



A Phase II Study of Bortezomib (Velcade[®]), Cyclophosphamide (Cytoxan[®]), Thalidomide (Thalomid[®]) and Dexamethasone as First-Line Therapy for Multiple Myeloma

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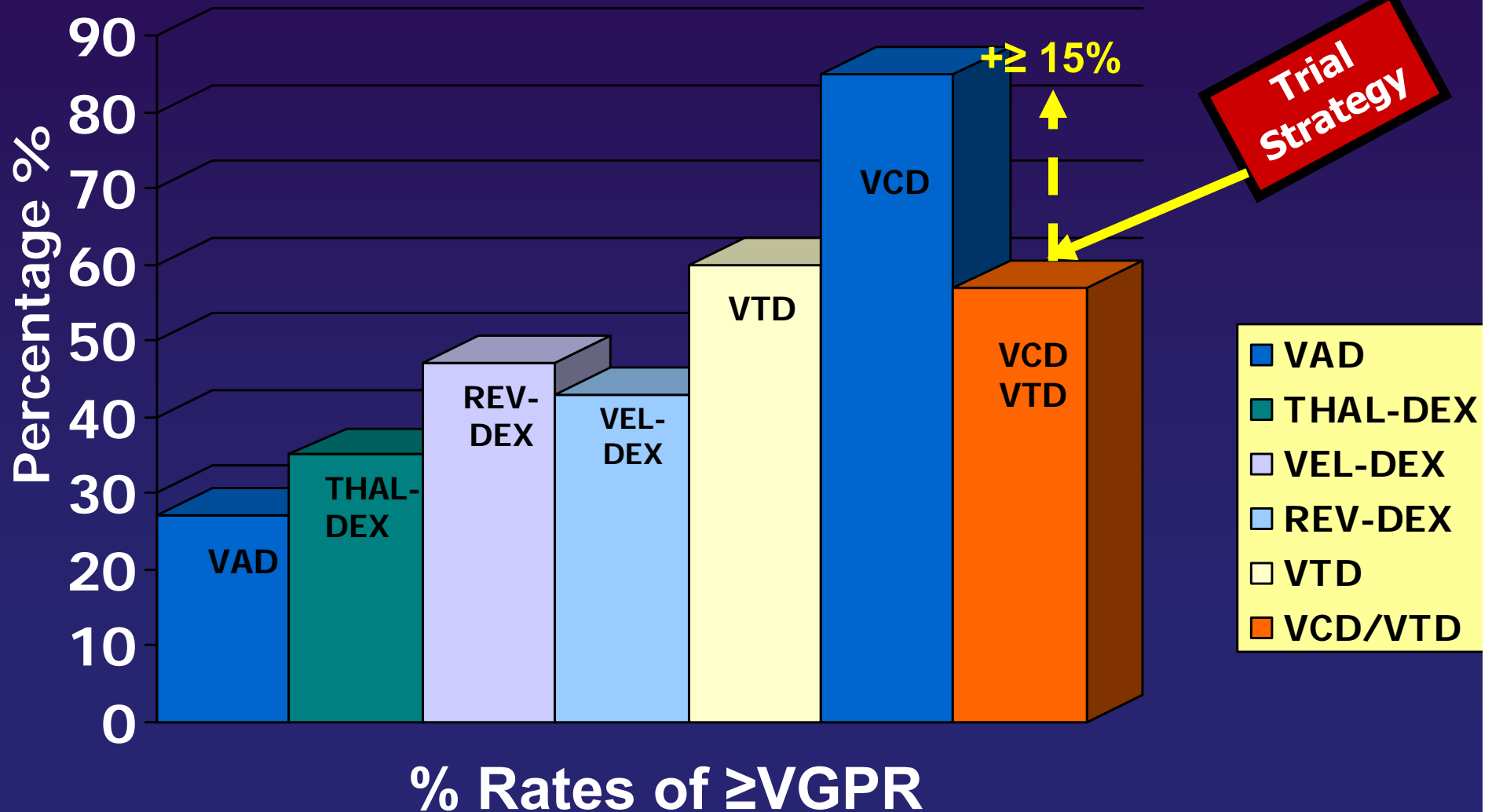
Disclosures

In compliance with ACCME policy, ASH requires the following disclosures to the activity audience:

Research Support/P.I.	Millennium Pharmaceuticals, Inc.
Employee	N/A
Consultant	Millennium Pharmaceuticals, Inc.,
Major Stockholder	N/A
Speakers' Bureau	Millennium Pharmaceuticals, Inc., Celgene, Inc.
Scientific Advisory Board	N/A

Presentation includes discussion of the following off-label use of a drug or medical device: frontline use of bortezomib in MM

Background Question: Which combo is best for induction?



A Phase II Trial with Bortezomib, Cyclophosphamide, Dexamethasone and Thalidomide in Previously Untreated Multiple Myeloma Patients

Objectives

▶ Primary Objective

- To assess the response rate to VCD/VTD in newly diagnosed myeloma patients
- To assess \geq VGPR rate versus Bortezomib/dexamethasone

▶ Secondary Objective

- To determine the safety and tolerability of VCD/VTD

Protocol Flow Diagram

Newly Diagnosed Untreated Myeloma

Bortezomib / **Cyclophosphamide** /
Dexamethasone

(1.3 mg/m²)*

(300mg/m²)**

(40mg)***

Three 21 day courses

Cycles 1-3

*Bortezomib days 1, 4, 8, 11

** Cyclophosphamide total dose/cycle 600mg/m²
(300mg/m² day 1& 8) IV

*** Dexamethasone 40mg single dose days 1, 2, 4, 5, 8, 9, 11, 12

Bortezomib / **Thalidomide** /
Dexamethasone

(1.0 mg/m²)

(**100mg daily**)

(40mg)

Three 21 day courses

Cycles 4-6

Further Protocol Evaluation



**Safety
Monitoring**



Post Study Evaluation @ 28 days



**Q3 Month
Follow-up**



SCT At Discretion Of Investigator

**Continue Response Assessment Until
Progression or Other Therapy**

Survival Followed Until Death

Baseline Patient Characteristics (N = 44)

Characteristic

Mean age, years (range)	58 years (38-83)
Male, %	68 %
Median KPS, % (range)	90 (60–90) %
β_2 -microglobulin ≥ 3.5 mg/L, %	51 %
Serum creatinine, ≥ 2 mg/dl (“B”)	16 %
Durie–Salmon stage III, %	72 %
ISS Stage II-III	72 %
Type of myeloma (%)	
IgG	67 %
IgA	14 %
Light-chain disease	19 %

Protocol Compliance

Completed 6 cycles 36/44 (82%)

Stopped at < 6 cycles n=8

1 CHF (C1)

1 Patient choice, bone pain (C1)

1 Encephalitis (C3)

1 Neuropathy (C3)

1 Neuropathy (C4) Proceeded to transplant

1 Neuropathy (C4)

1 Proceeded to transplant (C4), Pt/MD choice

1 Back pain (C5)

Response Evaluation

	Patient Numbers
Enrollment	44
Treated	44
Evaluable for Response	43 (98%)

Reasons for In-evaluability

1 patient refused further therapy
and follow-up during Cycle 1

Best Response (N=43)

CR	11	(26%)	}	56% \geq VGPR
nCR	4	(9%)		
VGPR	9	(21%)		
PR	17	(40%)	}	ORR 96%
Stable	2	(4%)		

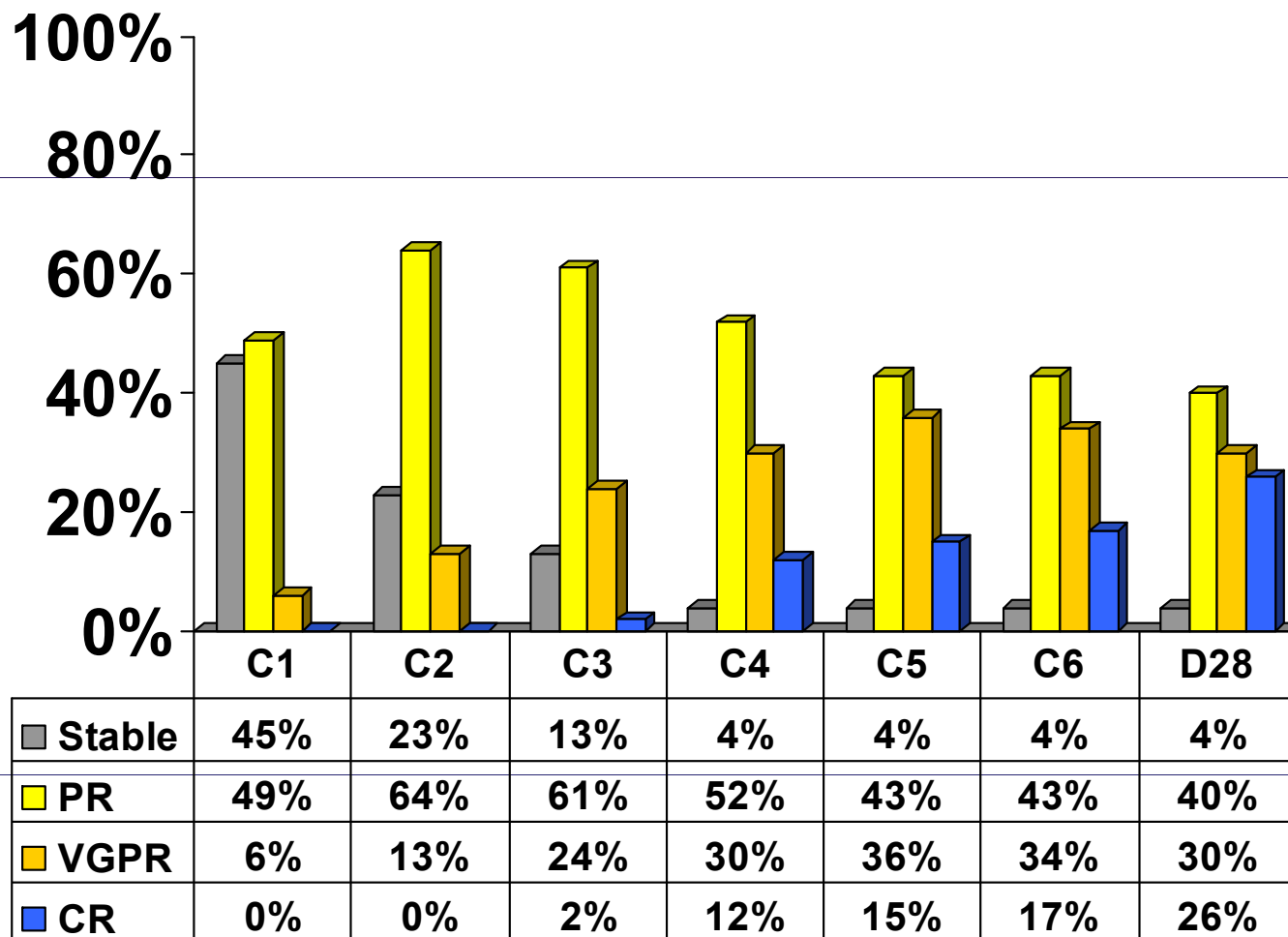
Intent to treat analysis including 1 patient inevaluable.

ORR 95%

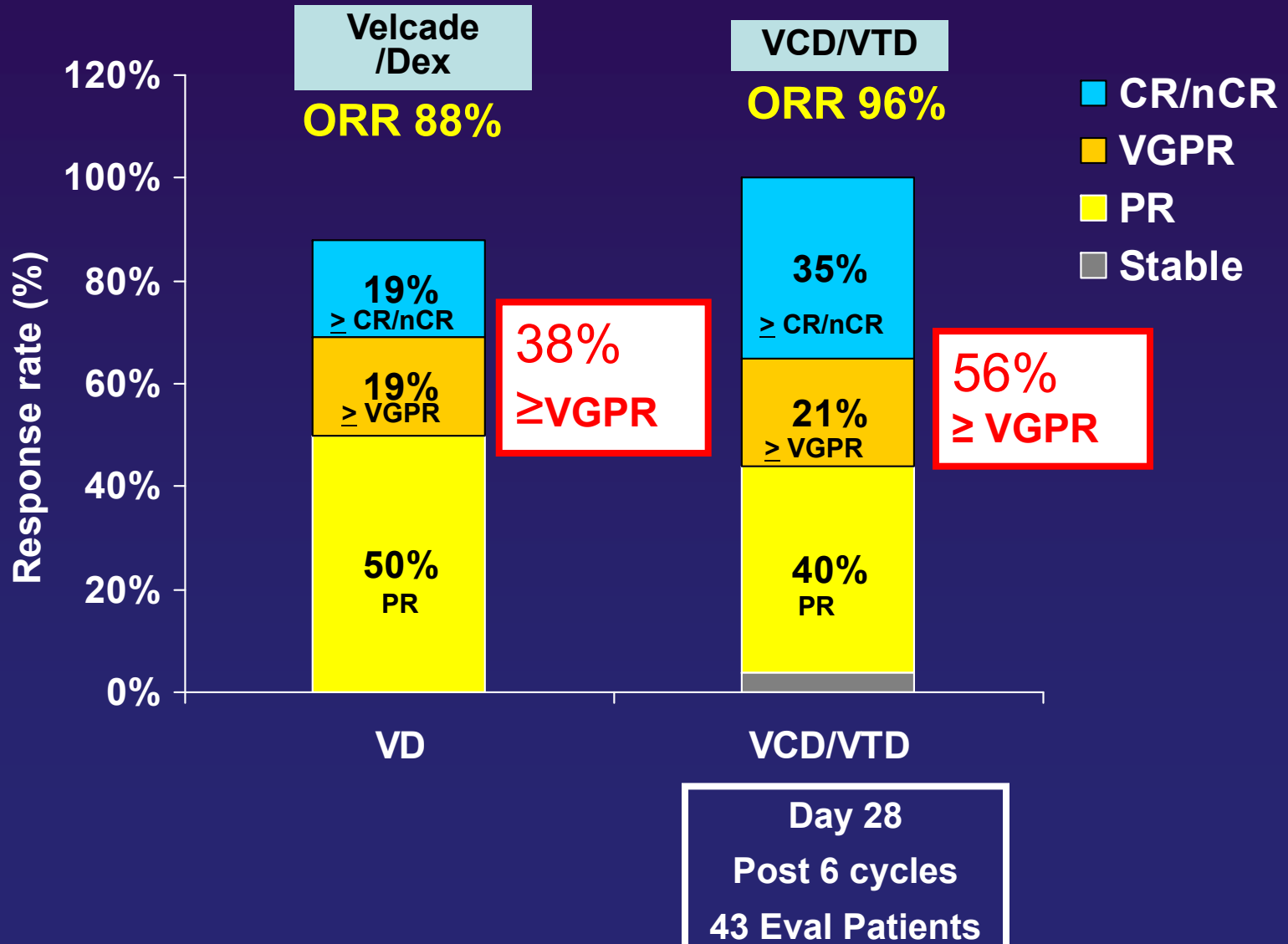
\geq VGPR 55%

Responses By Cycle

Stable
 PR
 VGPR
 CR



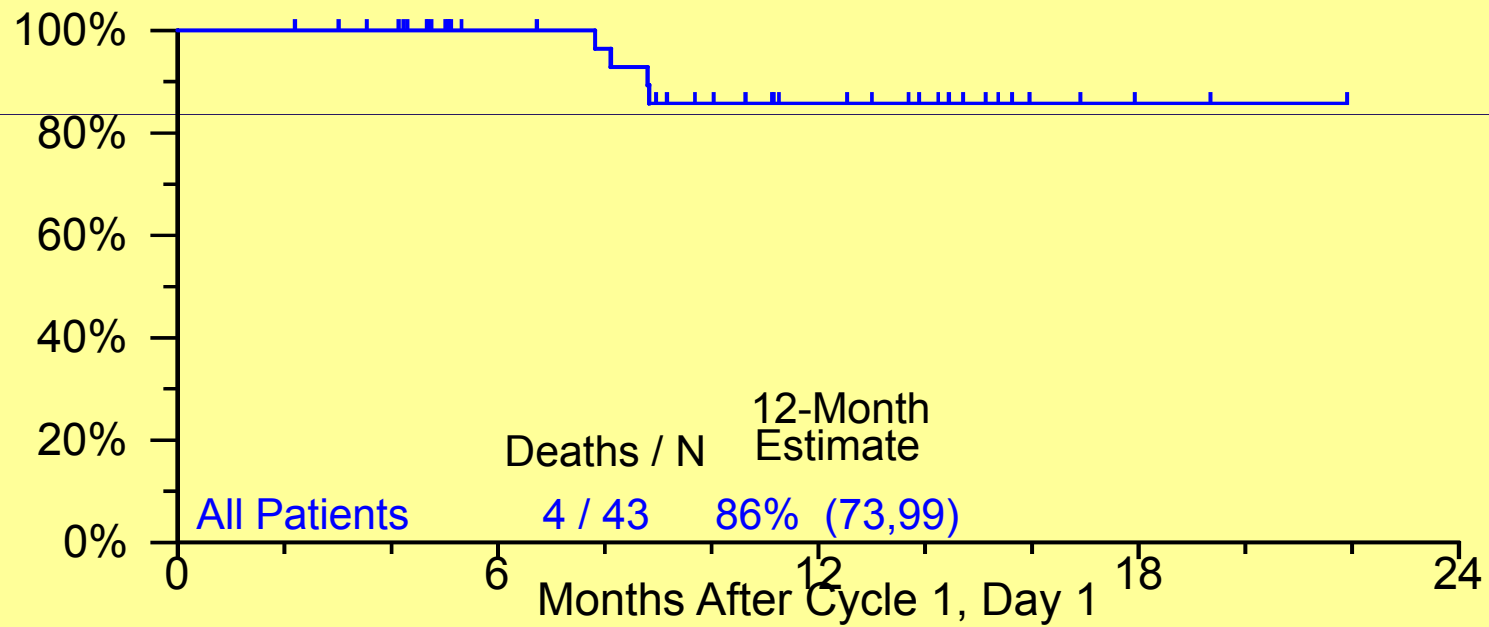
Comparison With Prior Study



Cytogenetic Data and Response

Conventional		≥VGPR	FISH		≥VGPR
Normal	29	14	Del 13, 17	8	5
Deletions	2	1	4;14	3	2
Hyperdiploid	4	2	11;14	3	1
n/a	9	7	Trisomy	1	0
			Hyperdiploid	5	4
			Normal	13	5
			n/a	13	9
All Patients	43	24			

Overall Survival (N=43)

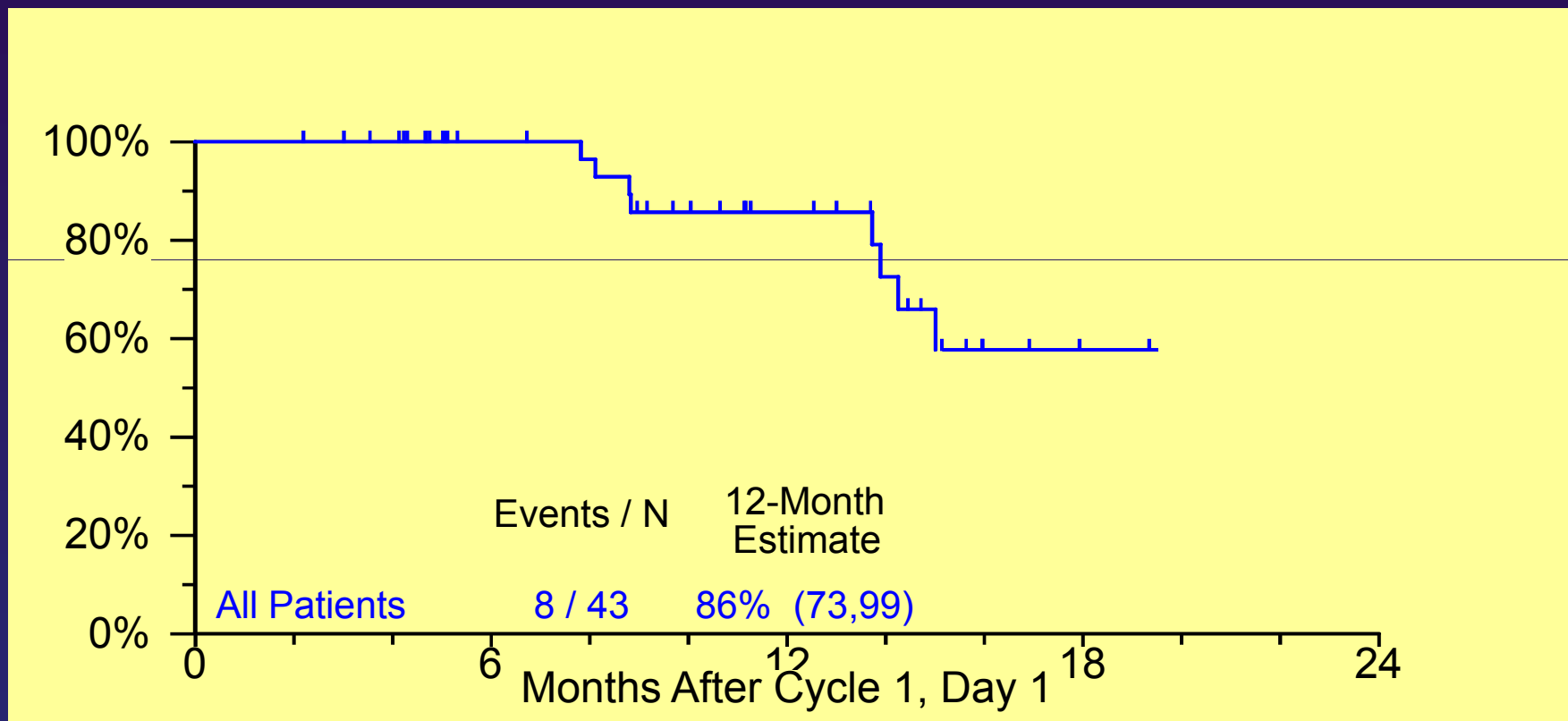


Median Follow Up 10.6 months

Cause of Death: 1 unrelated surgical death

3 “peri-transplant” related

Event-Free Survival (N=43)



8 Events

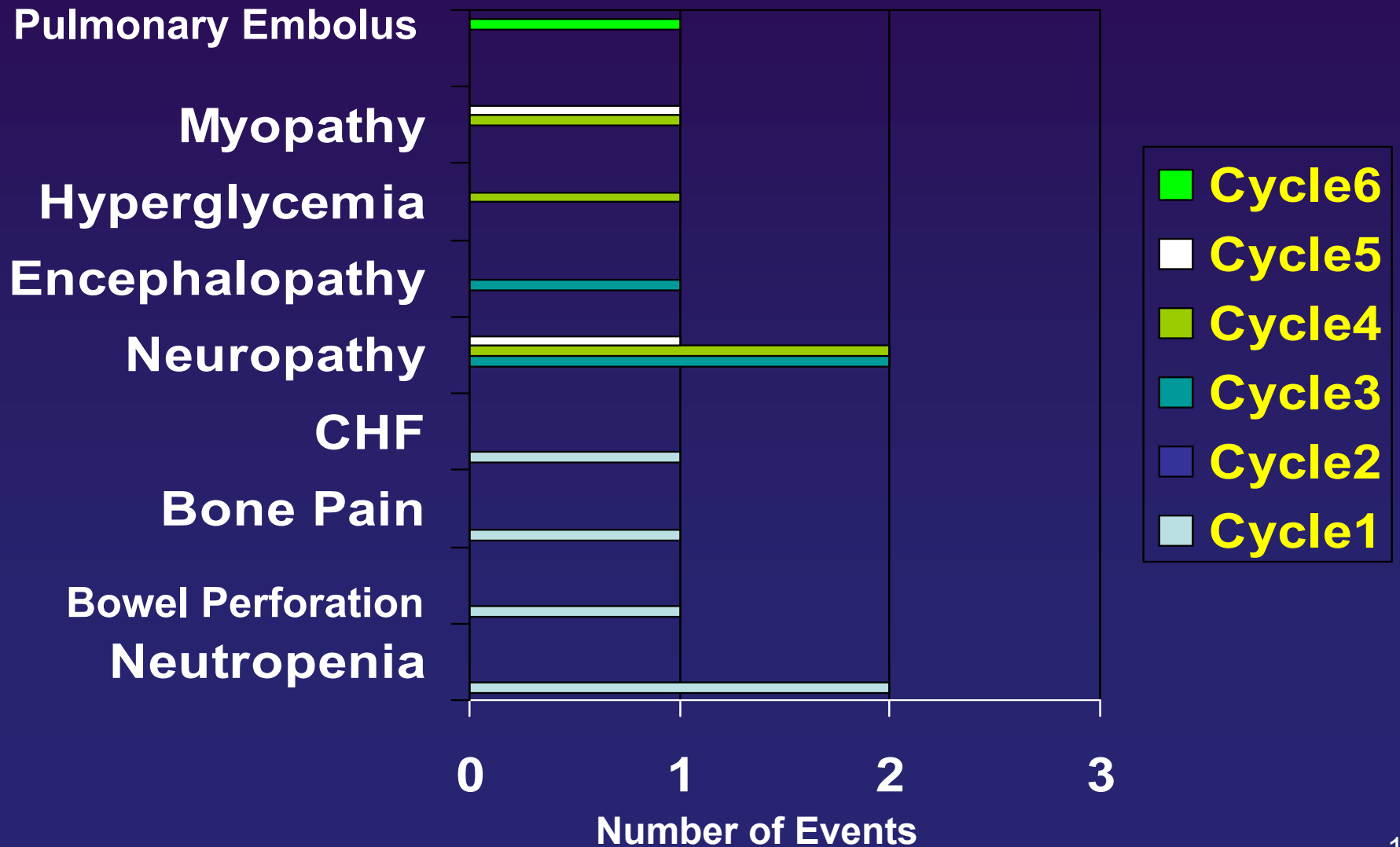
4 deaths all NOT disease related

4 relapses: 2 pre Tx, 2 post Tx

Transplant

- ▶ 22 patients proceeded to transplant to date
- ▶ Harvesting successful in 100%
- ▶ 3 patients died within 3 months post transplant:
 - 2 pneumonia in hospital
 - 1 influenza at home

Treatment Related Grade 2-4 Adverse Events Requiring Dose Adjustment/Delay



Overall Safety

- ▶ No protocol/therapy related deaths
- ▶ 11 Gd $\frac{3}{4}$ events requiring dose adjustment
- ▶ 10 Events: drug permanently stopped
 - Velcade 4
 - Thalidomide 3
 - Dexamethasone 1
 - Unclear 2

Conclusions

- ▶ Bortezomib combined first with Cyclophosphamide/Dexamethasone (3 cycles) followed by Thalidomide/Dexamethasone (3 cycles) is a very effective and safe frontline regimen

\geq PR	96%
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\geq VGPR	56%
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- ▶ Toxicities \geq Gd 2 were:

- Neuropathies

- Bortezomib 20%
- Thalidomide 15%

- Dexamethasone related 15%

- Cyclophosphamide 12%

Conclusions- cont.

- ▶ **Stem cell harvest and transplant have been completed in 22/43 (51%) currently.**
- ▶ **Overall adverse events were predictable and manageable.**
- ▶ **This regimen deserves further study; should be prospectively compared with VCD alone and VTD alone**