Treatment of Multiple Myeloma Novel Approaches

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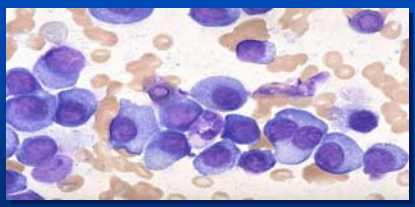
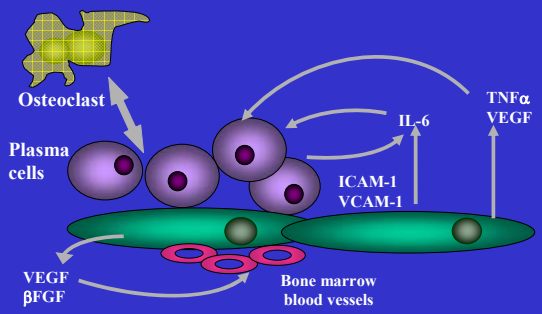
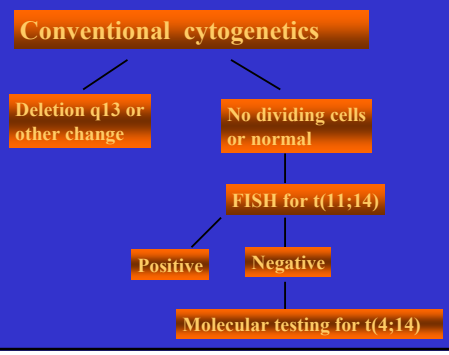
Plasma cells in bone marrow



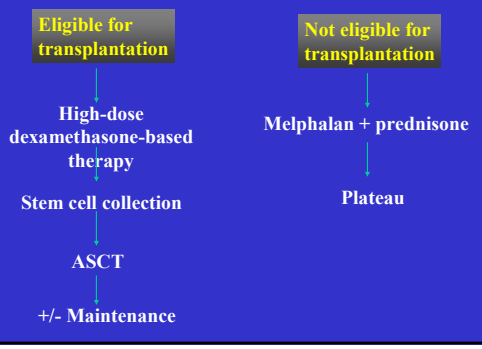
Adhesion Molecules and Growth Factors in Multiple Myeloma



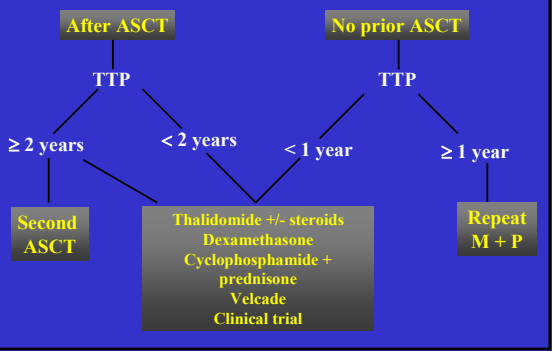
Algorithm for Cytogenetic Analysis for MM at PMH



Approach to Initial Therapy



Approach to Progressive MM



Novel Agents in Myeloma

- **Agents**
  - **Thalidomide**
  - **Bortezomib** (Velcade)
  - **Lenalidomide** (Revlimid)
- **Settings**
  - **Relapsed/refratory disease**
  - **Part of initial therapy**
  - **Maintenance**

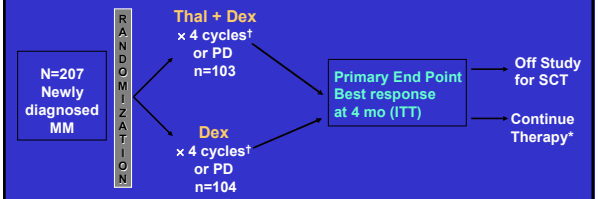
Thalidomide in Multiple Myeloma

- First "novel agent" for myeloma
- Has apoptotic, anti-angiogenic and immunomodulatory effects
- In relapsed/refractory disease, response rate ~30% as single agent and ~50% with dexamethasone
- Toxicities: sedation, constipation, rash, peripheral neuropathy and DVT

Thalidomide Trials in MM

- **Newly diagnosed patients**
  - **Thal + Dex versus Dex before ASCT**
  - **Combinations before ASCT**
  - **MP + thal versus MP in newly diagnosed elderly patients**
- **Thalidomide as maintenance therapy after ASCT**

Phase III Trial: Thal/Dex vs Dex in Patients With Newly Diagnosed MM



*Treatment beyond 4 cycles was permitted at physician discretion
†Cycle duration=1 month

Rajkumar SV et al. *Blood*. 2004;104:98a

Thal/Dex vs Dex in Newly Diagnosed MM
Results after 4 Cycles

Outcome	Thal/Dex (n=100) (%)	Dex (n=101) (%)
Best response (ECOG)*	58	42
Best response, corr	69	51
Median time to response (months)	1.1 (0.7–4.1)	1.1 (0.7–2.9)
CR (%)	3	0
Disease progression	3	5
Successful harvest	91	100

Rajkumar SV et al. *Blood*. 2004;104:98a

Thal/Dex vs Dex in Newly Diagnosed MM
Grade 3 or 4 Toxicities

Toxicity	Thal/Dex (n=100) (%)	Dex (n=101) (%)
Non-Heme	68	43
DVT	18	3
Rash	4	0
Bradycardia	1	0
Neuropathy	7	4
Any >/= gr 4	34	17

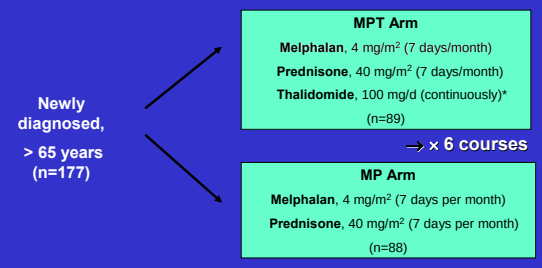
Rajkumar SV et al. *Blood*. 2004;104:98a

New Trials of Thalidomide in Newly Diagnosed Before ASCT

- Thal/Dex vs Dex
- Combinations
  - Velcade, thalidomide and Dex (VTD)
  - Pegylated liposomal doxorubicin + velcade + low dose Dex + thalidomide (Doxil + VdT)
  - VAD + thalidomide (VAD-thal)
  - VTD-PACE in Total Therapy 3
  - Cyclophosphamide + thalidomide + Dex (CTD)
  - Adriamycin + dex (AD) followed by thalidomide + Dex (DT)

Thalidomide With Melphalan and Prednisone in Elderly Patients With MM

Phase III Randomized Controlled Trial



*Thalidomide dose reduced to 50% if grade 2 toxicity; enoxaparin prophylaxis added to protocol December 2003

Palumbo A et al. *Blood.* 2004;104:63a [abstract 207]

Thalidomide With Melphalan and Prednisone in Elderly MM Patients

Response	MPT, %	MP, %
CR + nCR	28*	5
PR		
50% - 74%	16	28
75% - 99%	34	13
Total	50	41
Median EFS, mo	25.2*	13.7

*p < 0.001
Median follow-up, 13.6 months

Palumbo A et al. *Blood.* 2004;104:63a [abstract 207]

Thromboembolism in MPT Treated Elderly Patients Reduced With Prophylaxis

	Incidence, %	
Adverse Event	No LMWH (n= 61)	With LMWH[1] (n= 28)
DVT*	21.3	7.1
PE	4.9	0.0
Arterial occlusion	1.6	0.0

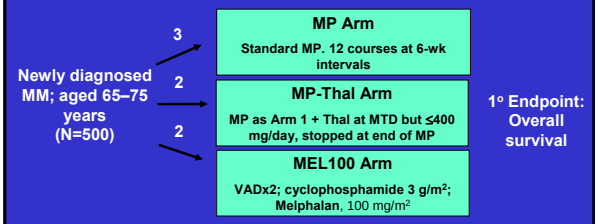
* *p*=0.003

[1]Enoxaparin, 0.4 mL/day for 4 months

Palumbo A et al. *Blood.* 2004;104::63a [abstract 207]

MP vs MP-Thal and MP vs Mel100 in Newly Diagnosed MM Aged 65–75 Years

IFM 99-06 Trial Design



All patients received clodronate

Facon T et al. *Blood.* 2004;104:63a [abstract 206]

MP vs MP-Thal and MP vs Mel 100 x2 in Newly Diagnosed MM Aged 65–75 Years

IFM 99-06 Trial Response to Treatment*

% of Patients at 12 Months			
Category of Response	MP (n= 153)	MP-Thal (n= 95)	MEL100 x2 (n= 92)
Complete response (%)	3	14	18
≥90% (%)	8	51	39
≥50% (%)	34	84	71

*2nd planned interim analysis; median follow-up time = 28 months

Facon T et al. *Blood.* 2004;104(part 1):63a [abstract 206]

IFM 99-06 Trial: Adverse Events Overview

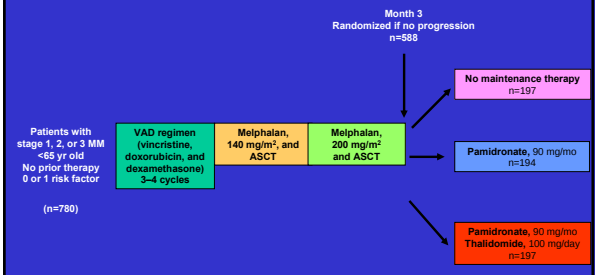
Incidence of DVT*, n (% of Patients)		
MP (n= 153)	MP-Thal (n= 99)	MEL 100 x2 (n= 92)
8 (5%)	12 (12%)	6 (6.5%)

- No toxic deaths related to DVT
- MP-Thal arm: DVT at median 3 mos (range 0.1-13 mos)
- MP-Thal arm: 36% peripheral neuropathy
- Hematologic/other adverse events as expected in each arm

Patients with history of DVT were excluded from trial

Facon T et al. *Blood.* 2004;104(part 1):63a [abstract 206]

Maintenance With Thalidomide After ASCT for MM



Attal M et al. *Blood.* 2004;104(part 1):155a [abstract 535]

Maintenance With Thalidomide After ASCT for MM

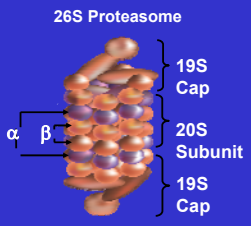
Preliminary Results

Endpoint	No maintenance	Pam	Thal/Pam	*p* value
Patients, n	197	194	197	0.04
Progression, %	25	24	15	0.04
Median PFS, mo	27	28	> 38	
3-yr PFS, %	34	37	56	0.01
Bone events, %	14	8	7	0.10
3-yr risk of bone events, %	65	26	24	0.04

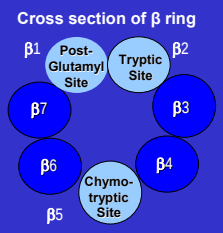
Attal M et al. *Blood.* 2004:104(part 1):155a [abstract 535]

Velcade (Bortezomib; PSI 341)

Proteasome Inhibition

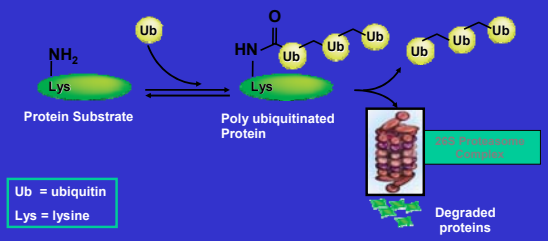


- Degrades ubiquitinated proteins
- Proteolysis is ATP-dependent



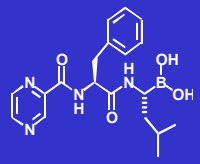
- Chymotryptic site is rate-limiting in protein degradation

Ubiquitin-Proteasome Pathway

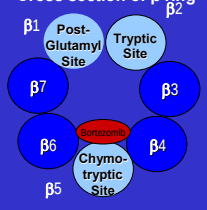


Velcade (Bortezomib)

Dipeptidyl boronic acid

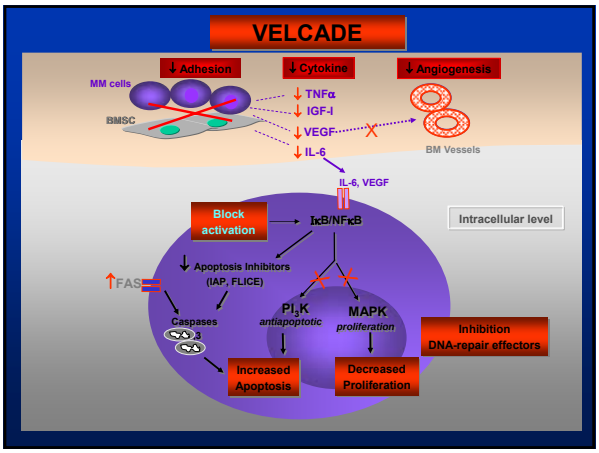


Cross section of β ring

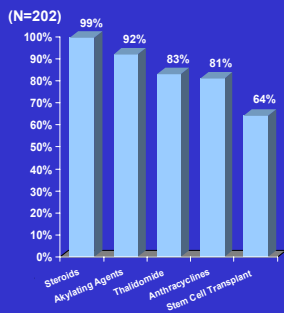


(reversible inhibitor of chymotryptic active site of proteasome B subunit)

Millennium Pharmaceuticals, Inc., 2003.



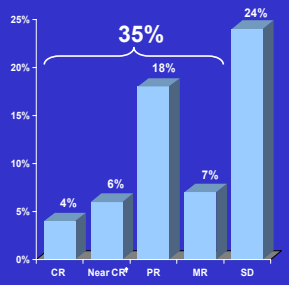
SUMMIT: Prior Therapy



- 6 median lines of prior therapy
- 92% of patients received at least 3 of the drug therapies listed (excluding stem cell transplant)

1. Millennium Pharmaceuticals, Inc., 2004.

SUMMIT: Response Rates with Bortezomib (N=193)*



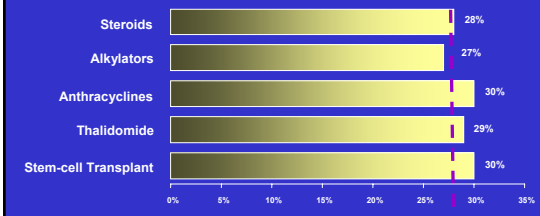
- 35% overall response (CR+PR+MR)
- 27% CR+PR
- 24% stable disease (SD)
- 59% of patients SD or better

*Of 202 patients, 193 were evaluable for response and duration of response
†Near CR met all the criteria for a CR, with the exception of detectable M protein by immunofixation
Numbers rounded to nearest integer.

Richardson et al. N Engl J Med. 2003;348:2609-2617.

SUMMIT: Response Rates Independent of the Types of Prior Therapy[1]

Percent response (CR+PR) to bortezomib alone by types of prior therapy in SUMMIT trial

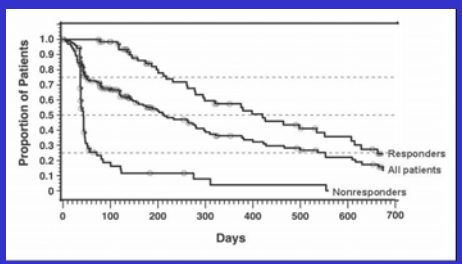


CR+PR = 27% (90% CI = (22.2, 33.2))

1. Millennium Pharmaceuticals, Inc., 2003

SUMMIT: Updated Time-to-Progression

- Median TTP: overall ~7 mo, responders ~13.9 mo, nonresponders ~1.3 mo



Richardson et al. EHA 2004; Abstract 304.

Bortezomib Trials in MM

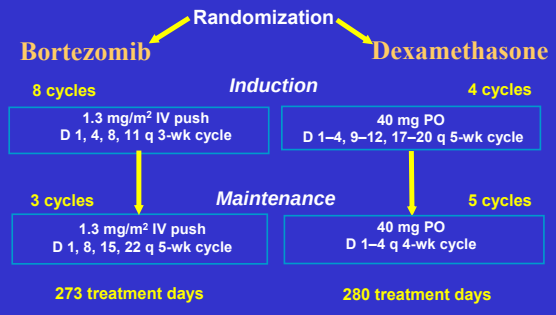
- Velcade versus Dex in relapsed MM (APEX study)
- Velcade combinations as part of initial therapy

APEX: Study Design

- International, randomized, open-label study in pts with relapsed or refractory MM
  - 669 pts enrolled at 94 centers
  - Endpoints
    - Primary: time to progression (TTP)
    - Secondary: survival, response rate (RR) and duration, time to skeletal events (TSE), incidence of ≥ G3 infection, safety
    - Exploratory: quality of life (QOL), pharmacogenomics
- Companion crossover study (M34101-040): bortezomib for pts progressing on Dex

Richardson et al. ASH 2004; Abstract 336.5.

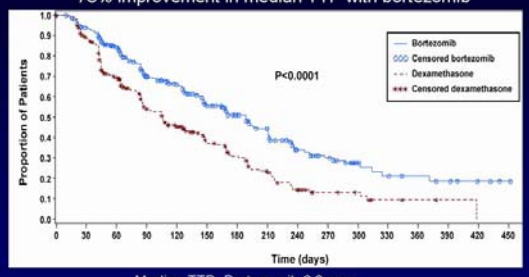
APEX: Treatment Plan



Richardson et al. ASH 2004; Abstract 336.5.

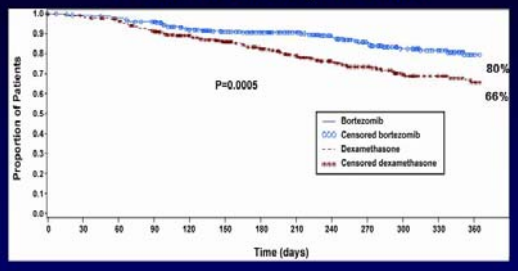
Time to Progression (N = 669)

78% improvement in median TTP with bortezomib



Median TTP: Bortezomib 6.2 mos
Dexamethasone 3.5 mos

1-Year Survival, N = 669



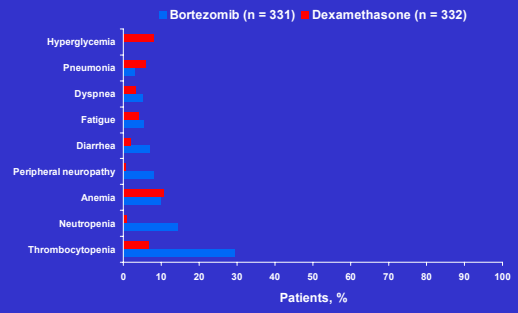
41% decreased risk of death with bortezomib

Adverse Events (All Pts)

	Bortezomib (n = 331) %	Dexamethasone (n = 332) %
Adverse events ≥ G3	75	60
Adverse events G4	14	16
Serious adverse events	44	43
Discontinuation due to adverse events	37	29
On-study deaths†	4	8

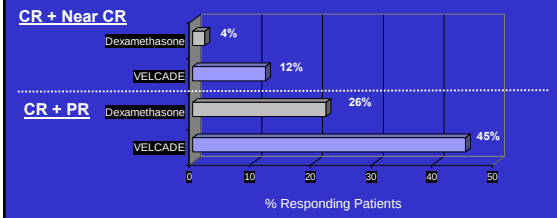
Richardson et al. ASH 2004; Abstract 336.5.

Treatment-Emergent ≥ Grade 3 Adverse Events



Richardson et al. ASH 2004; Abstract 336.5.

APEX – Endpoints in Second Line Patients

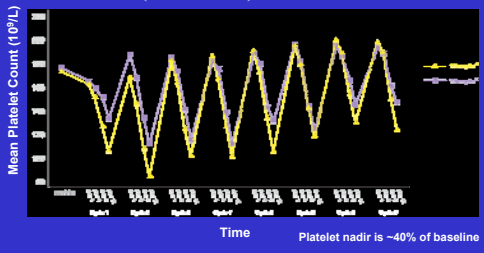


- 40% of patients relapsed/refractory after 1 prior therapy (n= 251)
- Statistically significant survival benefit with VELCADE in second line patients

Richardson et al. ASH 2004; Abstract 336.5.

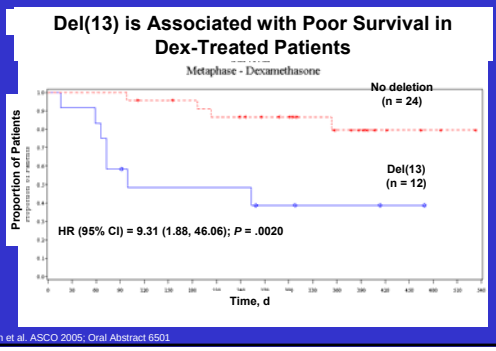
Management of Thrombocytopenia

- 43% overall incidence[1] of thrombocytopenia
  - 27% Grade 3 (10-50 x 10^9/L)
  - 3% Grade 4 (< 10 x 10^9/L)



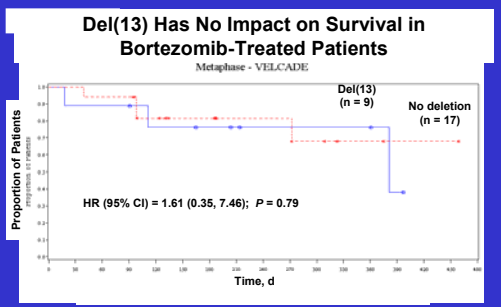
Platelet nadir is ~40% of baseline

Del(13) in Multiple Myeloma
APEX: Matched-Pairs Analysis



Jagannath et al. ASCO 2005; Oral Abstract 6501

Del(13) in Multiple Myeloma
APEX: Matched-Pairs Analysis



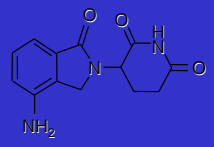
Jagannath et al. ASCO 2005; Oral Abstract 6501

Velcade Regimens Before ASCT

Study	N/Eval	Regimen	CR/nCR	CR+PR
Jagannath	32/23	Velcade +/- DEX	30%	83%
Popat	21/21	PAD	29%	95%
	11/9	Velcade + Adria (2 dose levels) + DEX	22%	100%
Harousseau	30	Velcade + DEX	17%	83%
Alexanian	30	VTD	NA	80%
		Velcade + thal + DEX		
Barlogie	57	Total Therapy T3	NA	NA
		VTD-PACE		
Uy	34	Velcade after thal or anthracycline	33%	89%
Orlowski	55/19	Velcade + Doxil	5%	80%

Lenalidomide (CC-5013; Revlimid™)

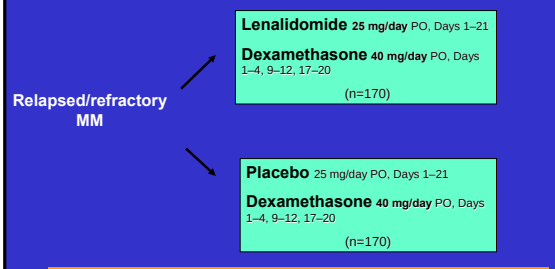
- More "potent" immunomodulator than thalidomide
- Fewer side effects: no significant constipation, neuropathy, or sedation
- DVT noted
- Not teratogenic



Lenalidomide (Revlimid) Trials

- Lenalidomide + Dex versus Dex alone in relapsed patients
- Pilot study of lenalidomide + Dex in newly diagnosed patients
- Others

Lenalidomide + Dex vs Placebo + Dex in Relapsed/Refractory MM



Endpoints: TTP, Response Rate, Overall Survival

Interim Analysis

Outcome	Lenalidomide + Dex (n=170)	Placebo + Dex (n=170)
TTP (mos)	NYR	5
Response rate	51%	23%
CR	19%	4%

Weber D et al.Haemotologica. 2005;99(s1):155a

Lenalidomide (CC-5013) and Dexamethasone for Newly Diagnosed MM

Rajkumar SV et al. *Blood.* 2004;104(part 1):98a [abstract 331]

Lenalidomide (CC-5013) and Dexamethasone for Newly Diagnosed MM

- 83% (25/30) achieved PR on intent-to-treat basis
- Combination appears active
- Final analysis awaited to confirm results
- Randomized phase III trials of lenalidomide/ Dex in newly diagnosed MM are ongoing (SWOG S0232, ECOG E4A03)

Rajkumar SV et al. *Blood.* 2004;104(part 1):98a [abstract 331]

Lenalidomide and Dex: Adverse Events Profile

Hematologic toxicity, %	Grade 1/2	Grade 3/4
Anemia	**3**	**7**
Neutropenia	**17**	**3**
Lymphopenia	**17**	**3**
Non-hematologic toxicity, %	Grade 1/2	Grade 3
DVT (all received prophylaxis)	**0**	**0**
Constipation	**7**	**0**
Sedation	**30**	**7**
Rash	**3**	**3**
Neuropathy	**17**	**0**
Anxiety	**7**	**7**

Rajkumar SV et al. *Blood.* 2004;104(part 1):98a [abstract 331]

Novel Agents in Multiple Myeloma Summary/Conclusions

- Effective in relapsed/refractory patients
- Combinations can produce high response rates (up to 89-90%) in newly diagnosed patients
  - CR/near CR rates up to 20-30%
- Toxicities profile different from conventional chemotherapy, but potentially manageable (DVT, peripheral neuropathy)

Novel Agents as Part of Initial Therapy in MM: Unanswered Questions

- Will the improved response rates translate into better overall survival?
- Should novel agents/combinations be used upfront or reserved for relapse?
- Will aggressive regimens replace ASCT?
- Will they prove to be necessary as maintenance therapy after ASCT?

Ongoing/Pending PMH Multiple Myeloma Trials

- **Newly diagnosed myeloma**
  - **Dex + Velcade + Doxil (DBd)**
  - **Velcade in t(4;14) myeloma**
- **Relapsed disease**
  - **Cyclophosphamide + prednisone + Velcade**
  - **Revlimid + Dex (expanded access)**
  - **BCL inhibitor (GeminX)**
  - **Irreversible proteasome inhibitor**
  - **Histone deacetylase inhibitor (SAHA)**

Thalidomide (Thalomid®)

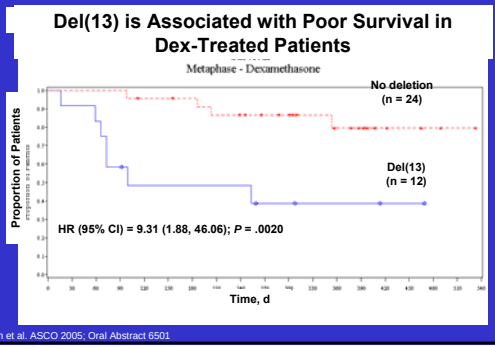
- Oral immunomodulator
- Derivative of glutamic acid
- Anti-angiogenic and apoptotic properties

Thal/Dex vs Dex in Newly Diagnosed MM
Conclusions

- Addition of thal improves depth of response compared with Dex alone
- Significant increases in non-heme toxicity and DVT
  - DVT might be managed by prophylactic anticoagulation
- Thal + Dex is a reasonable alternative to VAD or Dex alone

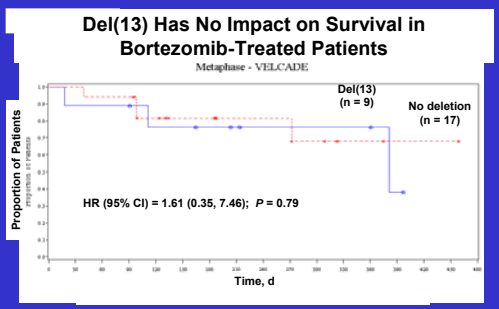
Rajkumar SV et al. *Blood*. 2004;104:98a

Del(13) in Multiple Myeloma
APEX: Matched-Pairs Analysis



Jagannath et al. ASCO 2005; Oral Abstract 6501

Del(13) in Multiple Myeloma
APEX: Matched-Pairs Analysis



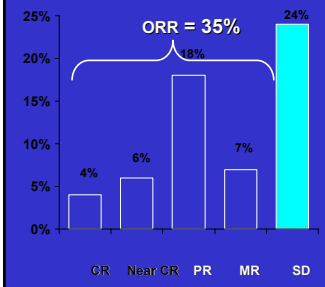
Jagannath et al. ASCO 2005; Oral Abstract 6501

APEX: Final Results (N=669)

- **Time to Progression:** 78% improvement on bortezomib arm (p< 0.0001)
  - Median TTP: Bortezomib 6.2 mos, Dex 3.5 mos
- **Survival:** Overall survival superior on bortezomib arm (p< 0.0013) including patients on dex who crossed over to bortezomib
  - 1 year survival: bortezomib 80%, Dex 65%
  - 41% decreased risk of death at year on bortezomib arm (p= 0.0005)

Richardson et al. ASH 2004; Abstract 336.5.

SUMMIT – Response Rates to VELCADE* Alone



- 193 evaluable patients
- 35% overall response (CR+PR+MR)
- 27% CR+PR
- 24% SD
- 59% of patients SD or better
- Assessed by Independent Review Committee

1 Richardson P et al. *N Engl J Med.* 2003;348:2609-2617.

Novel Agents in Myeloma

Thalidomide, Bortezomib (Velcade™), and Lenalidomide (Revlimid™)

- In relapsed/refractory disease
- As part of first line therapy
  - Before ASCT
  - In patients ineligible for ASCT
- As maintenance therapy after ASCT