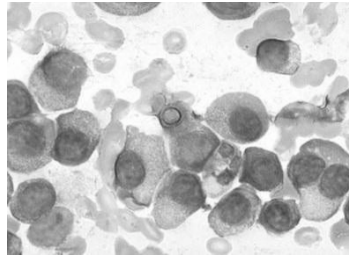


Multiple Myeloma: ASH 2008



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About These Slides

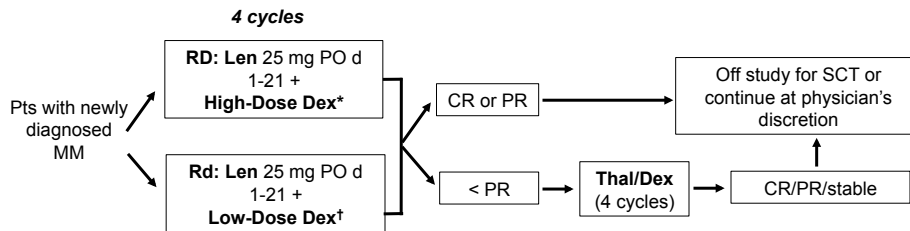
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Myeloma Patients Eligible for Transplantation

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.

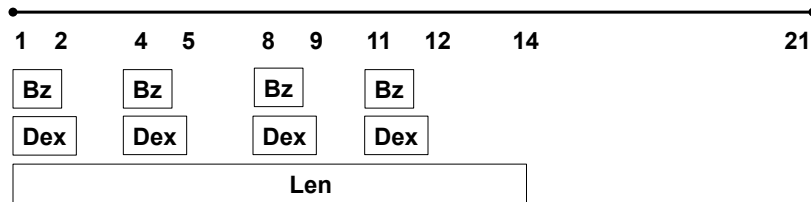
E4A03: Updated Follow-up Results — OS

- 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

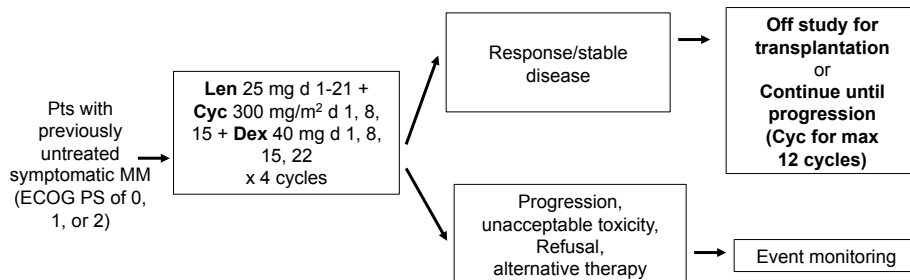
Response, n (%)	Patients (n = 65)
CR	17 (26)
nCR	12 (18)
PR*	36 (55)

*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.

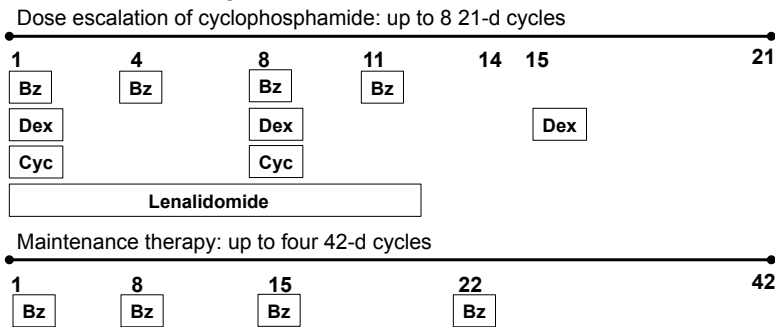
Len + Cyc/Dex in Newly Diagnosed Pts: Safety Data

- 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

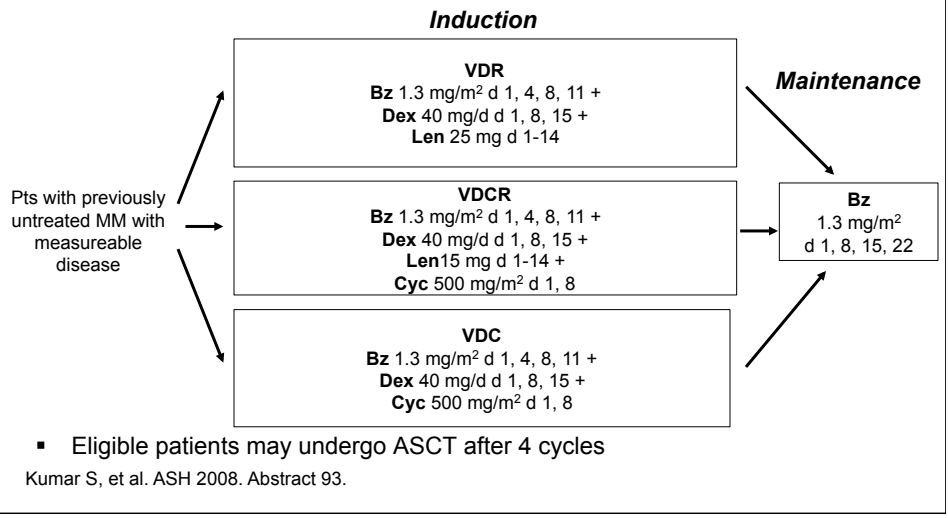
Response, n (%)	Patients (N = 25)
sCR	5 (20)
≥ CR	9 (36)
≥ VGPR	17 (68)
≥ PR	25 (100)

} ORR 100%

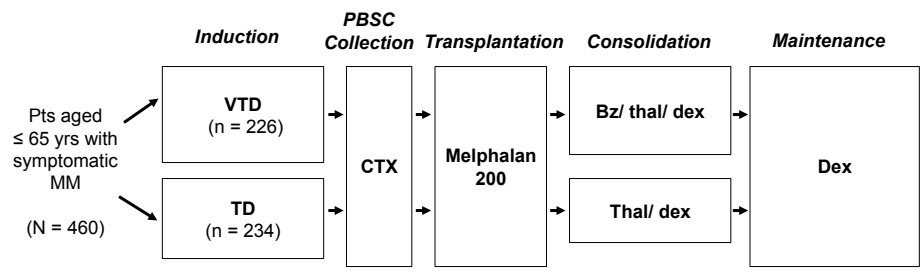
- Median treatment duration: 6 cycles (range: 3-12)

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

EVOLUTION: Ph II Enrollment Ongoing



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.

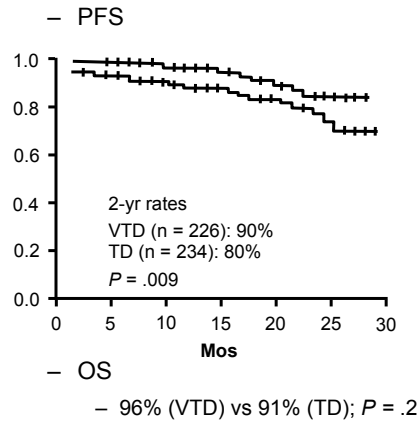
GIMEMA: Results

- 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

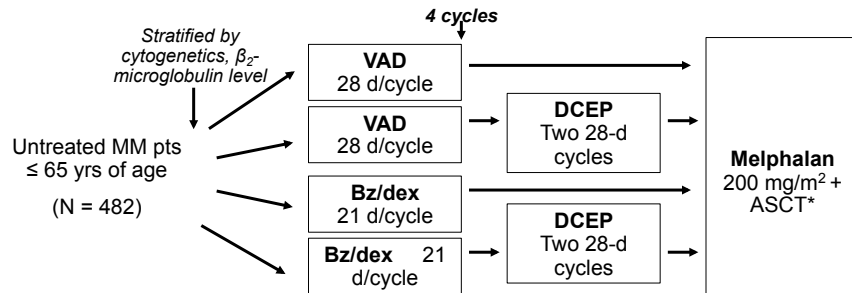
EBMT criteria (added nCR and VGPR categories)

- 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.

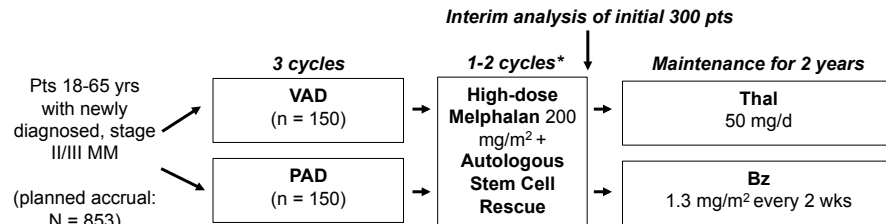
IFM2005/01 Trial: Updated Results

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.

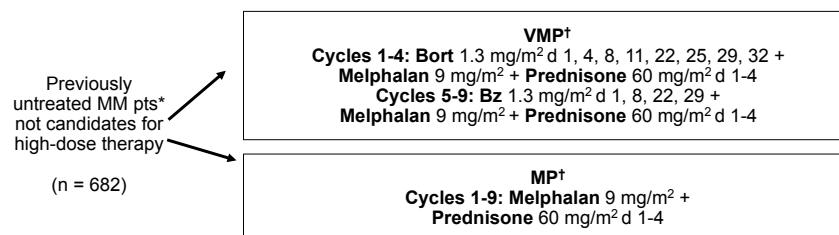
HOVON-65/GMMG-HD4: Interim Analysis of Response Data (ITT)

- 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

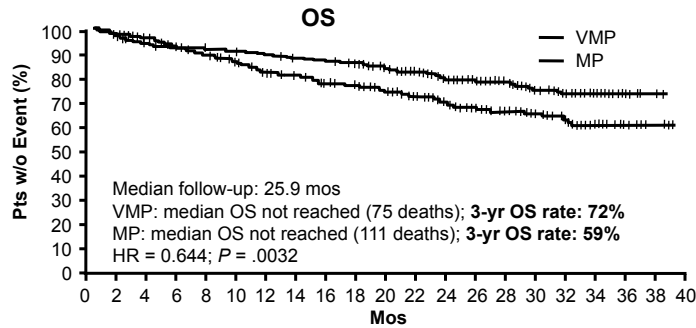


*Stratified by β_2 -microglobulin and albumin levels, region.
 †9 x 6-wk cycles.

- 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

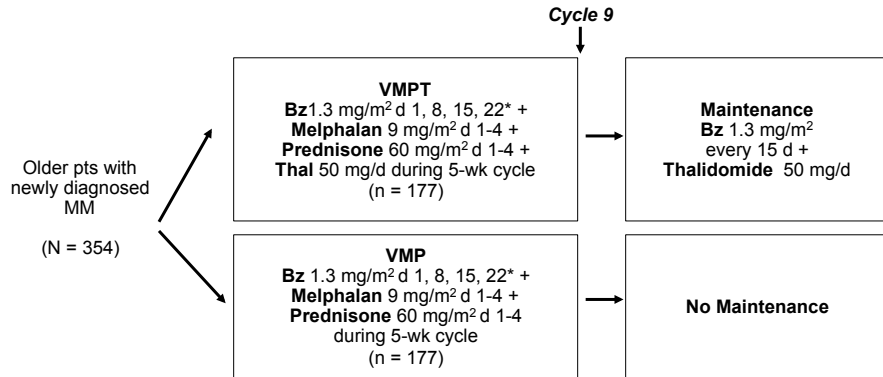
- Investigator-reported responses
- Pts relapsing post-MP therapy are not more resistant than those who were on MP
 - Bz use does not preclude IMiD use at relapse
 - Retreatment with bz is possible

*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.

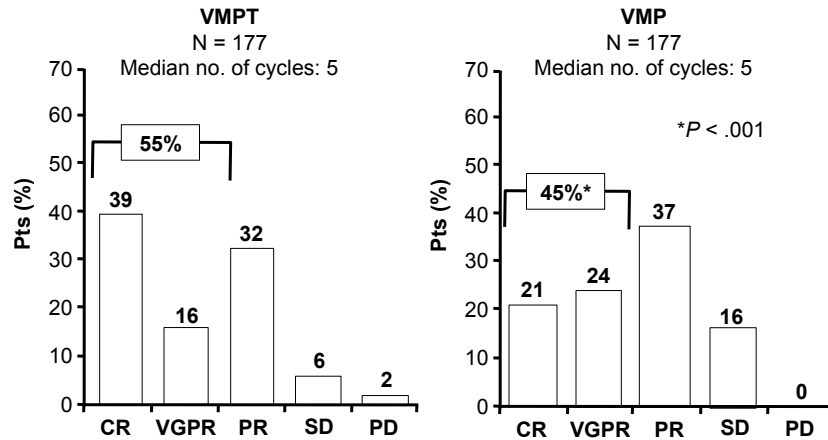
Ph III: VMPT vs VMP in Older Pts Newly Diagnosed With MM



*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.

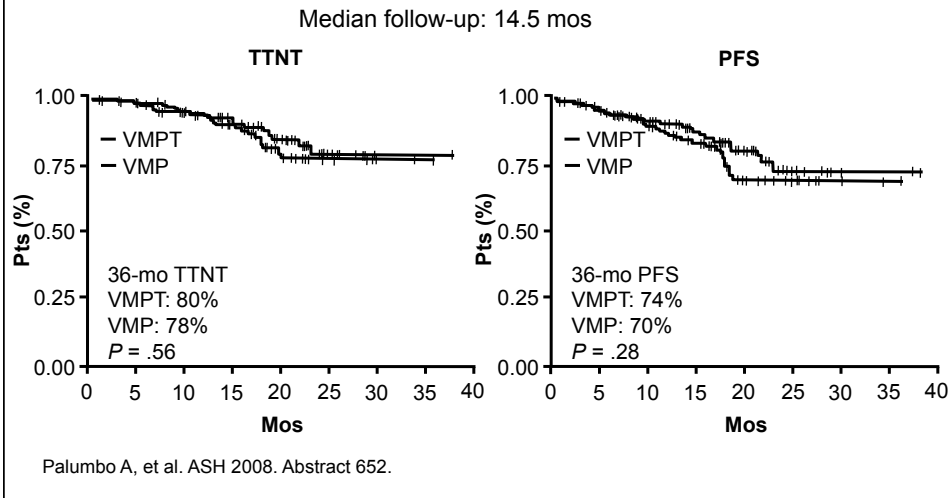
Palumbo A, et al. ASH 2008. Abstract 652.

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



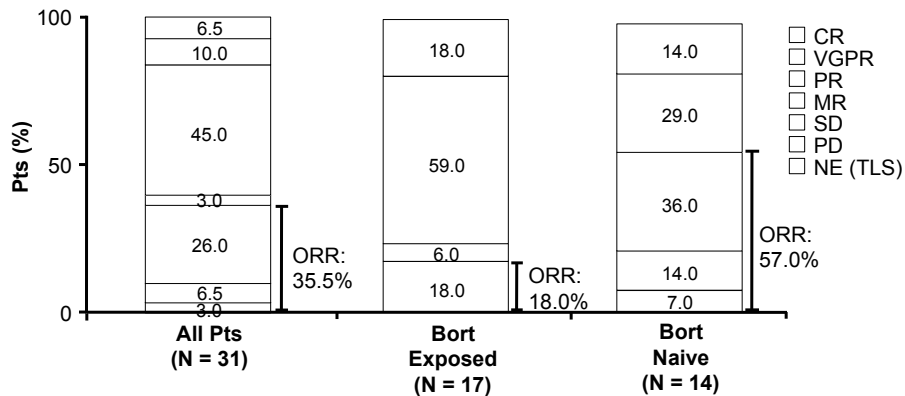
Novel Therapies in the Relapsed/ Refractory Setting

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 in Bz-Refractory Patients		
Response, %	Trial 1 (n = 33)*	Trial 2 (n = 21)*	Response, %	Trial 1 (n = 7)	Trial 2 (n = 8)
ORR	38	43	CR	0	0
MR	17	0	VGPR	0	0
SD	39	47	PR	29	38
PD	6	10	MR	29	0
			SD	42	50
			PD	0	12

*Evaluable pts.

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

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

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

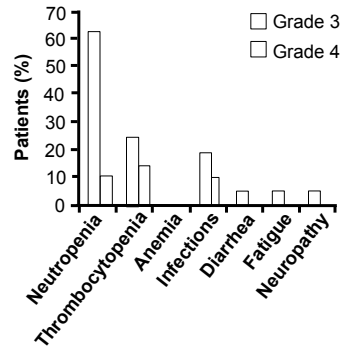
- CNTO 328: anti-IL-6 mAb
 - Has terminal half-life of ~ 16-18 d
 - CRP is a biomarker for anti-IL-6 therapy^[1]
 - Shown to enhance bortezomib effect in MM cells^[2]
- Two-part phase II trial including bz-naive pts with relapsed/refractory MM who received 1-3 lines of previous treatment

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

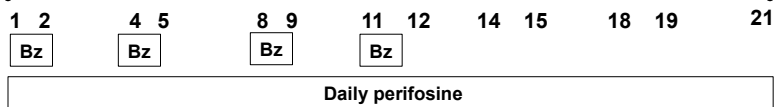


Rossi J, et al. ASH 2008. Abstract 867.

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.

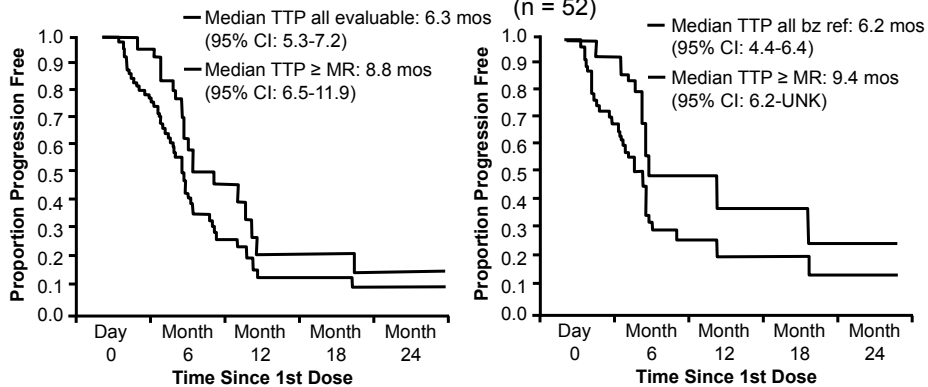
†Subset of the evaluable population.

- 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.