASCT^[1]
- Updated results confirmed by independent review response committee and include OS and PFS data^[2]
- Higher response rates with bz/dex compared with VAD postinduction therapy^[2]
- Postinduction response rates were significantly higher with bz/dex than with VAD across all prognostic subgroups^[2]

Response to Induction, %	VAD (± DCEP) (n = 242)	Bz/Dex (± DCEP) (n = 240)	P Value
≥ VGPR	16	39	< .0001
▪ CR	1	6	.0109
▪ CR + nCR	7	15	.0035
≥ PR	65	82	< .0001
MR + SD	28	13	--
PD	4	5	--
Death	3	0.5	--

1. Harousseau JL, et al. ASCO 2008. Abstract 8505.
2. Harousseau JL, et al. ASH 2008. Abstract.

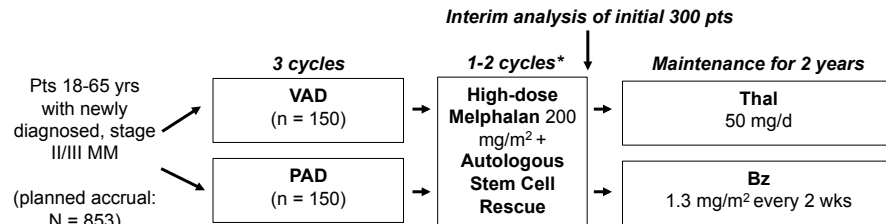
IFM2005/01 Trial: Updated Results

Outcome	VAD (± DCEP)	Bz/Dex (± DCEP)	P Value
Best response, %			
▪ ≥ VGPR	47	68	< .0001
▪ CR + nCR	32	39	< .0001
2-yr PFS, %	60	69	.0115
Median PFS duration, mos	28	Not reached	--
2-yr OS, %	88	90	.4689

- Bz/dex treatment associated with higher rates of PFS but not OS
- Toxicities (including hematologic) during induction therapy were similar between treatment arms
- Higher incidence of PN in bz/dex treatment arms, but toxicity was manageable
 - Grade 2: 8% vs 18% ($P = .002$)
 - Grade 3/4: 2% vs 7% ($P = .008$)

Harousseau JL, et al. ASH 2008. Abstract.

Ph III HOVON 65/GMMG-HD4: PAD vs VAD as Induction Prior to HDM in MM



*1 cycle in the Netherlands and 2 cycles in Germany.

- VAD: vincristine 4.0 mg and doxorubicin 9 mg/m² on d 1-4; dex 40 mg on d 1-4, 9-12, 17-20
- PAD: bz 1.3 mg/m² on d 1, 4, 8, 11; doxorubicin 9 mg/m² on d 1-4; dex 40 mg on d 1-4, 8-11, 7-20
- Primary endpoints
 - To evaluate the efficacy of bz as induction therapy before high-dose melphalan
 - To investigate the efficacy of bz maintenance treatment compared to thalidomide

Sonneveld P, et al. ASH 2008. Abstract 653.

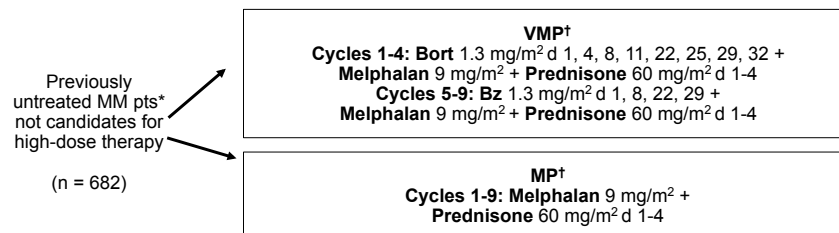
HOVON-65/GMMG-HD4: Interim Analysis of Response Data (ITT)

- Preliminary CR : 27% (PAD) vs 5% (VAD), $P = .001$
- 13q deletion did not have a significant effect on response
- Responses continued to improve with bz maintenance
- No difference in the incidence of thrombocytopenia, anemia, and leukocytopenia
- Grade 3/4 PN: 6% vs 16% for VAD and PAD, respectively ($P = .003$)

Sonneveld P, et al. ASH 2008. Abstract 653.

Myeloma Patients Ineligible for Transplantation

Ph III VISTA: Bz + MP vs MP in Newly Diagnosed Patients

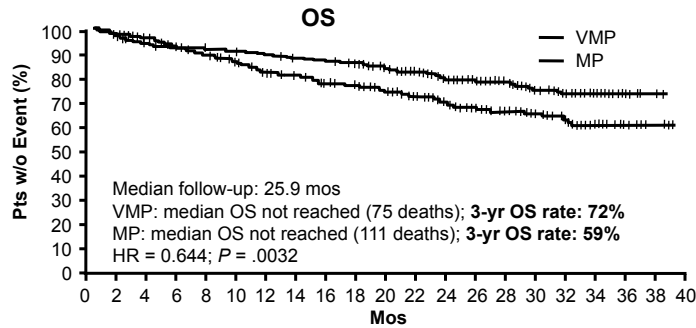


*Stratified by β_2 -microglobulin and albumin levels, region.
†9 x 6-wk cycles.

- Primary endpoint: TTP (by EGBMT criteria)
- Secondary endpoints: CR rate, ORR, DOR, OS, PFS, QoL, time to response, and time to next therapy
 - Previously published results showed superiority of bort arm across all efficacy endpoints

San Miguel JF, et al. N Engl J Med. 2008;359:906-917.

VISTA: Updated Results



- VMP associated with ~ 36% reduced risk of death
- 43% of pts in the MP arm who had subsequent therapy received bz upon disease progression
- Pts who received > 4 cycles of bz
 - 1- and 2-yr OS: 98.5% and 89%, respectively

San Miguel JF, et al. ASH 2008. Abstract 650.

VISTA: Best Responses With Subsequent Therapies

Subsequent Therapy, %*†	VMP (n = 129)		MP (n = 194)	
	CR	PR	CR	PR
Bz [†] or bz combination (n = 105)	(n = 21)		(n = 33)	
	6	33	10	45
Thal [†] or thal combination (n = 149)	(n = 63)		(n = 86)	
	4	44	3	52
Len [†] or len combination (n = 37)	(n = 25)		(n = 12)	
	4	52	0	55

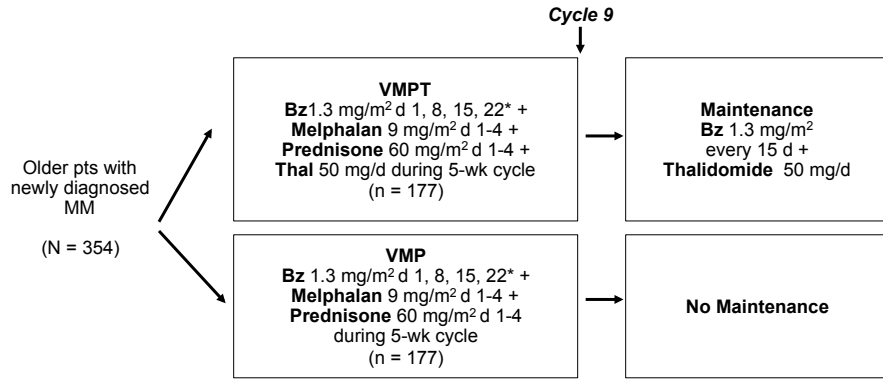
- Investigator-reported responses
- Pts relapsing post-MP therapy are not more resistant than those who were on MP
 - Bz use does not preclude IMiD use at relapse
 - Retreatment with bz is possible

*Other agents (eg, dex) were used as subsequent therapy, and pts could receive multiagent regimens.

† Single-agent therapy: bort, 36%; thalidomide, 37%; lenalidomide, 14%.

San Miguel JF, et al. ASH 2008. Abstract 650.

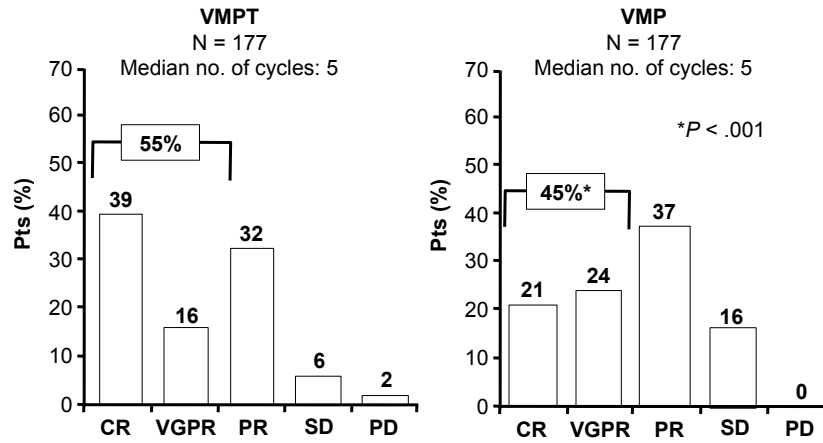
Ph III: VMPT vs VMP in Older Pts Newly Diagnosed With MM



*Protocol amended partway through study from twice-wkly bz dosing (d 1.4, 8, 11, 22, 25, 29, 32) to once-wkly bz dosing (d 1, 8, 15, 22); 61 pts in VMP arm and 70 pts in VMPT arm received twice-wkly bz dosing.

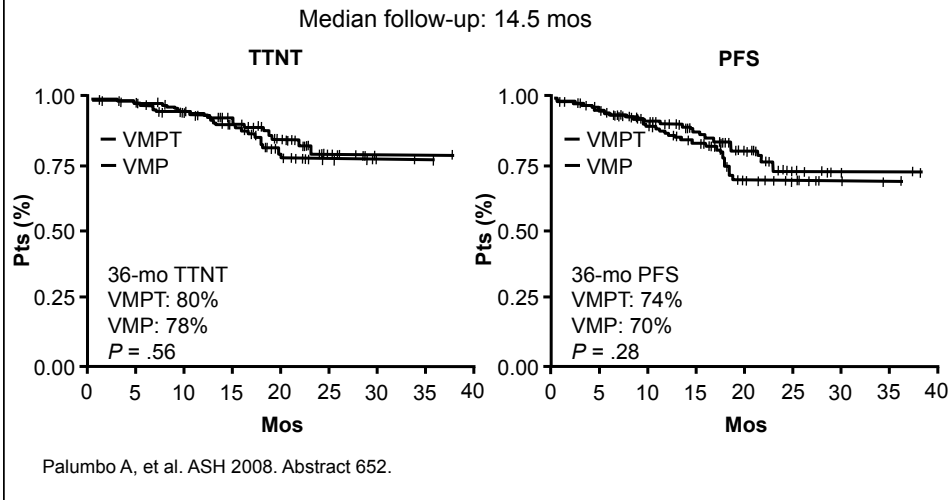
Palumbo A, et al. ASH 2008. Abstract 652.

VMPT vs VMP in Newly Diagnosed MM: Best Response



Palumbo A, et al. ASH 2008. Abstract 652.

VMPT vs VMP in Newly Diagnosed MM: TTNT and PFS



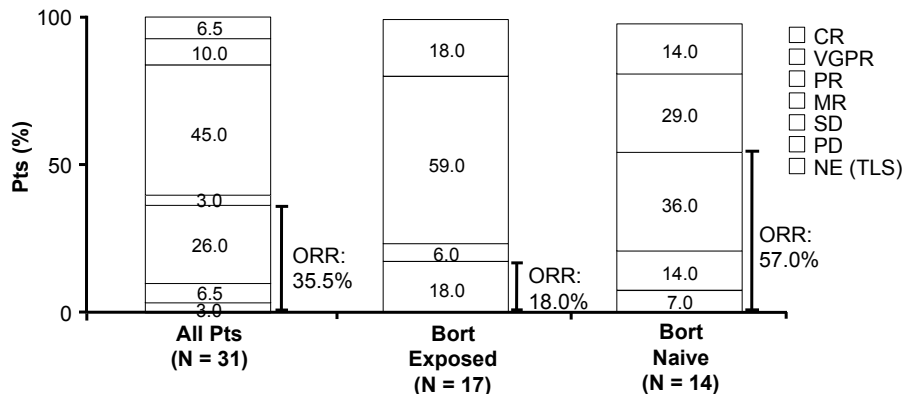
Novel Therapies in the Relapsed/ Refractory Setting

Ph II Open-Label Trial of Carfilzomib in Relapsed MM

- Novel proteasome inhibitor of the epoxyketone class
- Pts with relapsed/refractory MM who received no more than 3 previous therapies stratified into 3 cohorts
 - Bz naive
 - Bz responsive (> 6-mo response)
 - Bz nonresponsive (< 6-mo response)
- All pts received carfilzomib 20 mg/m² IV on d 1, 2, 8, 9, 15, and 16 every 28 d for up to 12 cycles
 - Dex 4 mg PO given before each dose in cycle 1
- Primary endpoint: ORR (CR + VGPR + PR)

Vij R, et al. ASH 2008. Abstract 865.
 Jagannath S, et al. ASH 2008. Abstract 864.

Carfilzomib: Response Summary



- 90% of responses occurred by the end of cycle 2
- Low incidence of PN (grade 1 reported in 1 pt, none ≥ grade 2)

Vij R, et al. ASH 2008. Abstract 865.

Carfilzomib: Results

- Clinical benefit response (CR + PR/VGPR + MR) achieved in 10/39 pts (26%)
 - PR: 5 pts
 - MR: 5 pts
 - SD: 16 pts
- Most common AEs: fatigue (65%), nausea (37%), URI (37%), diarrhea (33%)
- Hematologic toxicities: anemia (65%), thrombocytopenia (46%), neutropenia (20%) (all mainly grades 1/2)
- Increased creatinine seen in 15/46 pts (33%)
 - Treatment discontinued in 3 pts due to renal AE
- Acute renal failure seen in 4 pts (9%); 2 pts had possible tumor lysis

Jagannath S, et al. ASH 2008. Abstract 864.

Pomalidomide

- Pomalidomide (CC4047): IMiD agent with single-agent activity in phase I trials^[1,2]
 - Similar to thalidomide and lenalidomide in terms of structure but differs in terms of function
 - Favorable in vitro activity profile^[3]
 - Antiangiogenic activity
 - Antiinflammatory activity (monocytes)
 - Costimulation of T cells/NK cells
 - Inhibition of T regulatory cells
 - Antibody-dependent cellular toxicity

1. Schey SA, et al. J Clin Oncol. 2004;22:3269-3276. 2. Streetly M, et al. Br J Haematol. 2008;141:41-51. 3. Teo ST, et al. Drug Discov Today. 2005;10:107-114.

Pomalidomide + Low-Dose Dex in Relapsed MM: Ph II Trial

- Pts with previously treated, relapsed MM received
 - Pomalidomide 2 mg PO daily d 1-28
 - Dex 40 mg PO d 1, 8, 15, 22
 - Aspirin 325 mg PO d 1-28
- Primary objective: to evaluate response rate and duration of remission
 - Confirmed response: CR, PR, or VGPR based on International Myeloma Working Group Uniform Response criteria
- 23/37 pts (62%) had an objective response
 - VGPR: 9 pts (24%)
 - PR: 14 pts (38%)
 - SD: 6 pts (16%)
- Responses noted in 29% of 13 len-refractory pts among the first 37 pts enrolled in the trial
- Mild myelosuppression (32% grade 3/4 neutropenia)
- No DVT/PE

Lacy MQ, et al. ASH 2008. Abstract 866.

Vorinostat + Bz in Relapsed/Refractory MM: Ph I Experience

- Vorinostat: histone deacetylase enzyme inhibitor approved for cutaneous manifestations in progressive, recurrent, or persistent disease CTCL^[1]
 - Shown to enhance apoptosis caused by bz in MM cells^[2]
 - Pretreatment increases sensitivity to proteasome inhibition^[3]

Trial 1 (N = 34) ^[4]		
Cohort	Vorinostat, mg (d 1-14)	Bz mg/m ²
1	200 BID	0.7 (d 4, 8, 11, 15)
2	200 BID	0.9 (d 4, 8, 11, 15)
3	400 QD	0.9 (d 1, 4, 8, 11)
4	400 QD	1.1 (d 1, 4, 8, 11)
5	400 QD	1.3 (d 1, 4, 8, 11)

21-d cycle for ≤ 8 cycles; dex 20 mg/d on d 1-4, 9-12 allowed for PD at cycle 2

Trial 2 (N = 23) ^[4]		
Cohort	Vorinostat, mg (d 4-11)	Bz mg/m ²
1a	100 BID	1.0 (d 1, 4, 8, 11)
1	200 BID	1.3 (d 1, 4, 8, 11)
2	200 QD	1.3 (d 1, 4, 8, 11)
3	400 QD	1.3 (d 1, 4, 8, 11)
4	500 QD	1.3 (d 1, 4, 8, 11)

21-d cycle for ≤ 8 cycles; dex 20 mg/d on d 4-8, 9-12 allowed for < PR after cycle 2

1. Vorinostat [package insert]. 2. Pei XY, et al. Clin Cancer Res. 2004;10:3859-3852.
3. Mitsiades CS, et al. Proc Natl Acad Sci U S A. 2004;101:540-545.
4. Weber D, et al. ASH 2008. Abstract 871.

Vorinostat + Bz in Relapsed/ Refractory MM: Ph I Results

Summary of Efficacy		
Response, %	Trial 1 (n = 33)*	Trial 2 (n = 21)*
ORR	38	43
MR	17	0
SD	39	47
PD	6	10

*Evaluable pts.

- Well tolerated; AEs included fatigue, GI symptoms (diarrhea), thrombocytopenia

Response in Bz-Refractory Patients		
Response, %	Trial 1 (n = 7)	Trial 2 (n = 8)
CR	0	0
VGPR	0	0
PR	29	38
MR	29	0
SD	42	50
PD	0	12

Weber D, et al. ASH 2008. Abstract 871.

CNTO 328 + Bz in Relapsed/ Refractory MM: Ph II Trial

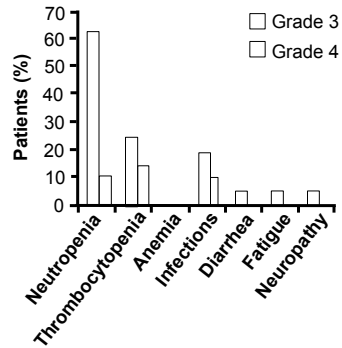
- CNTO 328: anti-IL-6 mAb
 - Has terminal half-life of ~ 16-18 d
 - CRP is a biomarker for anti-IL-6 therapy^[1]
 - Shown to enhance bortezomib effect in MM cells^[2]
- Two-part phase II trial including bz-naive pts with relapsed/refractory MM who received 1-3 lines of previous treatment

Part 1	<ul style="list-style-type: none"> CNTO 328 6 mg/kg IV, every 2 wks + bz 1.3 mg/m² IV d 1, 4, 8, 11, every 3 wks N = 21 Safety run-in
Part 2	<ul style="list-style-type: none"> Bz ± CNTO 328 (N = 270) Pts randomized 1:1 to receive <ul style="list-style-type: none"> Bz + CNTO 328 Bz + placebo

1. Rossi JF, et al. Bone Marrow Transplant. 2005;36:771-779. 2. Voorhees PM, et al. Clin Cancer Res. 2007;13:6469-6478. 2. Rossi J, et al. ASH 2008. Abstract 867.

CNTO 328 + Bz in Relapsed/ Refractory MM: Part 1 Results (Ph II)

- Responses by EBMT criteria
 - CR or PR: 12 pts (57%; 3 CR, 9 PR)
- Median TTP: 8.7 mos (range: 1.2-22.4)
- Part 2 of study ongoing

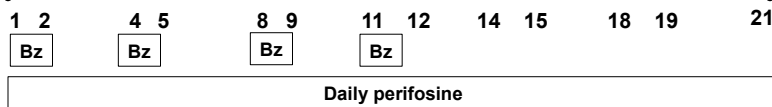


Rossi J, et al. ASH 2008. Abstract 867.

Perifosine + Bz ± Dex for Relapsed/ Refractory MM (Previous Bz): Ph I/II

- Perifosine: orally available novel AKT inhibitor
 - Observed to influence tumor proliferation and metastasis
 - Toxicity spectrum differs from that of conventional cytotoxic agents^[1]
- Observed to enhance cytotoxicity induced by bz in MM cells^[2]

Study design: 21-d cycle



If PD, add:



- Primary objectives
 - Phase I: define MTD of perifosine/bort regimen
 - Phase II: response rate (CR + PR + MR)

1. Richardson P, et al. ASH 2008. Abstract 870.
2. Hideshima T, et al. Blood. 2006;107:4053-4062.

Perifosine + Bz ± Dex for Relapsed/ Refractory MM: Results

Evaluable Pts,* n (%)	ORR (CR/nCR + PR + MR)	
	All Evaluable Pts (N = 72)	Bz-Refractory Pts (n = 52)
Perifosine + bort	17 (24)	8 (15)
With dex added†	10 (14)	8 (15)
Best response	27 (38)	16 (31)

*≥ 2 cycles.

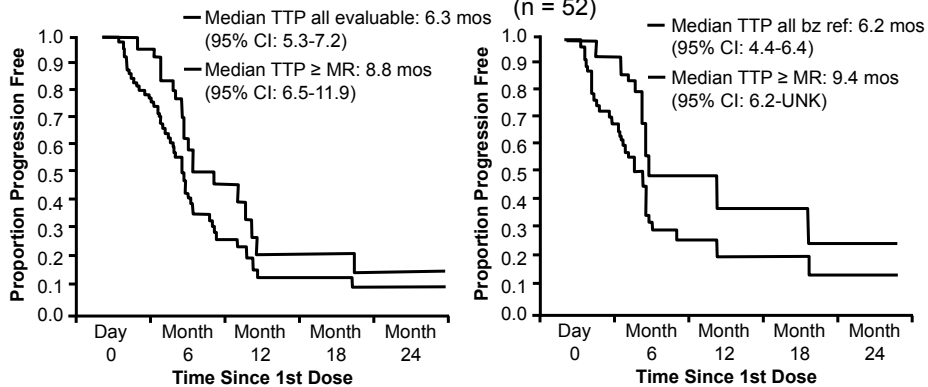
†Subset of the evaluable population.

- All pts had to have received bz; 83% of pts were refractory
- Perifosine 50 mg QD + bort 1.3 mg/m² identified as MTD

Richardson P, et al. ASH 2008. Abstract 870.

Perifosine + Bz ± Dex for Relapsed/ Refractory MM: TTP Results

- Secondary endpoint: TTP
- All evaluable pts (N = 72)
- Bz-refractory pts (n = 52)



Richardson P, et al. ASH 2008. Abstract 870.