VELCADE
výsledky klinických studií
a
srovnání s dostupnou léčbou

Roman Hájek

ČEJKOVICE 2.4.2005

Obsah

- Phase I Trials
- Phase II Summary – SUMMIT (025) & CREST (024)
- Phase II – SUMMIT, CREST & Extension Trial (029)
- Phase III Trial – APEX (039)
- Combination Trials – Relapsed/Refractory
- Front-line & Pre-Transplant Trials
- Peri-Transplant Trials
- Handling & Dosing Guidelines

Bortezomib = inhibitor of proteasome

- Intracellular proteolysis is regulated by ubiquitin; ubiquitinated proteins are targeted to proteasome for destruction
- 90% proteins including critical regulatory intracellular proteins are degradated via ubiquitin-proteasome pathway
- Many of those proteins possess critical role in regulation of key intracellular signaling pathways that are altered during cancerogenesis

Proteasome manipulation could effectively influence cellular signaling in cancer cells

SUMMIT (025): A Phase II Study of VELCADE® for Injection in Patients With Relapsed and Refractory Multiple Myeloma

Paul G. Richardson,[1] Bart Barlogie,[2] James Berenson,[3] Seema Singhal,[4] Ann Traynor,[4] Sundar Jagannath,[5] David Irwin,[6] Vincent Raikumar,[7] Gordan Srkalovic,[8] Melissa Alsina,[9] Raymor... Orlowski,[12] David Kuter,[13] Steven Limentani,[14] ... Michael Kauffman,[15] Julian Adams... C. Anderson[1]

[1]Dana-Farber Cancer Institute, [2]University of Arkansas, [3]Cedars-Sinai Medical Center, [4]Northwestern University Medical Center, [5]St Vincent's Comprehensive Cancer Center, [6]Alta Bates Cancer Center, [7]Mayo Clinic, [8]Cleveland Clinic Foundation, [9]H. Lee Moffitt Cancer Center, [10]M.D. Anderson Cancer Center, [11]Carol G. Simon Cancer Center, [12]University of North Carolina at Chapel Hill, [3]Massachusetts G... [15]Millennium Pha...

202 pts

Richardson P et al. *N Engl J Med.* 2003;348:2609-2...

CREST (024) A Phase II Multicenter Randomized Study of the Proteasome Inhibitor VELCADE® in Multiple Myeloma Patients Relapsed After Front-Line Therapy

Sundar Jagannath,[1] Bart Barlogie,[2] James Berenson,[3] David Siegel,[4] David Irwin,[5] Paul G. Richardson,[6] Mi... Steven A. Limentani,[9] Melissa Alsina,[10] Dix... Julian Adams,[11] David ... on[6]

[1]St. Vincent's Catholic Medical Center, [2]University of Arkansas, [3]Cedars-Sinai Medical Center, [4]Carol G. Simon Cancer Center, [5]Alta Bates Comprehensive Cancer Center, [6]Dana-Farber Cancer Institute, [7]New York Presbyterian Hospital, [8]M.D. Anderson Cancer Center, [9]Charlotte Medical Clinic, [10]H. Lee Moffitt Cancer Center, and [11]Millennium Pharmaceuticals, Inc.

54 pts

Phase III Study 039 (APEX) and 040

APEX Study Overview

- International, randomised Phase III trial (APEX)
  - VELCADE® versus high-dose dexamethasone
  - Evaluation of time to progression
  - Assessment of dose modification to minim...
- Rollover p... with PD after h...

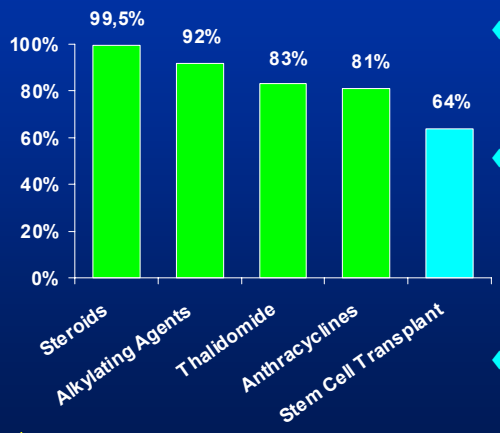
670 pts.

Obsah

- Phase I Trials
- **Phase II Summary – SUMMIT (025) & CREST (024)**
- Phase II – SUMMIT, CREST & Extension Trial (029)
- Phase III Trial – APEX (039)
- Combination Trials – Relapsed/Refractory
- Front-line & Pre-Transplant Trials
- Peri-Transplant Trials
- Handling & Dosing Guidelines

SUMMIT (025):

SUMMIT – Prior Therapy

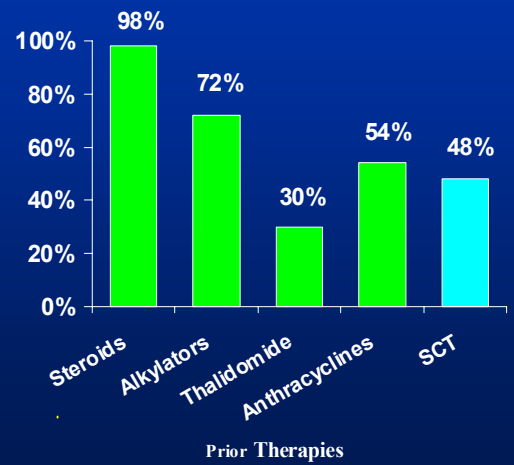


- Median number of lines of prior therapy = 6 (range 2-15)
- 92% of patients received at least 3 of the drug therapies listed here (excluding stem cell transplant)
- 91% of patients were refractory to the last prior therapy

Adapted from data in Richardson P et al. *N Engl J Med.* 2003;348:2609-2617.
Richardson P et al. ASCO 2003. Abstract 2338.

CREST (024)

CREST – Previous Therapy



- Median lines of prior therapy = 1
- Median number of prior regimens = 3 (range 1-7)

Jagannath S et al. ASH 2002. Abstract 3207.

SUMMIT (025):	CREST (024)
SUMMIT – Prior Therapy	**CREST – Previous Therapy**

SUMMIT – Conclusions

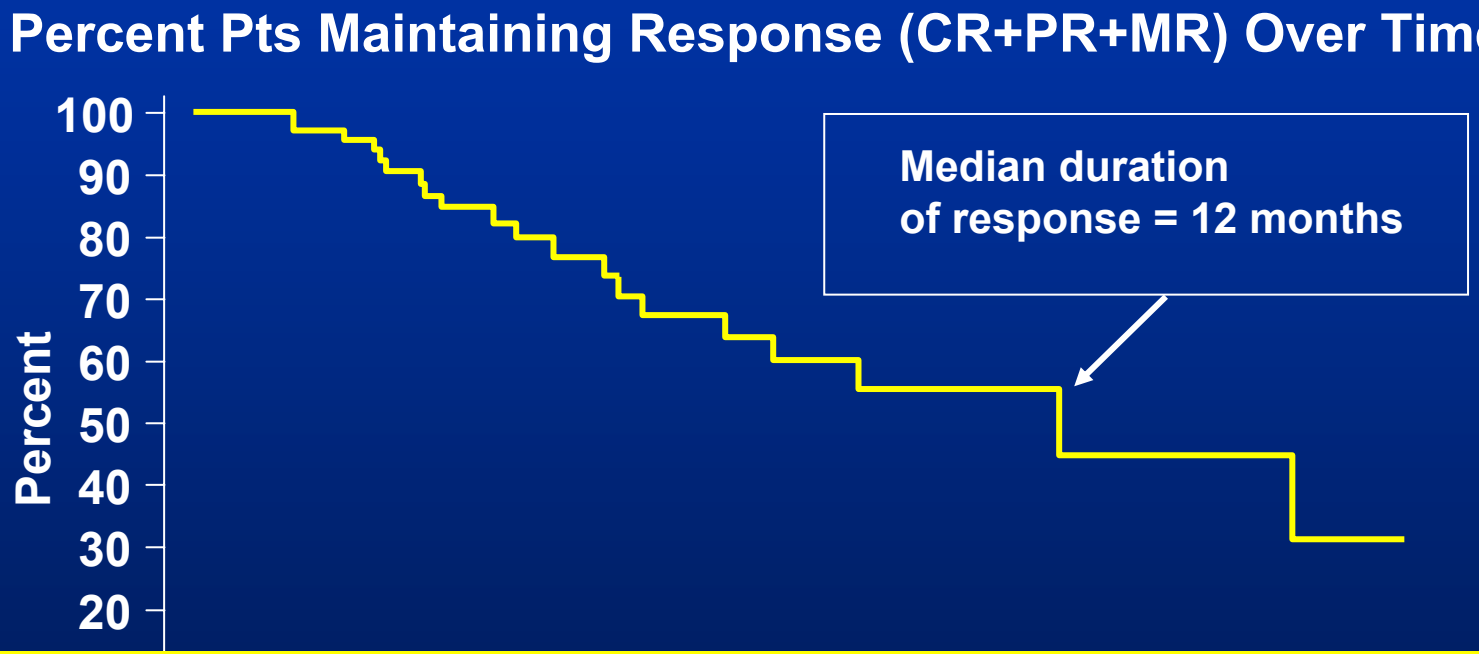
- VELCADE® was active in relapsed and refractory multiple myeloma pts
- Overall response rates
  - CR: 4%
  - Near CR: 6%
  - CR+PR: 27%
  - CR+PR+MR: 35%
- Median duration of response (CR+PR): 12.7 months
- Median overall survival: 17 months

CREST Study – Conclusions

- Confirms intrinsic activity of both 1.3 and 1.0 mg/m^2 doses
  - CRs observed at both 1.3 and 1.0 mg/m^2
  - Overall response
    - 50% in 1.3 mg/m^2
    - 33% in 1.0 mg/m^2
- Differences in side effects between doses require further analysis

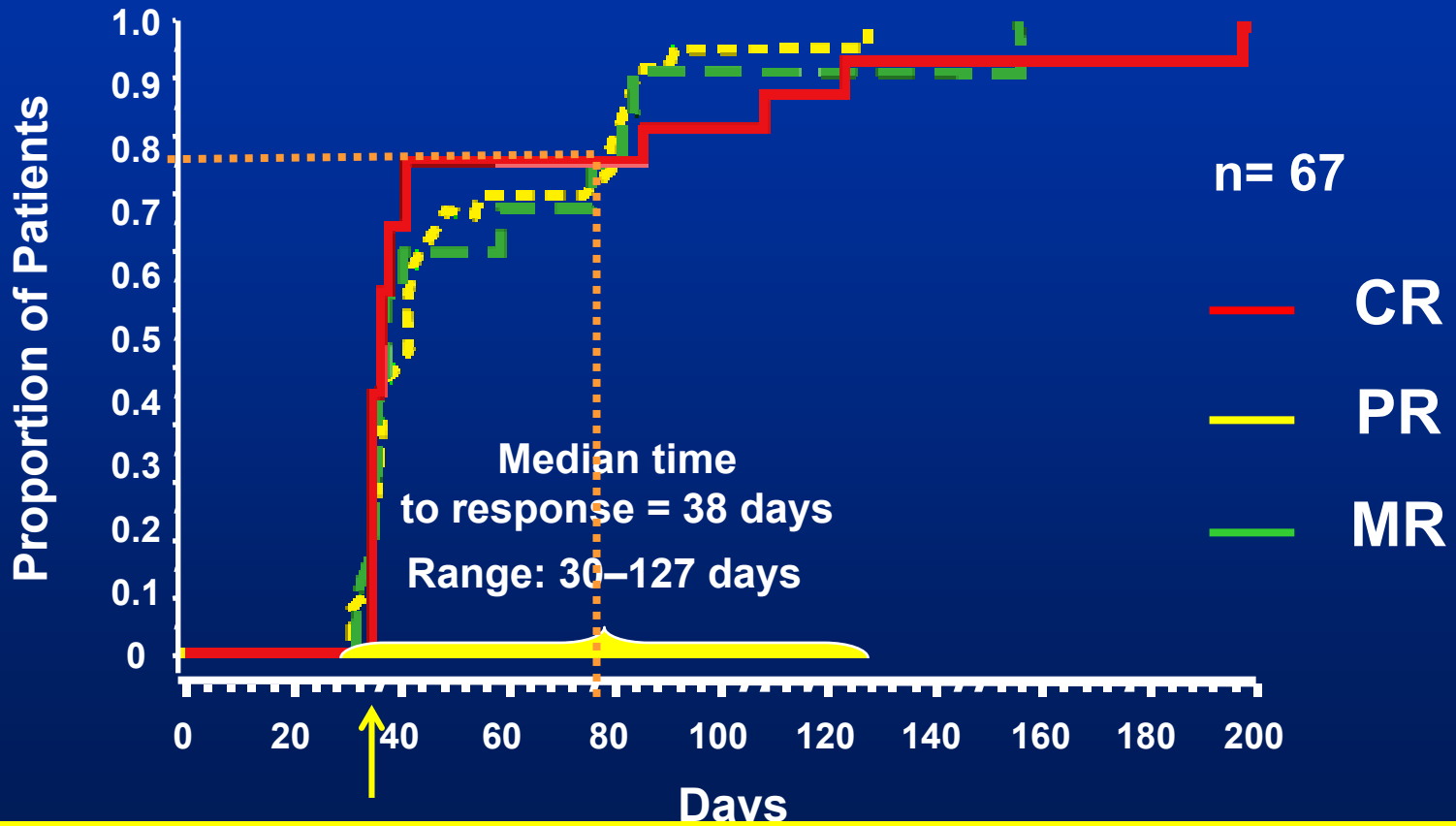
Velmi dobrá léčebná účinnost u vysoce předléčených nemocných
Nevede k vyléčení. Prodlužuje dobu do relapsu
Na dávce závislá léčebná odpověď ?
SUMMIT prototyp velmi dobré klinické studie,
CREST menší studie ukazující význam na dávce závislé léčebné účinnosti a toxicity,

SUMMIT:
Duration of Response with VELCADE®



Ve studii překonal Velcade „magickou biologickou hranici“
Je-li obecně každá další doba do relapsu kratší, při použití Velcade tomu tak není.
Reaguje-li nemocný na Velcade minimálně MR, má šanci na oddálení další aktivity onemocnění s mediánem 12 měsíců při relapsu č. >3
Kolik to bude pro méně předléčené nemocné ?
Podobně platí pro nereagující na monoterapii, byl-li přidán dexametazon !

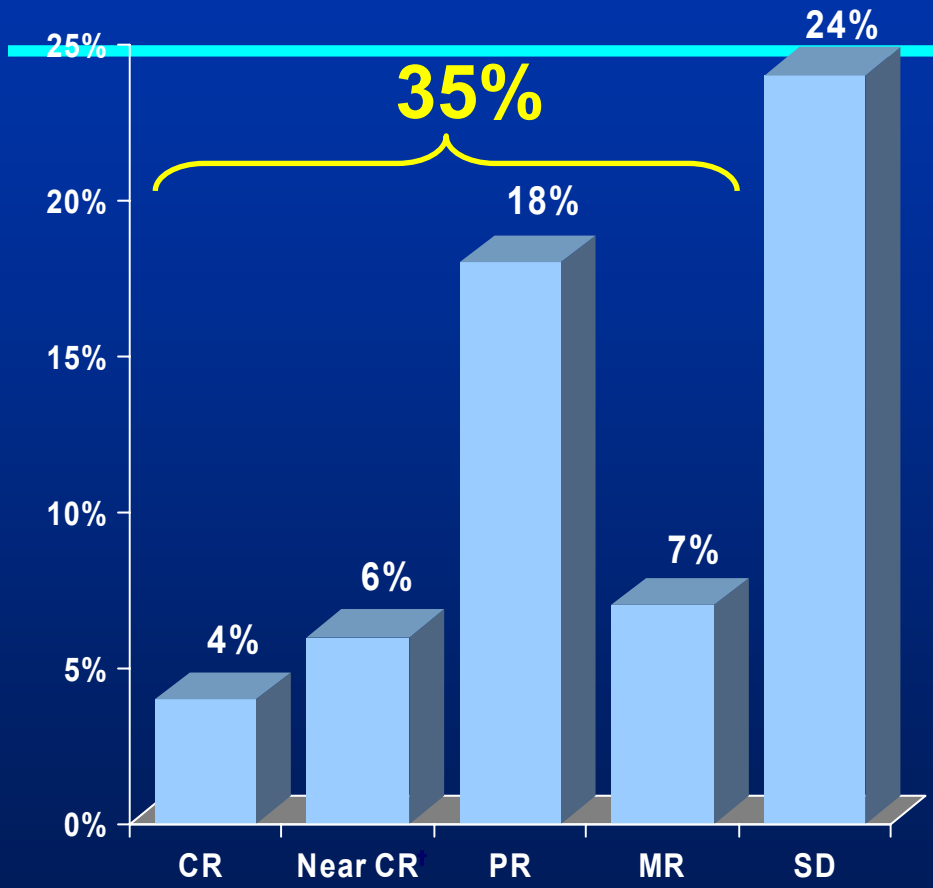
SUMMIT: Time to Response with VELCADE® Alone



Rychlý potenciál k poklesu MIG dává možnost časně reagovat a léčbu včas přerušit, respektive dříve použít kombinaci s kortikoidy.

Zachránit více nemocných v časné fázi primoléčby v budoucnosti, kde ztrácíme 30 % nemocných

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

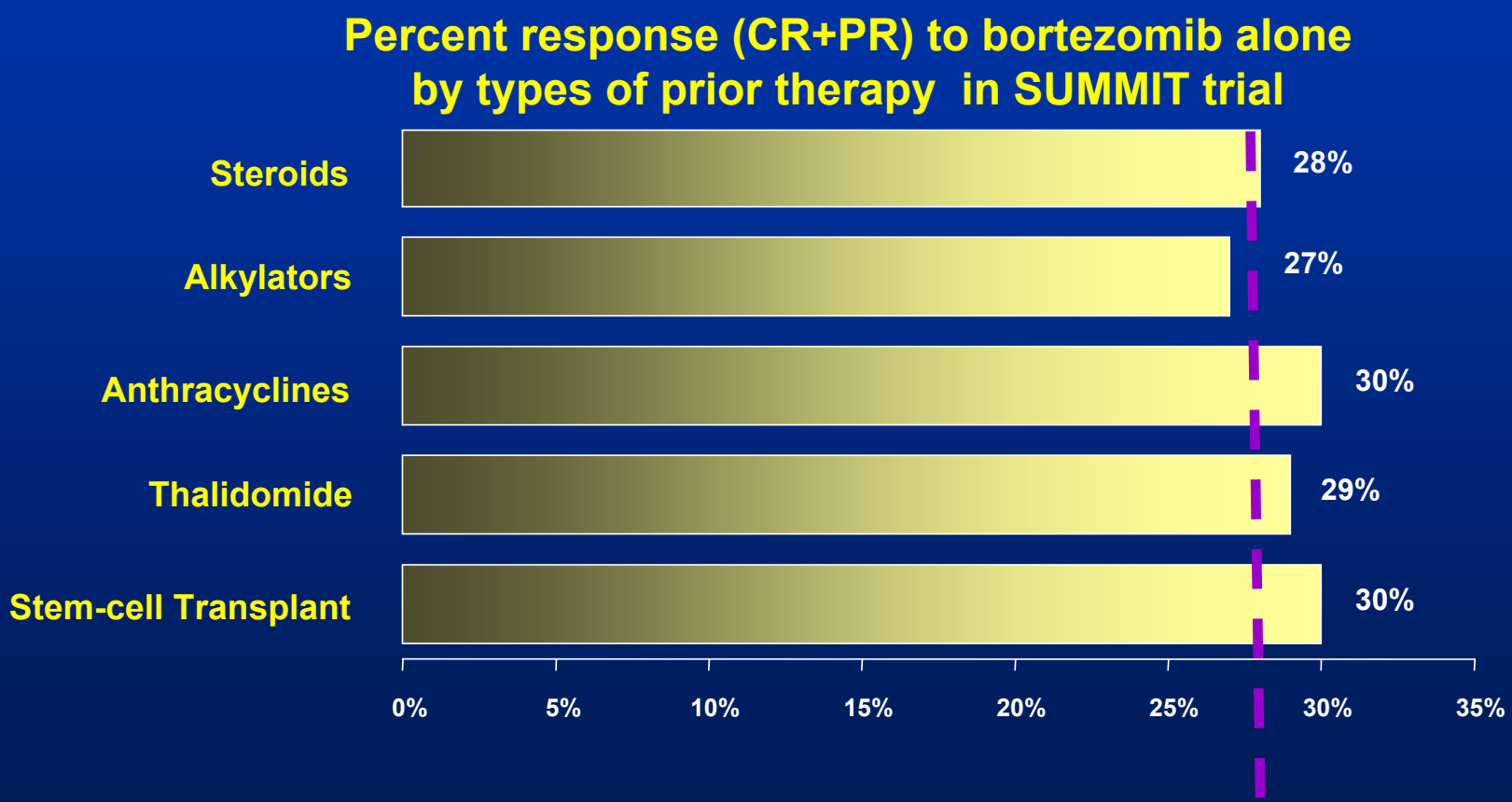
† Near CR met all the criteria for a CR, with the exception of detectable M protein by immunofixation

Numbers rounded to nearest integer.

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

SUMMIT:

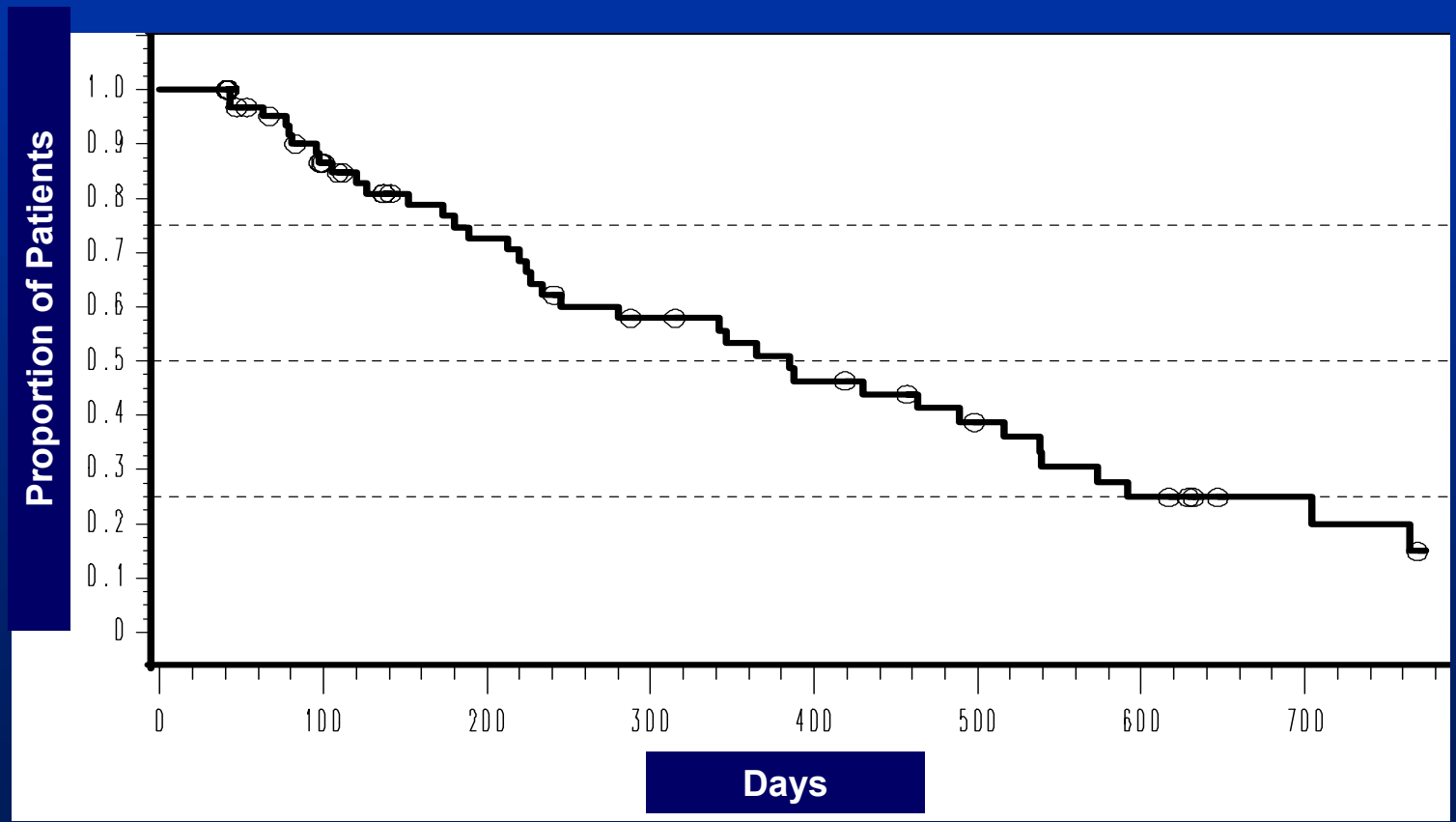
Response Rates Independent of the Types of Prior Therapy[1]



1. Millennium Pharmaceuticals, Inc. , 2003

SUMMIT:
Updated Duration of Response – Bortezomib Alone

Median DOR: 385 d or ~12.7 mo (CR + PR + MR; n = 67)



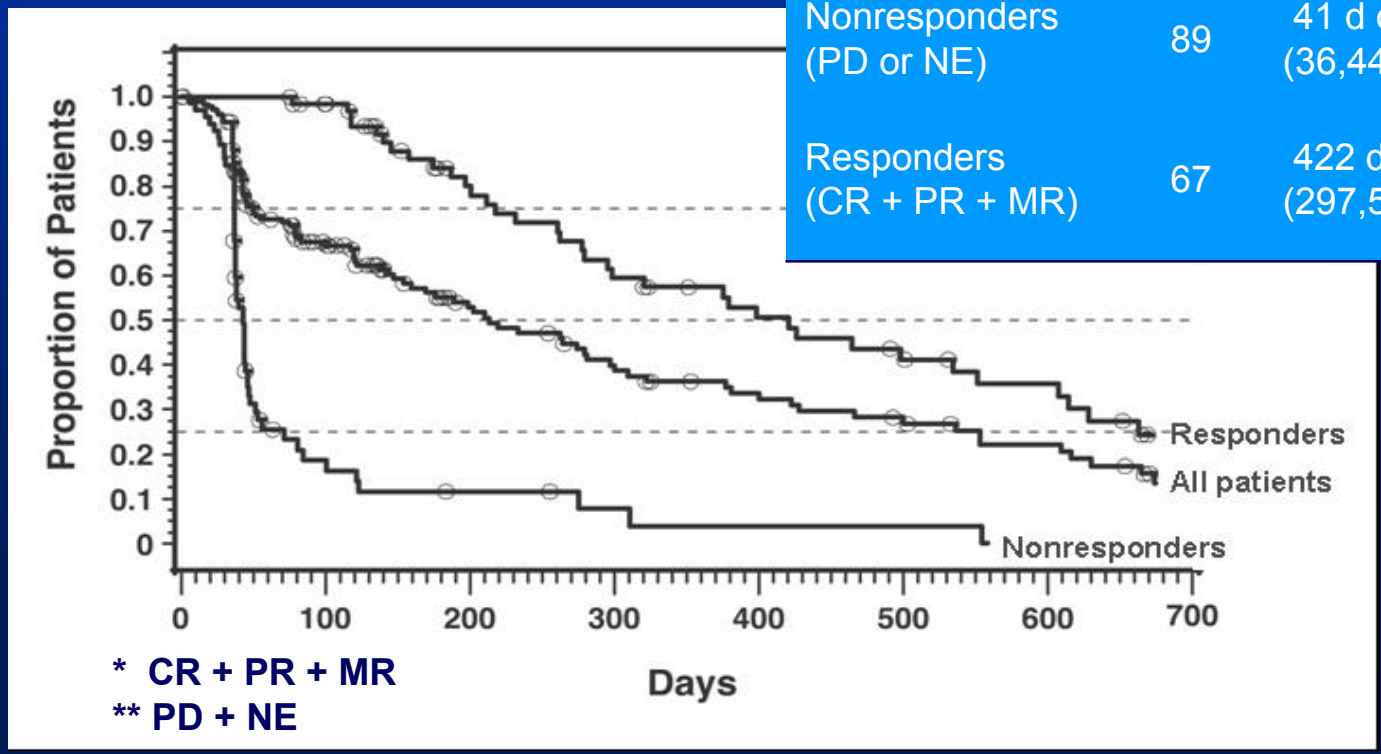
- Historically, the mean DOR ranges between 3 and 7 months with re-treatment in relapsed myeloma[1]

Richardson et al. EHA 2004; Abstract 304.

SUMMIT: Updated Time-to-Progression

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

	N*	Median TTP (95% CI)
All patients	202	213 d or ~ 7.0 mo (154,297 d)
Nonresponders (PD or NE)	89	41 d or ~ 1.3 mo (36,44 d)
Responders (CR + PR + MR)	67	422 d or ~ 13.9 mo (297,553 d)



* CR + PR + MR
** PD + NE

Richardson et al. EHA 2004; Abstract 304.

SUMMIT: Updated Overall Survival
Bortezomib Alone or in Combination with Dexamethasone

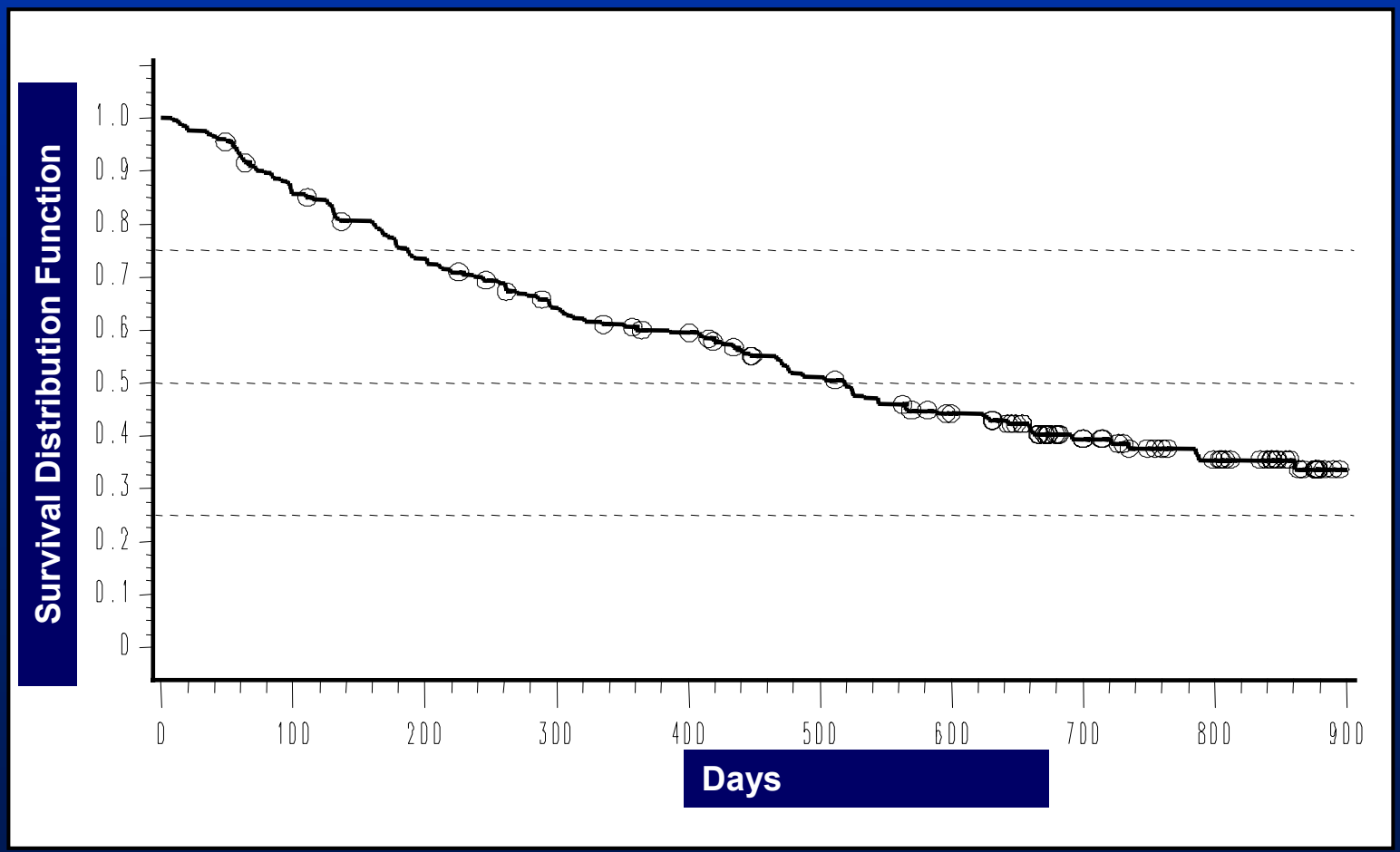
	N*	Median Survival (95% CI)
All patients	202	518 d or ~ 17.0 mo (434,643 d)
Nonresponders (PD, NE)	87	244 d or ~ 8.0 mo (132,312 d)
Responders (CR + PR + MR)	78	Not yet reached

*Survival: ITT population; no censoring

Richardson et al. EHA 2004; Abstract 304.

SUMMIT: Updated Overall Survival

Median Survival: ~ 17.0 mo (N = 202)



Richardson et al. EHA 2004; Abstract 304.

Additional Response with Bortezomib + Dexamethasone

- Patients with progressive disease after first 2 cycles or stable disease at 4 cycles to bortezomib alone were allowed to add dexamethasone
  - 20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12 of each treatment cycle
- Improved responses were observed in 22 patients
  - SUMMIT: 18% (11% MR and 7% PR)
  - CREST 1.0 or 1.3 mg/m^2: 33%
- Toxicities of combination therapy were manageable and not increased compared with single-agent bortezomib
- Responses to combination therapy were seen in patients refractory to dex and bortezomib as single agents

Jagannath et al. EHA 2004; Abstract 369.

SUMMIT: Conclusions

Bortezomib demonstrated encouraging activity in a heavily pre-treated multiple myeloma patient population who had received at least 2 prior therapies and had progressed on their most recent therapy

- **Overall response rates**
  - **New England Journal of Medicine, 193 patients evaluable[1]**
    - **10% CR and near CR**
    - **35% CR+PR+MR**
    - **59% Stable disease or better**
- **Updated median duration of response: 12.7 months (8.2, NE)[2]**
- **Updated median overall survival: 17.0 months (434, 643 d)**
- **Manageable toxicities**

NE = not estimable

1. Richardson et al. *N Engl J Med.* 2003;348:2609-2617.
2. Richardson et al. EHA 2004.

Toxicity of Bortezomib therapy

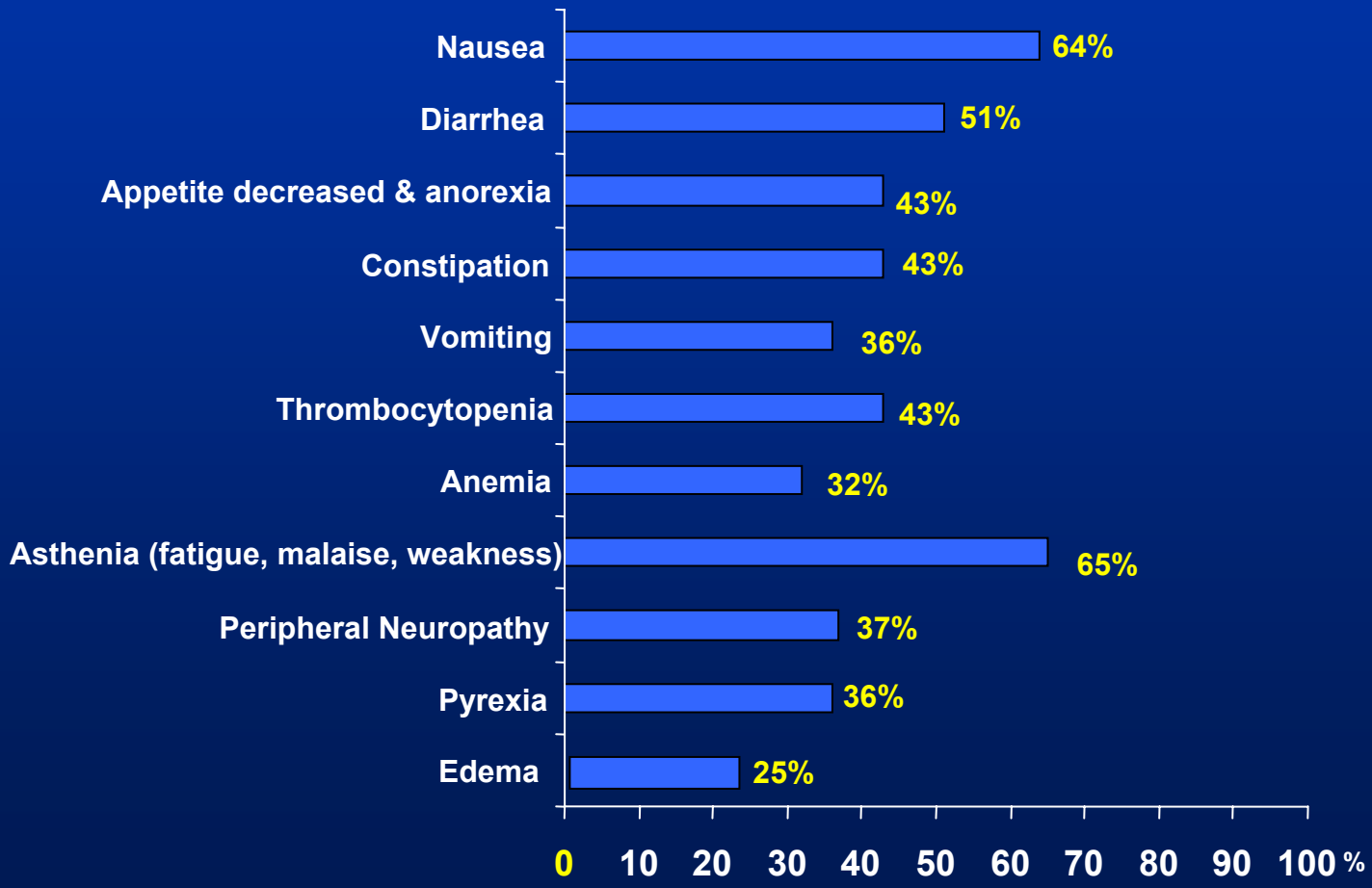
SUMMIT: Most Common Adverse Events

N=202	Grades 1-2*	Grade 3*	Grade 4*
Nevolnost	58%	6%	0%
Průjem	41%	7%	1%
Slabost	37%	12%	0%
Trombocytopenie	13%	28%	3%
Zácpa	41%	2%	0%
Zvracení	27%	8%	1%
Nechutenství	32%	2%	0%
Periferní neuropatie	22%	12%	0%
Horečka	30%	4%	0%
Anémie	23%	8%	0%
Otoky	25%	1%	0%

*National Cancer Institute Common Toxicity

Combined Safety Data from SUMMIT and CREST Trials*†[1]

On-Study adverse events (≥30% overall) in Phase II clinical trials at 1.3 mg/m^2 dose (N=228)



*AEs reported for all events, drug related or not. †NCI CTC, Version 2.0). 1.Millennium Pharmaceuticals, Inc., 2004.

Bortezomib: Asthenic Conditions[1]

- Incidence of Asthenic Conditions (fatigue, malaise, weakness)
  - Overall incidence 65%
  - Grade 3* 18%
  - Grade 4* <1%
  - Discontinued due to fatigue 2%
- First onset of fatigue most often reported during 1st and 2nd cycles of therapy
- Most patients in clinical trials were able to continue therapy despite fatigue

*NCI CTC, Version 2.0

1. Millennium Pharmaceuticals, Inc., 2004.

Bortezomib: Gastrointestinal Toxicities by Grade[1]

N=228	Grades 1-2*	Grade 3*	Grade 4*
Nausea	58%	6%	0%
Diarrhea	43%	7%	<1%
Appetite decreased & anorexia	41%	3%	0%
Constipation	40%	2%	0%
Vomiting	29%	7%	<1%

- Patients should be advised regarding appropriate measures to avoid dehydration
- Administer fluids and electrolytes if patient becomes dehydrated
- Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness, or fainting spells
- Administration of antiemetics and antidiarrheals as needed

*NCI CTC, Version 2.0

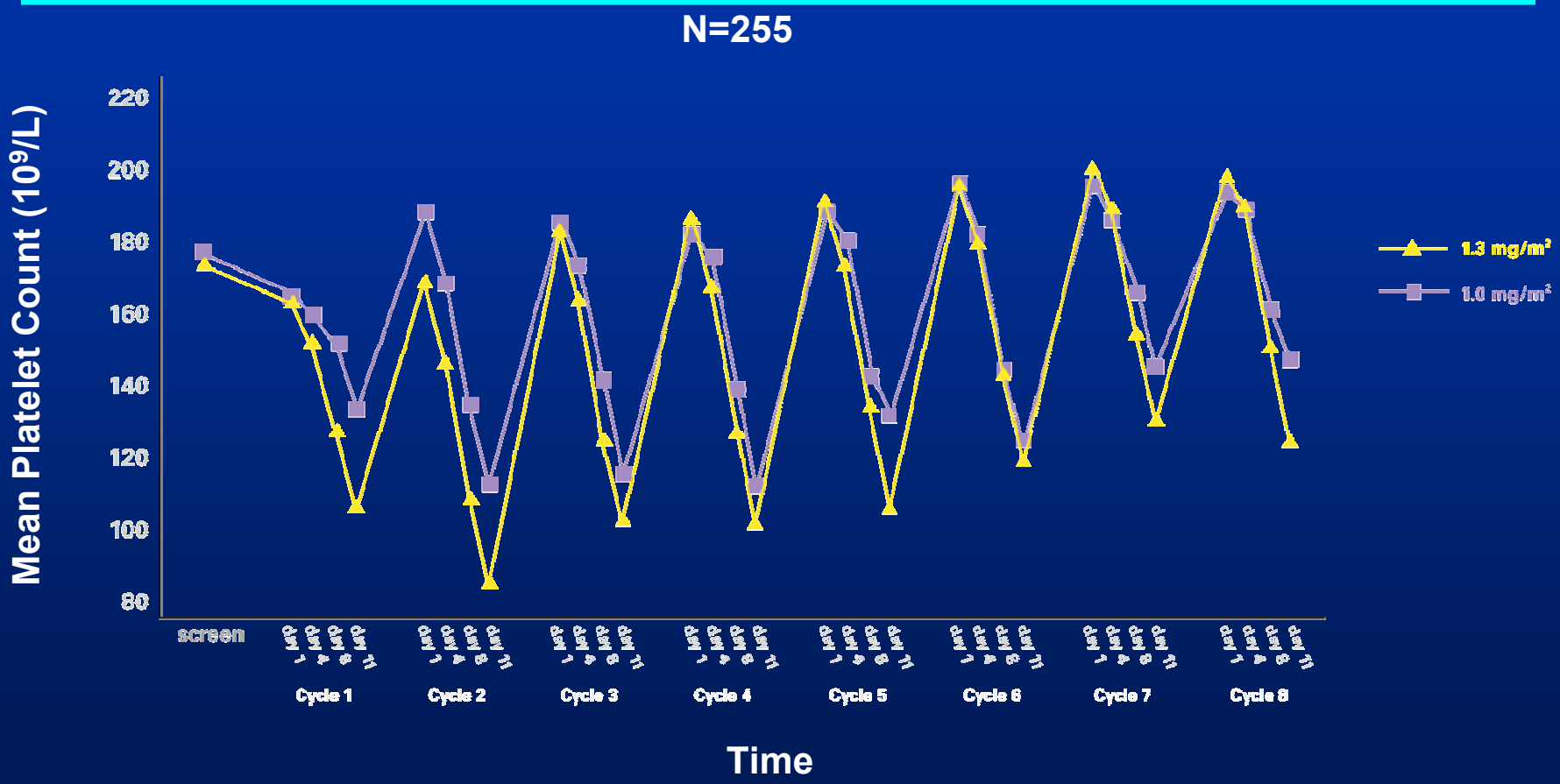
1. Millennium Pharmaceuticals, Inc., 2004.

Bortezomib: Thrombocytopenia[1]

Evaluation of the Degree of Thrombocytopenia and Associated Risk Factors Following Bortezomib Therapy for Relapsed and/or Refractory Multiple Myeloma

Lonial et al. Programs and abstracts of the 9th Annual Congress of the European Hematology Association, 2004; Geneva. Abstract 371

Bortezomib: Platelet Count Kinetics[1]



1. Lonial et al. ASH 2003, Abstract 1632.

Bortezomib: Managing Thrombocytopenia[1]

Characteristics

- Dose related decrease in platelet count during treatment period (days 1-11) with return to baseline during the rest period (days 12-21)
- Nadir ~40% of baseline
- Gastrointestinal and intracerebral hemorrhages have been reported

Recommendations

- Frequently monitor platelet count throughout treatment; transfusions can be given at physician's discretion
- Observe patients for signs of thrombocytopenia, such as bleeding or bruising
- Mechanisms of platelet reduction are probably unique
  - Treatment may need to be held with serious Grade 4 thrombocytopenia
  - Treatment may be reinitiated at a reduced dose after resolution of toxicities

1. Millennium Pharmaceuticals, Inc., 2004.

Bortezomib: Other Hematologic Toxicities[1]

Hematologic toxicities	Anemia	Neutropenia
– Overall incidence	32%	24%
– Grade 3*	9%	13%
– Grade 4*	0	3%
– Discontinuation	<1%	<1%

- Although pyrexia occurred in 36% of patients, the incidence of febrile neutropenia was <1%
- Frequently monitor complete blood count (CBC) throughout treatment
- Management may include the use of growth factors or red blood cell transfusions at physician's discretion

*NCI CTC, Version 2.0

1. Millennium Pharmaceuticals, Inc., 2004.

Peripheral Neuropathy with Bortezomib in Phase II Multiple Myeloma Studies[1]

- Incidence of Treatment Emergent Peripheral Neuropathy
  - Overall 37%
  - Grade 3* 14%
  - Grade 4* 0%
  - Discontinuation due to events 6%
- Peripheral neuropathy is predominantly sensory, although cases of mixed sensorimotor neuropathy have been reported
- Symptoms include: numbness, burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort or neuropathic pain

*NCI CTC, Version 2.0

1. Millennium Pharmaceuticals, Inc., 2004. 1.3 mg/m^2 dose population

Recommended Bortezomib Dose Modification for the Management of PN

Severity of Peripheral Neuropathy Signs/Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesia and/or loss of reflexes without pain or loss of function)	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue bortezomib

Bortezomib: Managing Peripheral Neuropathy[1]

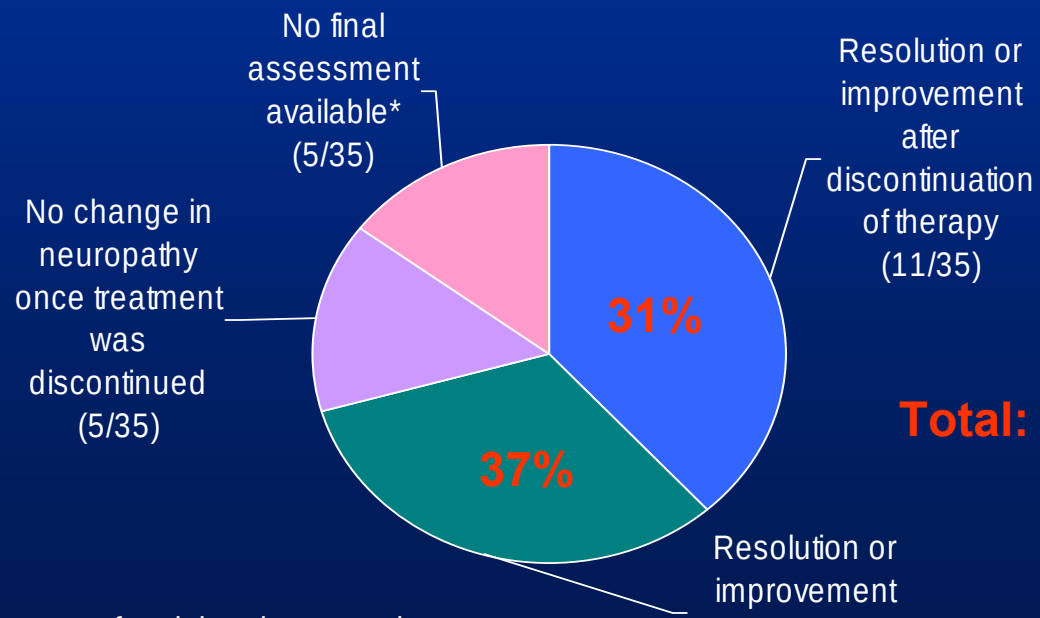
Recommendations

- Monitor patients for symptoms of neuropathy and/or pain at each treatment visit
- Patients should contact their physician if they experience new or worsening symptoms of peripheral neuropathy
- Early detection and appropriate dose/schedule modification may result in the resolution or improvement of neuropathy

1. Millennium Pharmaceuticals, Inc., 2004.

Outcome of PN After Follow-Up Improvement in 2/3 of patients

- **Follow-up of 35 patients with grade 3/4 peripheral neuropathy or neuropathy leading to discontinuation**
- **Overall a total of 25 (71%) of the 35 patients had the PN event resolve or improve based on last available follow-up information**



Total: 37%+31% = 68%

* 5 pts died before final assessment of peripheral neuropathy could be made.

1.Richardson et al. ASH 2003; Abstract 512.

Bortezomib: Hypotension Characteristics & Precautions[1]

Characteristic

- 12% of patients experience hypotension
- Orthostatic/postural hypotension, usually mild to moderate (Grade 1 or 2 in severity) may occur throughout therapy

Precautions

- Caution should be used when treating patients with a history of syncope, who are receiving medications known to be associated with hypotension, or who are dehydrated

1. Millennium Pharmaceuticals, Inc., 2004.

Bortezomib: Managing Treatment-related Hypotension[1]

Recommendations for patients

- Seek medical advice if they experience symptoms of dizziness, light-headedness, or fainting spells
- Maintain hydration
- Exercise caution when operating machinery including automobiles

Management may include

- Adjustment of antihypertensive medications
- Rehydration
- Administration of mineralocorticoids

1. Millennium Pharmaceuticals, Inc., 2004.

Obsah

- Phase I Trials
- Phase II Summary – SUMMIT (025) & CREST (024)
- Phase II – SUMMIT, CREST & Extension Trial (029)
- **Phase III Trial – APEX (039)**
- Combination Trials – Relapsed/Refractory
- Front-line & Pre-Transplant Trials
- Peri-Transplant Trials
- Handling & Dosing Guidelines

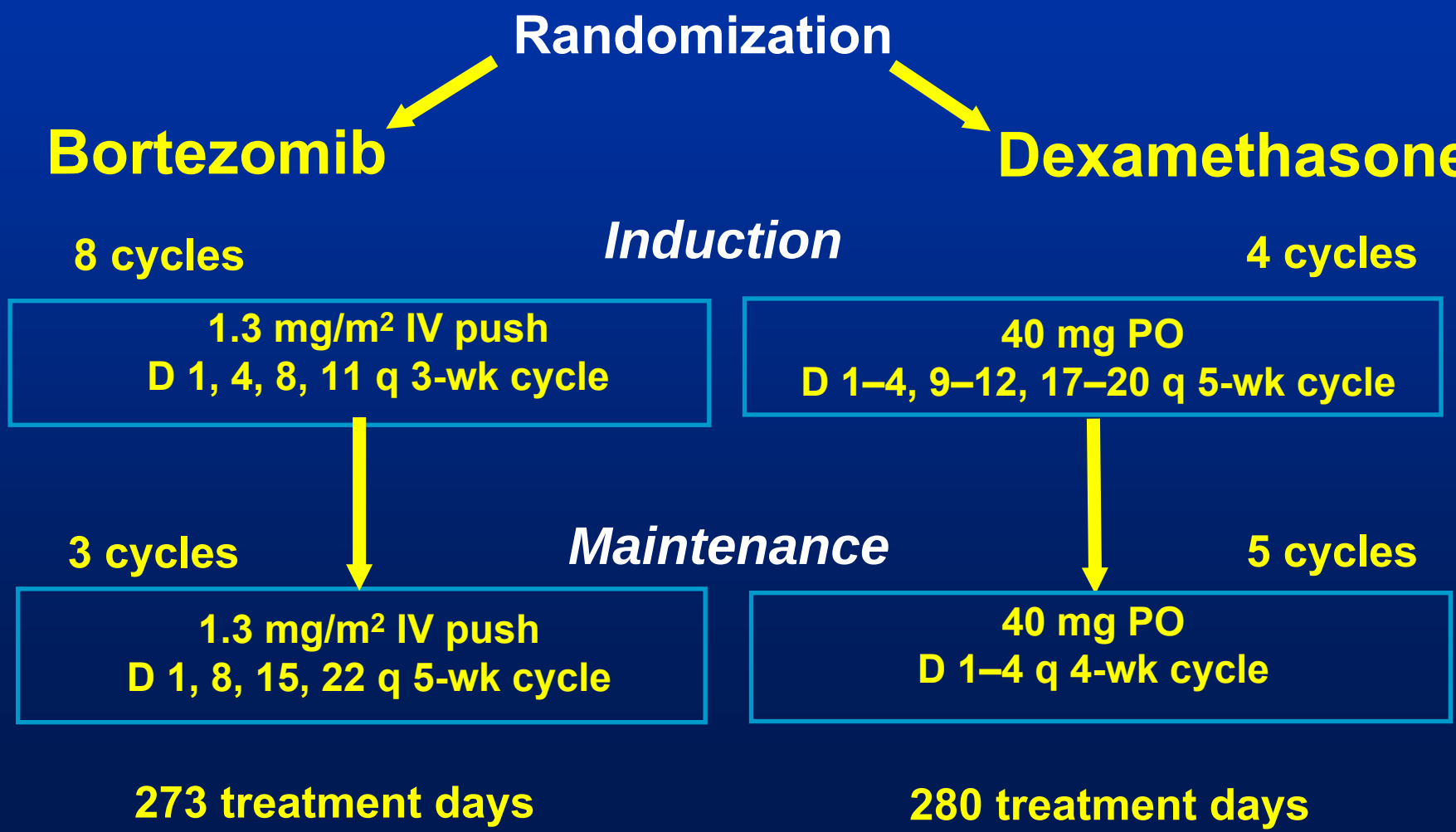
APEX Study Protocol

- **Study Design**
  - International, randomized, open-label study in relapsed or refractory MM (N=669)
  - Endpoints :
  - **Primary:** time to progression (TTP)
    Secondary: survival, response rate (RR) and duration, time to skeletal events (TSE), ≥ G3 infection, safety
  - Companion crossover study (M34101-040) available to patients progressing on dex
- **Eligibility Criteria**

Inclusion	Exclusion
♦ Relapsed or refractory MM following 1–3 prior lines of therapy ♦ Measurable disease (M-protein or plasmacytoma) ♦ Platelets ≥ 50,000/μL ♦ Creatinine clearance ≥ 20 mL/min	♦ Refractory to high-dose dex (> 500 mg over 10 wk) – < PR to or PD within 6 mo after discontinuation of dex – ≥ G3 dex-related toxicity leading to discontinuation ♦ Peripheral neuropathy ≥ G2

Richardson et al. ASH 2004; Abstract 336.5

APEX: Treatment Plan



APEX: Patient and Disease Characteristics

	Bortezomib n = 333	Dexamethasone n = 336
Male, %	56	60
Median age, y (maximum)	62.0	61.0
IgG/ IgA/ IgD/ IgM, %	60/23/2/< 1	59/24/1/0
1 prior line of treatment, %*	40	35
Relapsed during or ≤ 6 months after most recent treatment, %*	64	65
KPS ≥ 70, %	94	96
Median serum β_2-microglobulin*†	3.7	3.6
Median platelet count, 10^3cells/μL‡	192.5	188.0
Median hemoglobin, g/dL	10.8	10.9

*Stratification factor.
†Bortezomib n = 324; dex n = 328.
‡Bortezomib n = 330; dex n = 335.

Richardson et al. ASH 2004; Abstract 336.5.

APEX: Disposition

	Bortezomib n	Dexamethasone n
Randomized (ITT)	333	336
Discontinued		
Progressive disease	98 (29%)	174 (52%)
Adverse event	121 (37%)	96 (29%)
Maintenance Phase*	75 (23%)	93 (28%)
Ongoing§	92 (28%)	50 (15%)
Crossover to -040	NA	147 (44%)

* **Bortezomib cycles 9-11, Dex cycles 5-9**

§ **Pts on-study as of January 13, 2004; NA = not applicable**

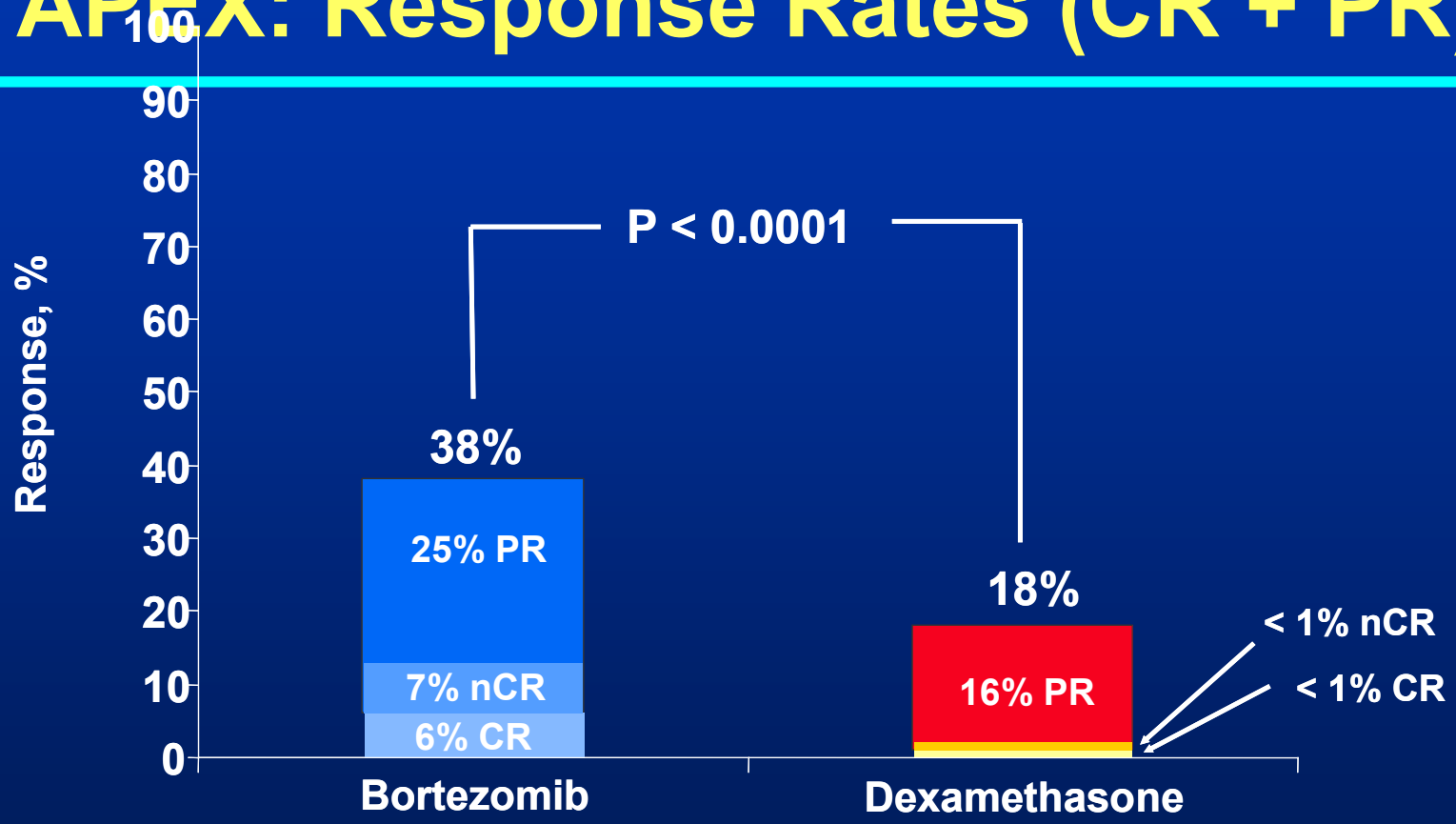
Richardson et al. ASH 2004; Abstract 336.5.

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 (HR 0.57, $p< 0.0013$) including patients on dex who crossed over to bortezomib
  - 1 year survival: Bortezomib 80%, Dex 65% (HR = 0.53, P=.0005)
  - 41% decreased risk of death at year on bortezomib arm (p=0.0005)

Richardson et al. ASH 2004; Abstract 336.5.

APEX: Response Rates (CR + PR)



Median TTR = 43 d in both arms
DOR: Bortezomib 8.0 mos vs dex 5.6 mos
Median follow-up ~8.3 months

Richardson et al. ASH 2004; Abstract 336.5.

APEX: Patients at First Relapse (Second-Line, n = 251)

	Bortezomib (n = 132)	Dexamethasone (n = 119)	P-value
Median TTP, mos	7.0	5.6	0.0021
1-year survival, %	89	72	0.0098
CR, % (n/N)	6 (8/128)	2 (2/110)	0.0842
CR + PR, % (n/N)	45 (57/128)	26 (29/110)	0.0035
Near CR, % (n/N)	6 (8/128)	2 (2/110)	NC
DOR, mos	8.1	6.2	NC

NC = not calculated

Richardson et al. ASH 2004; Abstract 336.5.

Other Secondary Efficacy Endpoints

- Time to first skeletal event
  - Median not reached in either arm
  - Results similar (hazard ratio 0.76, P=0.3153)
- Incidence of infections ≥ grade 3
  - Bortezomib 13% versus dex 16%
  - P=0.188

Richardson et al. ASH 2004; Abstract 336.5.

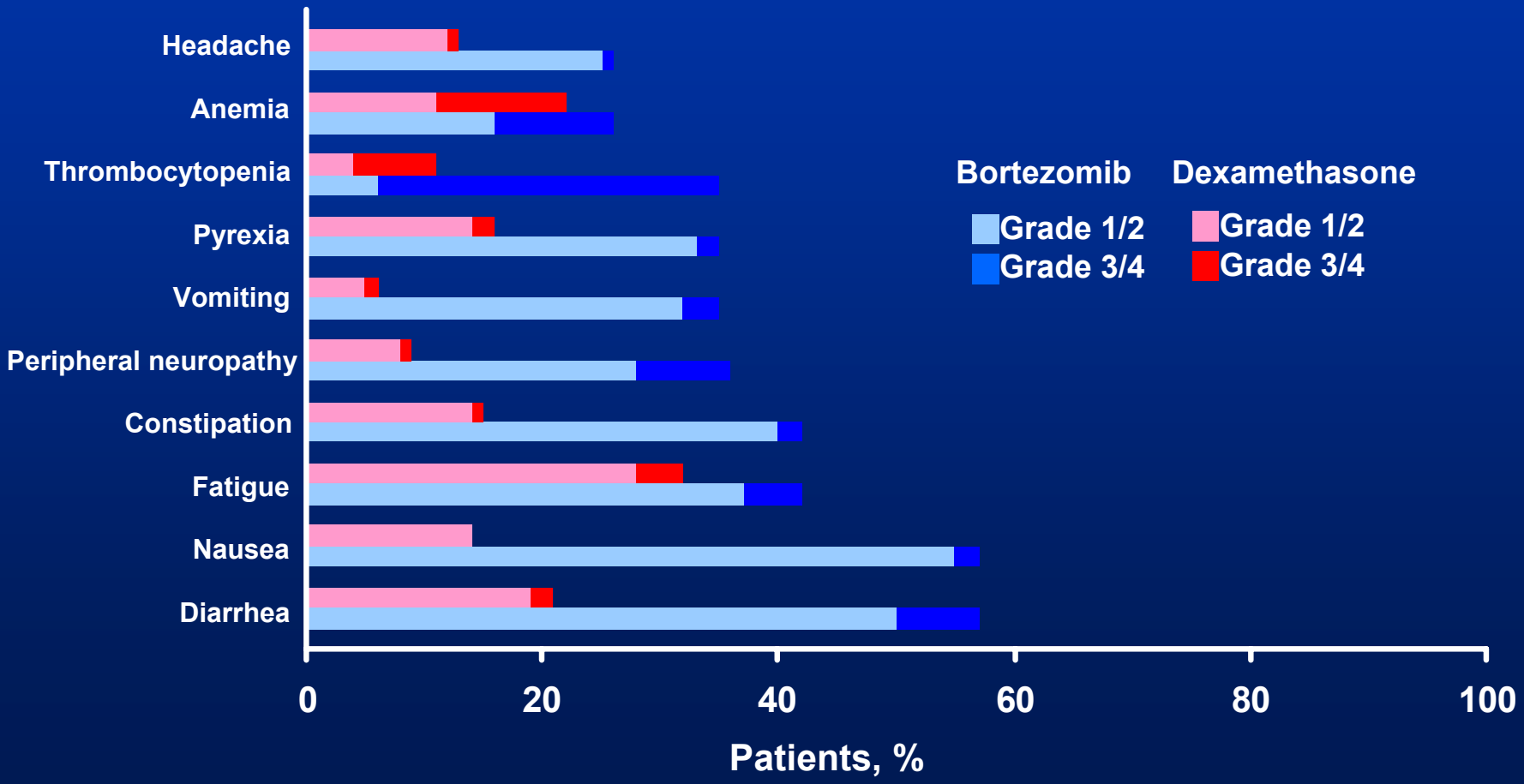
Adverse Events (All Pts)

	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

† Deaths within 30 days after last dose or > 30 days if drug related

Richardson et al. ASH 2004; Abstract 336.5.

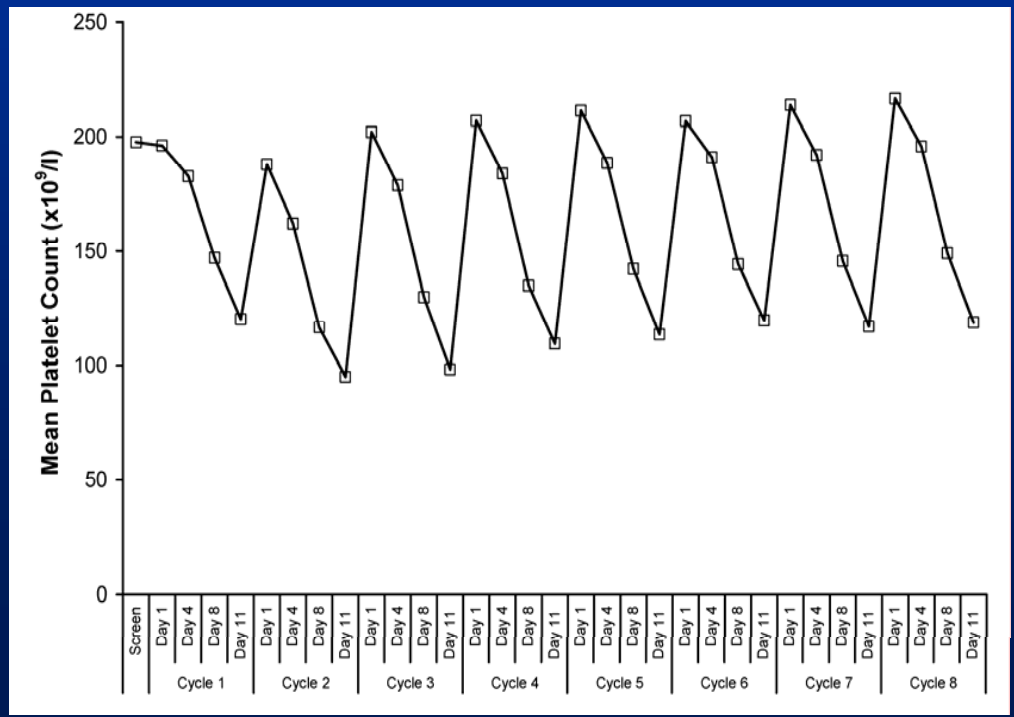
Most Frequent Adverse Events (AEs)



Richardson et al. ASH 2004; Abstract 336.5.

APEX: Thrombocytopenia

- Transient and Cyclical
- Platelet nadir at day 11
- Platelet count returns toward baseline during the rest period (days 12-21)



Richardson et al. ASH 2004; Abstract 336.5.

Peripheral Neuropathy Outcome Consistent with Phase II Trials

Baseline Peripheral Neuropathy in APEX

- 69% of 310 patients on bortezomib reported symptoms of PN at baseline (FACT/GOG-Ntx score >0)
- Baseline score directly correlated with the development of ≥ Grade 3

Treatment Emergent Peripheral Neuropathy in APEX

- Peripheral neuropathy reported in:
  - 36% bortezomib (≥Grade 3 = 8%)
  - 9% Dex (≥Grade 3 < 1%)

Improvement / Resolution of Peripheral Neuropathy in APEX

- Improvement or resolution in PN grade ≥ 2 in 51% of pts†
- Median time to improvement or resolution from first onset = 107 days (~ 3.5 months)

Richardson et al. ASH 2004; Abstract 336.5.

Safety Summary

	Bortezomib (n = 331)	Dexamethasone (n = 332)
Significant bleeding	4%	5%
Cardiac disorders	15%	13%
Psychiatric disorders	35%	49%
Psychotic disorders	0%	2%
Infections: Herpes zoster*	13%	5%

*** Prophylactic use (per investigator) of antivirals: Bortezomib 5% vs Dex 10%**

APEX: Conclusions

- Bortezomib demonstrated superior efficacy to high-dose dexamethasone in relapsed MM
  - Significant TTP benefit (P<.0001)
    - 78% increase in median TTP
  - Response rate advantage (P<.0001)
    - 38% vs. 18% (CR + PR)
    - 13% vs. 2% (CR + nCR)
  - Superior overall and 1 yr survival
  - 41% decreased risk of death at one year on bortezomib

Richardson et al. ASH 2004; Abstract 336.5.

APEX: Conclusions (cont.)

- As second line therapy, bortezomib demonstrated superior efficacy to high-dose dexamethasone
  - Statistically significant TTP benefit (p=0.0021)
  - Response rate superior (p=.0035)
  - Survival advantage (at 1 yr, p=.0098)
- Adverse events with bortezomib were manageable and predictable → favorable risk-benefit ratio

Richardson et al. ASH 2004; Abstract 336.5.

SUMMIT (025): A Phase II Study of VELCADE® for Injection in Patients With Relapsed and Refractory Multiple Myeloma

Paul G. Richardson,[1] Bart Barlogie,[2] James Berenson,[3] Seema Singhal,[4] Ann Traynor,[4] Sundar Jagannath,[5] David Irwin,[6] Vincent Rajkumar,[7] Gordan Srkalovic,[8] Melissa Alsina,[9] Raymor... Orlowski,[12] David Kuter,[13] Steven Limentani,[14] ... Michael Kauffman,[15] Julian Adams... C. Anderson[1]

[1]Dana-Farber Cancer Institute, [2]University of Arkansas, [3]Cedars-Sinai Medical Center, [4]Northwestern University Medical Center, [5]St Vincent's Comprehensive Cancer Center, [6]Alta Bates Cancer Center, [7]Mayo Clinic, [8]Cleveland Clinic Foundation, [9]H. Lee Moffitt Cancer Center, [10]M.D. Anderson Cancer Center, [11]Carol G. Simon Cancer Center, [12]University of North Carolina at Chapel Hill, [13]Massachusetts G... [15]Millennium Pha...

202 pts

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

CREST (024) A Phase II Multicenter Randomized Study of the Proteasome Inhibitor VELCADE® in Multiple Myeloma Patients Relapsed After Front-Line Therapy

Sundar Jagannath,[1] Bart Barlogie,[2] James Berenson,[3] David Siegel,[4] David Irwin,[5] Paul G. Richardson,[6] Mi... Steven A. Limentani,[9] Melissa Alsina,[10] Dix... Julian Adams,[11] David ... on[6]

[1]St. Vincent's Catholic Medical Center, [2]University of Arkansas, [3]Cedars-Sinai Medical Center, [4]Carol G. Simon Cancer Center, [5]Alta Bates Comprehensive Cancer Center, [6]Dana-Farber Cancer Institute, [7]New York Presbyterian Hospital, [8]M.D. Anderson Cancer Center, [9]Charlotte Medical Clinic, [10]H. Lee Moffitt Cancer Center, and [11]Millennium Pharmaceuticals, Inc.

54 pts

Phase III Study 039 (APEX) and 040

670 pts.

Velmi dobrá léčebná účinnost u vysoce předléčených nemocných

Nevede k vyléčení. Prodlužuje dobu do relapsu

Na dávce závislá léčebná odpověď ?

SUMMIT dobrá studie, CREST malá nejasná studie,

Studie APEX prokazuje jasně lepší účinnost oproti dexametazonu v prvním relapsu onemocnění.

STUDIE PŘEDČASNĚ UKONČENA A NEMOCNÝM V RAMENU S DEX POVOLEN VELCADE !

Obsah

- Phase I Trials
- Phase II Summary – SUMMIT (025) & CREST (024)
- Phase II – SUMMIT, CREST & Extension Trial (029)
- Phase III Trial – APEX (039)
- **Combination Trials – Relapsed/Refractory**
- Front-line & Pre-Transplant Trials
- Peri-Transplant Trials
- Handling & Dosing Guidelines

Combination Data in Relapsed and Refractory Multiple Myeloma

- Bortezomib has been combined with many other active agents for multiple myeloma with manageable toxicity
- In phase I trials, response rates >50% (CR + PR + MR) were reported and CRs were obtained
- Responses seen in patients who have received and/or been refractory to other agents and to bortezomib

Summary of Combination Data (Relapsed/Refractory MM Patients)

Study	N	Regimen	CR/nCR	CR+PR	Other Data of Note
Orlowski	22	Bortezomib + Doxil	36%	73%	No additive toxicity
Berenson	28	Bortezomib +Melphalan	11%	43%	Most toxicities hematologic
Zangari Abstract	79	Bortezomib + Thalidomide, Dex added for suboptimal response	~17%	~52%	PN appeared manageable, 9% grade 3
Channan-Khan	16	Bortezomib + Doxil + Thalidomide	15%	38%	Well tolerated without any significant grade 3/4 non-heme. toxicities
Hollmig	20	Bortezomib + Adriamycin + Thalidomide + Dexamethasone	25%	63% PR	

Marked Activity of VELCADE® Plus Thalidomide (V + T) in Advanced and Refractory Multiple Myeloma

Maurizio Zangari, Bart Barlogie, Klaus Hollmig, Athanasios Fassas, Erik Rasmussen, Raymond Thertulien, Giampaolo Talamo, Choon-Kee Lee, Guido Tricot

Institute for Research & Therapy, University of Arkansas for Medical Sciences, Little Rock, AR, USA; Cancer Research and Biostatistics, Fred Hutchinson Cancer Center, Seattle, WA, USA

Zangari et al ASH 2004 Abstract 1480

V + T: Conclusions

- VTD combination is tolerable in heavily pretreated, relapsed or refractory patients
- 52% CR + PR, 5% CR, 17% CR + nCR
- Peripheral neuropathy appears manageable
- Responses observed in patients who had previously received thalidomide + dexamethasone, however prior thalidomide (67%) was associated with inferior survival
- 68% of patients alive at 12 months

Zangari et al ASH 2004 Abstract 1480

Phase II Study of VELCADE and DOXIL in Combination With Low-Dose Thalidomide (VDT) as Salvage Therapy for Patients With Relapsed or Refractory Multiple Myeloma or Waldenström's Macroglobulinemia

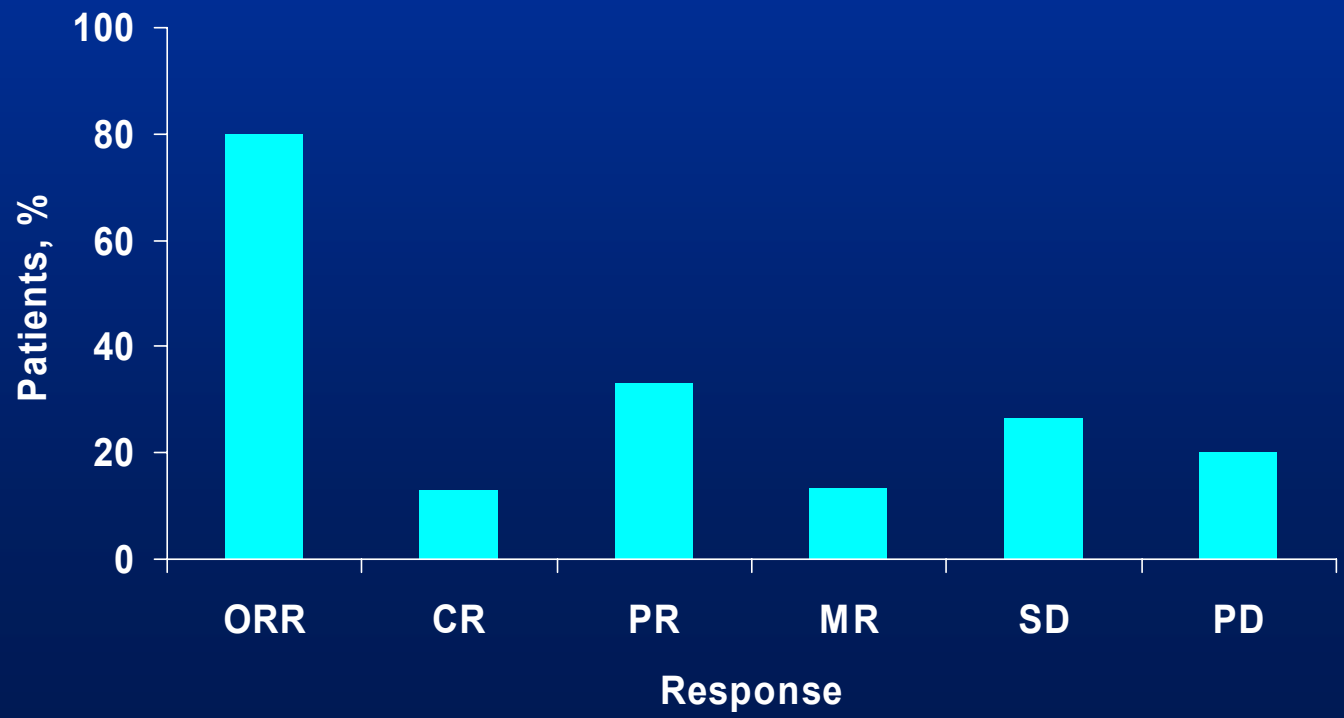
Asher Alban Chanan-Khan, Kena C. Miller, Philip McCarthy, Laurie A. DiMiceli, Jihnee Yu, Zale P. Bernstein, Myron S. Czuczman

Dept. of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA

Chanan-Khan et al ASH 2004 Abstract 2421

VDT: Results

- 13 patients have received at least 1 cycle and are evaluable for response
- Overall response rate (CR + PR) = 54% (2 CR, 5 PR)



Chanan-Khan et al ASH 2004 Abstract 2421

Summary: VELCADE + Doxil + Thalidomide

- Salvage therapy for relapsed / refractory myeloma
- Dosing –
  - Bortezomib 1.3 mg/m^2 or 1.3 mg/m^2 on days 1, 4, 15, and 18 q28 days
  - Doxil 20 mg/m^2 days 1 & 15 q28 days
  - Daily oral thalidomide 200 mg
  - Low dose coumadin (1-2 mg/day)
- 13 evaluable patients
- 54% response rate (CR+PR)
  - 2 CR and 5 PR
- No significant neuropathy noted – 1 patient grade 3
- No DVT

Chanan-Khan et al ASH 2004 Abstract 2421

Bortezomib + Adriamycin + Thalidomide + Dexamethasone (VATD) is an Effective Regimen in Patients With Refractory or Relapsed Multiple Myeloma

Klaus Hollmig, Julie Stover, Giampaolo Talamo, Athanasios Fassas, Choon-Kee Lee, Elias Anaissie, Guido Tricot, Bart Barlogie

Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Hollmig et al ASH 2004 Abstract 2399

VATD: Treatment

- Bortezomib 0.8 – 1.3 mg/m^2 days 1, 4, 8, and 11
- Adriamycin 2.5 to 5 mg/m^2/day continuous infusion days 1-4 and 9-12 (metronomic therapy)
- Thalidomide 50 or 100 mg/day days 1-12
- Dexamethasone 20 or 40 mg/day days 1-4 and 9-12

Hollmig et al ASH 2004 Abstract 2399

VATD: Conclusions

- Adriamycin can be safely added to VTD and this addition may overcome resistance to bortezomib-based regimens
- Indication of possible synergy with anthracyclines
- Overall response rate (CR + PR) 63% in heavily pre-treated patients

Hollmig et al ASH 2004 Abstract 2399

Obsah

- Phase I Trials
- Phase II Summary – SUMMIT (025) & CREST (024)
- Phase II – SUMMIT, CREST & Extension Trial (029)
- Phase III Trial – APEX (039)
- Combination Trials – Relapsed/Refractory
- **Front-line & Pre-Transplant Trials**
- Peri-Transplant Trials
- Handling & Dosing Guidelines

ASH 2004
Bortezomib Front-Line in MM

Study	N	Regimen	CR/nCR	CR+PR	Stem Cell Harvest
Jagannath	**32**	**Vc +/- dex → SCT**	**25%**	**88%**	8/8 successful harvests, 6 PBSCT
Cavenagh	**21**	PAD Vc + Adria + dex → **SCT**	**29%** **57%**	**95%** **95%**	20/21 successfully mobilized, 18 PBSCT
Harousseau	**30**	V-HD Dex Vc + high dose dex → **SCT**	**17%**	**73%**	SC harvest adequate for all 29 patients collected
Alexanian	**30**	VTD Vc + thal + dex → **SCT**	**NA**	**80%**	PBSC collected in 12/12 pt, 12 PBSCT
Barlogie	**57**	TT3 Vc + DT-PACE → **SCT x2** → VDT-PACE + Thal dex	**80%**	**NA**	Robust mobilization, harvest after cycle 1 is preferable
Uy	**34**	Vc after thal or anthracycline → **SCT**	**33%**	**89%**	SC harvest adequate for all patients in 1 or 2 collections
Mateos/ San Miguel	**11**	MPV Vc + mel + prednisone	**18%**	**91%**	Not done
Richardson	**33**	Vc single-agent	**4%**	**45%**	Not reported

VTD (VELCADE®, Thalidomide, Dexamethasone) as Primary Therapy for Newly-Diagnosed Multiple Myeloma

Raymond Alexanian, Luhua M. Wang, Donna M. Weber, Kay B. Delasalle

Lymphoma/Myeloma, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Alexanian et al. ASH 2004 Abstract 210

VTD: Methods

- Previously untreated patients with multiple myeloma eligible for transplant
- 28- day treatment cycle, 2 cycles
- Institutional experience of 30 patients
  - Bortezomib 1.0 to 1.9 mg/m^2 days 1, 4, 8, 11 q 28 days
  - Thalidomide 100-200 mg each evening
  - Dexamethasone 20 mg/m^2 days 1-4, 9-12, 17-20 q 28 days

Dose (mg/m^2)	# Patients
1.0	2
1.3	12
1.5	10
1.7	5
1.9	1
Total	30

Alexanian et al. ASH 2004 Abstract 210

Summary: VTD

- Primary therapy for newly diagnosed multiple myeloma
- Dosing VTD for 2 cycles prior to transplant:
  - V (Bortezomib) days 1, 4, 8, 11 q 28 days ranging 1.0 – 1.9 mg/m^2
  - Majority of patients received 1.3 or 1.5 mg/m^2 (22/30)
  - Thal 100-200 mg daily
  - Dexamethasone 20 mg/m2 days 1-4, 9-12, 17-20 q28 days
- 80% response rate (Reduction ≥75% M protein and >95% Bence Jones)
- 94% Response Rate in patients receiving ≥ 1.5 mg/m^2
- Median time to remission 0.6 month vs 1.1 months with TD historical control (P < .01)
- PBSC collected in all 12 patients mobilized with G-CSF

Alexanian et al. ASH 2004 Abstract 210

Total Therapy 3 for Newly Diagnosed Myeloma, Incorporating VELCADE® into Remission Induction with DT PACE: Early Results Regarding Efficacy, PBSC Mobilization and Toxicities

Bart Barlogie, Klaus Hollmig, Maurizio Zangari, Julie Stover, Lisa Jackson, Teresa Milner, Athanasios Fassas, Guido Tricot

Myeloma Institute for Research & Therapy, Myeloma Institute for Research and Therapy, University of Arkansas Medical Sciences, Little Rock, AR, USA

Barlogie et al. ASH 2004 Abstract 538

Total Therapy 3 (TT3): Methods

Induction and Mobilization: Vc + DT-PACE x 2 cycles

- Bortezomib 1.0 mg/m^2 d1,4 or d1,4,8 or d1,4,8,11
- Dexamethasone 40 mg P.O. + thalidomide 200 mg P.O. q.d. d1-4
- 4-day continuous infusion of cisplatin 10 mg/m^2/d, adriamycin 10 mg/m^2/d, cyclophosphamide 400 mg/m^2/d, + etoposide 40 mg/m^2/d d1-4

↓

PBSC Collection

- Collection after 1-2 cycles (~d14 post chemo)
- Target of **20 million CD34 cells/kg**

↓

MEL 200 mg/m^2 based ASCT x 2 (2-3 months apart)

↓

Consolidation: VDT-PACE x 2 + TD

↓

Maintenance: VTD → TD

Barlogie et al. ASH 2004 Abstract 538

TT3: Conclusions

- VDT-PACE demonstrated promising activity as an induction regimen
  - Bortezomib in combination with DT-PACE permits robust stem cell mobilization after Cycle 1
- TT3, which includes Bortezomib, compares favorably to TT2 as historical contol
  - Only 2 cycles of induction
  - Estimated CR rate after TT3: 80% vs ~60% for TT2
  - Time to 99% M-protein reduction faster in TT3 than TT2 (p= .02)

Barlogie et al. ASH 2004 Abstract 538

A Phase I/II National, Multicenter, Open-Label Study of Bortezomib Plus Melphalan and Prednisone in Elderly Untreated Multiple Myeloma Patients

M. V. Mateos,[1] Joan Bladé,[1] J. Diaz Mediavilla,[1] J. J. Lahuerta,[1] M. J. Terol,[1] J. Hernández,[1] M. J. Moro[1], J. Bargay,[1] J. M. Ribera,[1] J. De Larubia,[1] A. Sureda,[1] D. Carrera,[1] F. de Arriba,[1] L. Palomera,[1] M. Hernández,[1] J. García Laraña,[1] A. Alegre,[1] F. Próper,[1] P. Rivas,[1] D. L. Esseltine,[2] D. Schenkein,[2] J. F. San Miguel[1]

[1]Hematology, Grupo Español de MM (GEM/PETHEMA), Spain
[2]Millennium Pharmaceuticals, Inc., Cambridge, MA, United States

Mateos et al. ASH 2004; Abstract 3462

Summary: VMP

- Elderly patients with previously untreated multiple myeloma (≥ 65 years)
- Dosing - Four 6-week cycles:
  - V (bortezomib) d 1, 4, 8, 11, 22, 26, 29, 32
  - Melphalan 9 mg/m² po d 1-4
  - Prednisone 60 mg/m² po d 1-4
  - Followed by 5-week cycles x 5
- CR + PR of 91% - 1 CR; 1 nCR; 8 PR out of 11 evaluable patients
- No DLTs reported at both 1.0 mg/m^2 and 1.3mg/m^2
- Basis for VISTA Phase 3 trial: VMP vs. MP

Mateos et al. ASH 2004;

Alternativní léčba druhého relapsu

- Nemáme jinou účinnou alternativní léčbu !
- Současný stav je:

STAV:	standardní léčba	medián EFS
NOVÁ DG.	Auto TKD	30-35 měs.
RELAPS č. 1	Auto TKD č. 2/THAL	15-25 měs.
RELAPS č. 2	THAL/DEX/CAD….	6-9 měs.

Velcade při použití v průměru u 6 relapsu onemocnění prodlužoval
celkové přežití o 16 měsíců
a dobu do relapsu o 12 měsíců

Výhody Velcade

- rychlý účinek
- nenahraditelný u rezistentních onemocnění
- bezpečné intravenózní podání
- nedělá alopecii, nemá trombogenní potenciál,
- starší nemocní jej podobně tolerují jako mladší nemocní
- vhodný lék do kombinace (synergismus protinádorového účinku s dexametazonem, thalidomidem a cytostatiky bez synergismu vedlejších účinků léků (např. trombocytopenie u melfalanu + velcade)
- nepoškozuje kmenové krvetvorné buňky
- používání u nemocných s ledvinným selháním
- prodlužuje dobu do relapsu i celkové přežití

Nevýhody Velcade

- časování (zvláště pro nemocné s dojížděním)
- ekonomická náročnost
- frekventní neurotoxicita, únava, trombocytopenie
- nevede k vyléčení
- neujasněné dávkování, počet cyklů
- neujasněná optimální kombinace s jinými léky

Očekávaný vývoj

- kombinace s jinými léky prokážou výrazně lepší dlouhodobé výsledky oproti monoterapii léků
- Velcade bude používán u transplantačních režimů
- V prvním relapsu bude vedle imidů zvažovaným lékem volby
- V primoléčbě bude rozhodujícím faktorem ekonomické srovnání se standardní léčbou

Závěry - použití Velcade u nemocných s pokročilým myelomem

- Jde pravděpodobně o nejúčinnější lék současnosti pro nemocné s pokročilým MM.
- Současnou schválenou indikací je druhý relaps či progrese onemocnění
- Odhad indikovaných nemocných v ČR je 70 ročně
- Odhad indikovaných nemocných v SR je 35 ročně

Závěry - použití Velcade u nemocných s pokročilým myelomem

- Léčba je ekonomicky náročná a indikace by měla být bedlivě zvažovaná
- Doporuční CMG , resp. myelomové sekce ČHS je indikovat léčbu Velcade v šesti referenčních centrech CMG s vysokou frekvencí a kvalitou péče o nemocné s MM

Děkuji
za pozornost