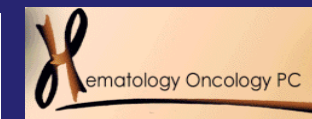
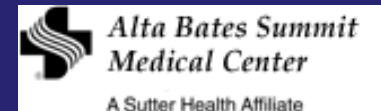
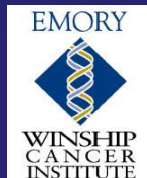


PERIFOSINE PLUS BORTEZOMIB AND DEXAMETHASONE EXTENDS PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL IN RELAPSED / REFRACTORY MULTIPLE MYELOMA PATIENTS PREVIOUSLY TREATED WITH BORTEZOMIB: UPDATED RESULTS OF THE PHASE III TRIAL

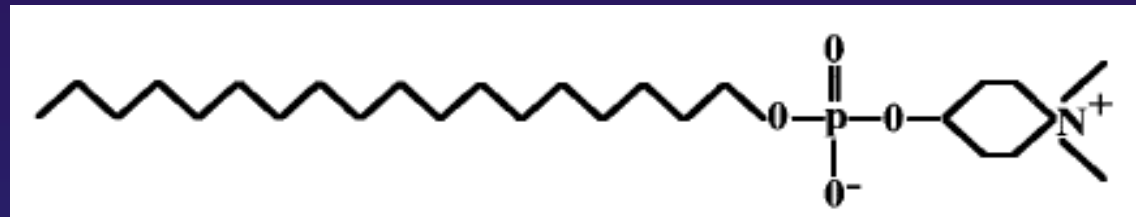
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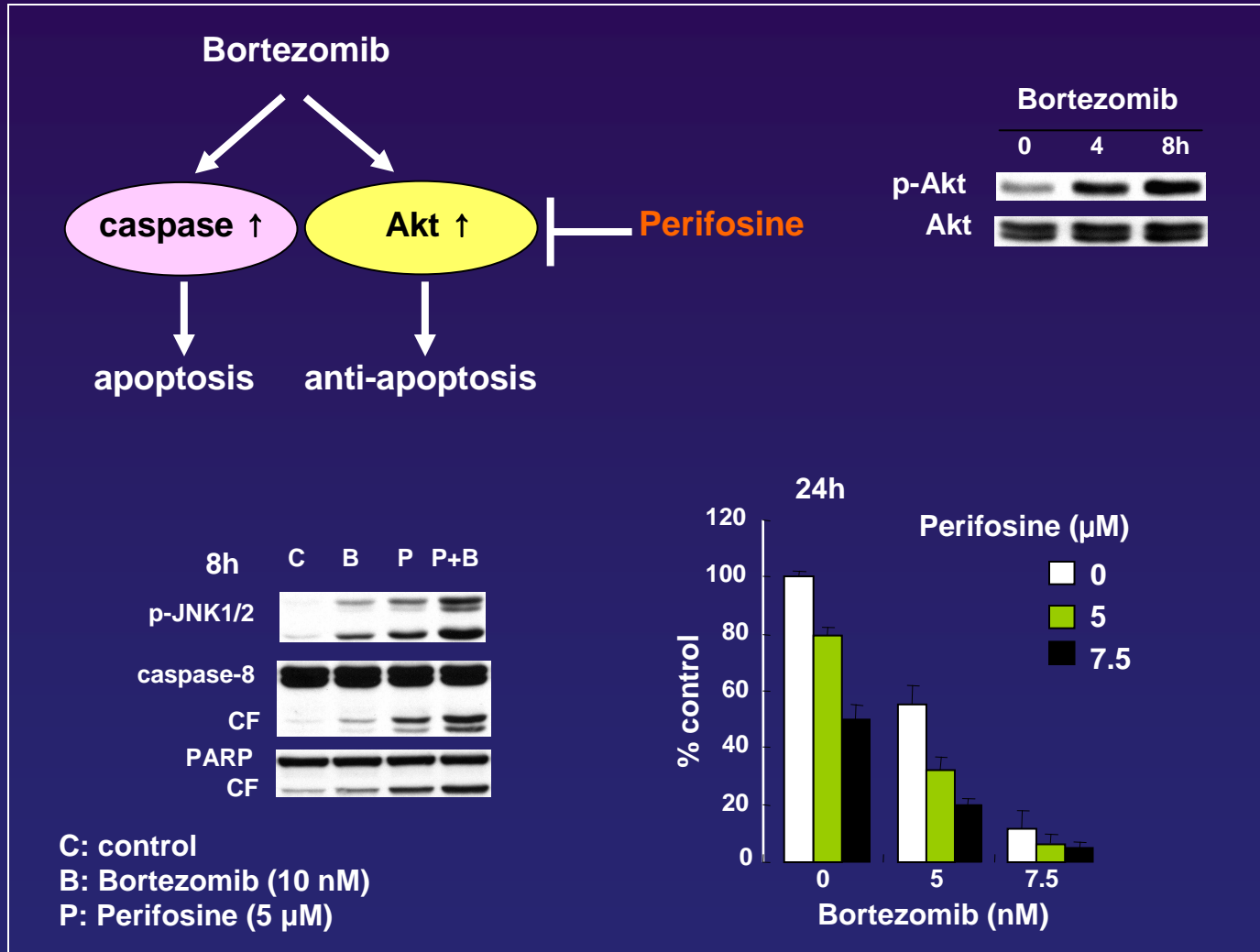
Perifosine: Novel AKT Inhibitor

- Orally bio-available alkylphospholipid
 - Known to affect tumor proliferation and metastasis
 - Different spectrum of toxicity vs conventional cytotoxic agents

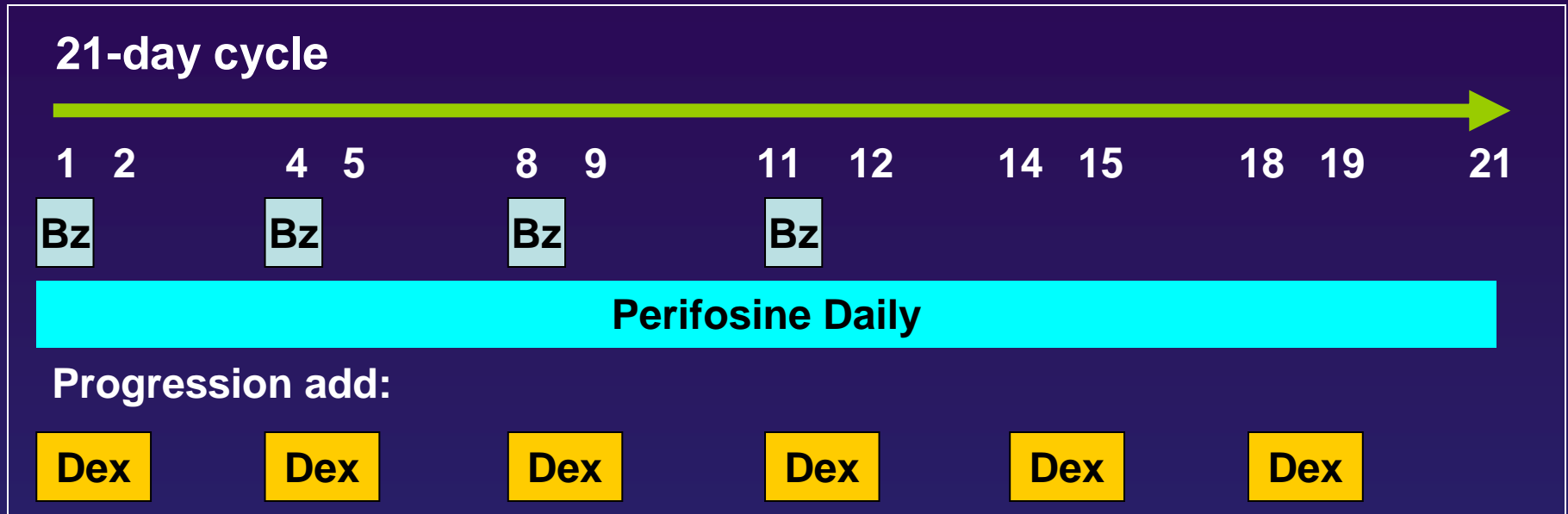


- Preclinical rationale in MM ¹
 - Activity in a number of cell lines including those resistant to anti-MM drugs (dex, mel, dox)
 - Correlation of activity with inhibition of Akt activation
 - Synergy with other approved anti-MM drugs, especially bortezomib (esp. via JNK and NFkB)

Akt Inhibitor Perifosine Enhances Bortezomib-Induced Cytotoxicity in MM Cells



Perifosine + Bortezomib: Phase I/II Study Design



Bortezomib: 1.3 mg/m² (dose reductions permitted to 1.0 and to 0.7 mg/m²)

Perifosine: 50 mg or 100 mg daily (dose / schedule reductions permitted)

Dexamethasone: 20 mg 4x/wk (dose / schedule reductions permitted)

- Pts to receive up to 8 cycles of perifosine + bortezomib (+/- dex). After 8 cycles, pts without progression may continue on treatment
- Maintenance therapy permitted in pts \geq SD using wkly schedule of Bz (days 1 and 8)

Phase I / II Objectives

- **Primary:**

- Phase I: Define MTD of Perifosine + Bortezomib
- Phase II: Response rate (CR + PR + MR)

- **Secondary:**

- Progression-free Survival (PFS)
- Time to Progression (TTP)
- Overall Survival (OS)
- Safety
- Correlative Studies

Eligibility / Response and AE Assessment

■ Inclusion criteria:

- Pts with relapsed and/or refractory MM previously treated with bortezomib (no limit on # of prior Bz)
- Prior XRT and anti-MM agents ≥ 2 wks before study entry
- Bisphosphonates permitted
- ECOG PFS 0 - 2

■ Exclusion criteria:

- PNY of \geq G3, painful G2
- Renal insufficiency (serum creatinine > 3 mg/dL)
- Plts $< 50,000$ cells/mm³, ANC ≤ 500 cells/mm³ and Hb < 8.0 g/dL
- ALT or AST $\geq 2.5x$ ULN and/or bilirubin $\geq 1.5x$ ULN
- Plasma Cell Leukemia

■ Response / AE Assessment:

- Toxicities graded by NCI CTCAE v3.0
- Response by modified EBMT criteria^{1,2} and International Uniform Criteria (UC)³ (After cycle 2, then after each cycle – confirmed by 2 assessments 6 wks apart)

¹ Bladé J *et al.* Br J Haematol 1998;102:1115–23

² Richardson PG, *et al.* NEJM 2003;348:2609–17

³ Durie BG *et al.* Leukemia 2006;20:1467–73

Baseline Characteristics: Phase I/II

	N = 84*
Median age, years (range)	63 (35 - 89)
Male, n (%)	51 (61%)
Myeloma type, n (%)	
IgG	66 (79%)
IgA	18 (21%)
Durie-Salmon Stage III at diagnosis, n (%)	56 (67%)
Serum β_2-microglobulin, median (range)	4.0 mg/L (0.6-39.7)
> 4.0 mg/L, n (%)	46 (55%)
ECOG PS 1 and 2, n (%)	68 (81%)

* Enrolled Pts

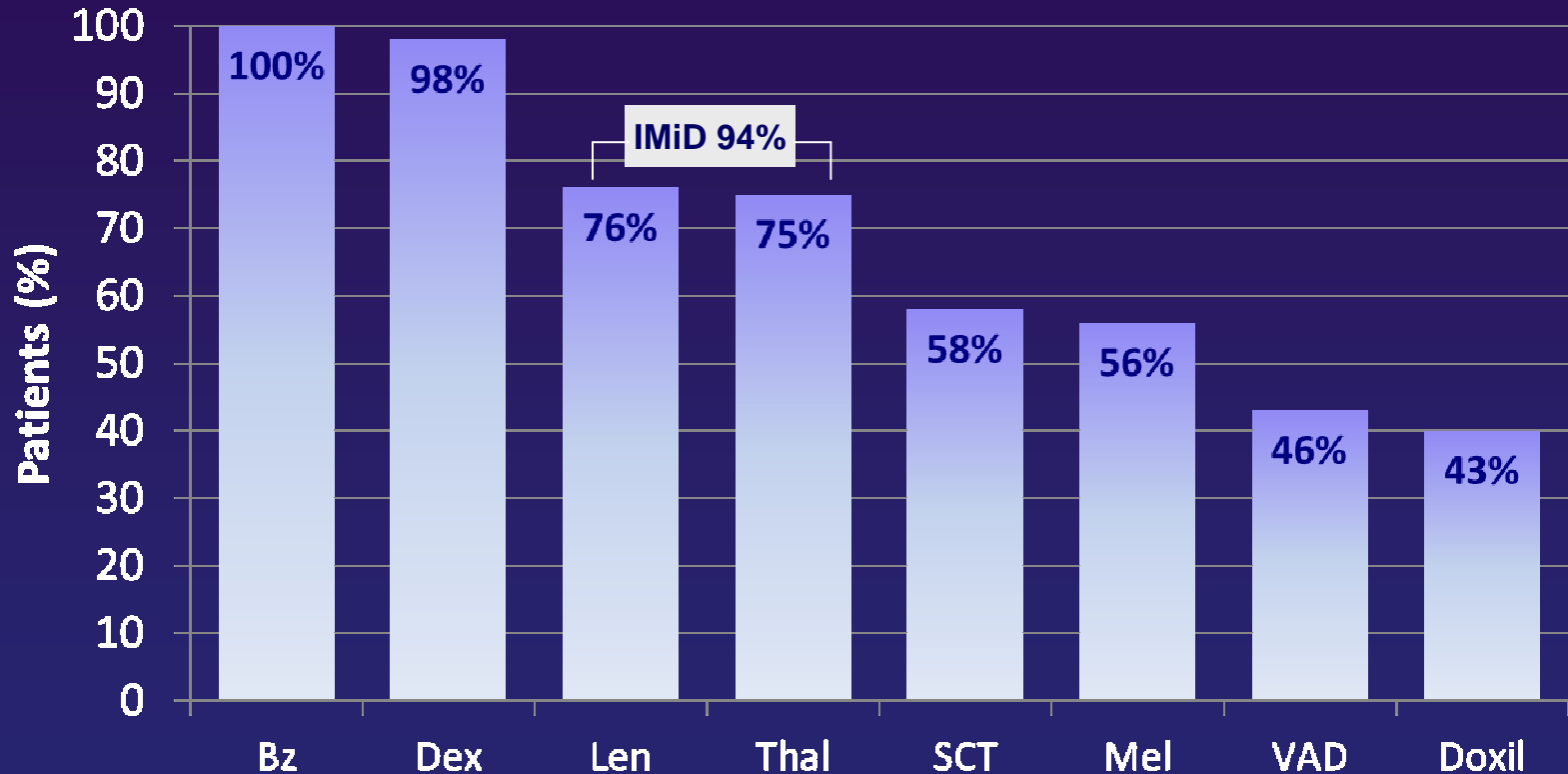
Baseline Characteristics: Phase I/II

	N = 84*
Disease status, n (%)	
Relapsed and Refractory ¹	74 (88%)
Refractory to Any Bortezomib Regimen**	61 (73%)
Bortez / Dex Refractory	43 (51%)
Cytogenetics (Normal / Abnormal / Unknown)	37 / 36 / 11
Median Prior Therapies, n (range)	5 (1 - 13)
Median Interval: Diagnosis to Inclusion	4.5 years

** Bortezomib Refractory

Progressing on or within 60 days of a bortezomib –based regimen

Prior Therapies IMiDs



- Median prior lines of Bortezomib: 2 (1- 4)

Most common toxicities

Grade 1 & 2 Adverse Event: $\geq 20\%$	
Nausea	63%
Diarrhea	57%
Fatigue	43%
Musculoskeletal Pain	42%
Upper Respiratory Infection	33%
Anorexia	33%
Constipation	31%
Peripheral Neuropathy	29%
Vomiting	29%
Coughing	25%
Dyspnea	24%
Bruising	21%
Edema	21%
Renal Insufficiency	20%

Grade 3 & 4 Adverse Event: $\geq 10\%$	
Thrombocytopenia	23%
Neutropenia	15%
Anemia	14%
Pneumonia	12%
Musculoskeletal Pain	11%
Bleeding	10%

Dose Reductions		
Agent	Dose	Pts
Perifosine (mg)	100 to 50	2
	50 qd to qod	8
Bortezomib (mg/m ²)	1.3 to 1.0	29*
	1.0 to 0.7	2
* 8 pts dose reduced to weekly Bz for convenience		
Dex (mg)	20 to 10	16

- No unexpected toxicities, with 2 G3, no G ≥ 4 PNY
- GI / Pain / Fatigue AE's manageable
- Hyperglycemia (with dex): 10% G 1-2 ,1 G 3
- No treatment-related mortality

Efficacy: Best Response

- **Best Response (EBMT/UC) in 73 evaluable* pts**
 - 3 CR/nCR (4%)
 - 13 PR (18%)
 - 14 MR (19%)
 - 30 SD (41%)
- **Overall response rate:**
 - CR/nCR + PR + MR: 41%

* Evaluable Pts (≥ 2 cycles); 11 pts inevaluable: 5 due to toxicity (4 not related, 1 related), 3 rapid PD (< 1 cycle), 3 patient refusal / withdrawal

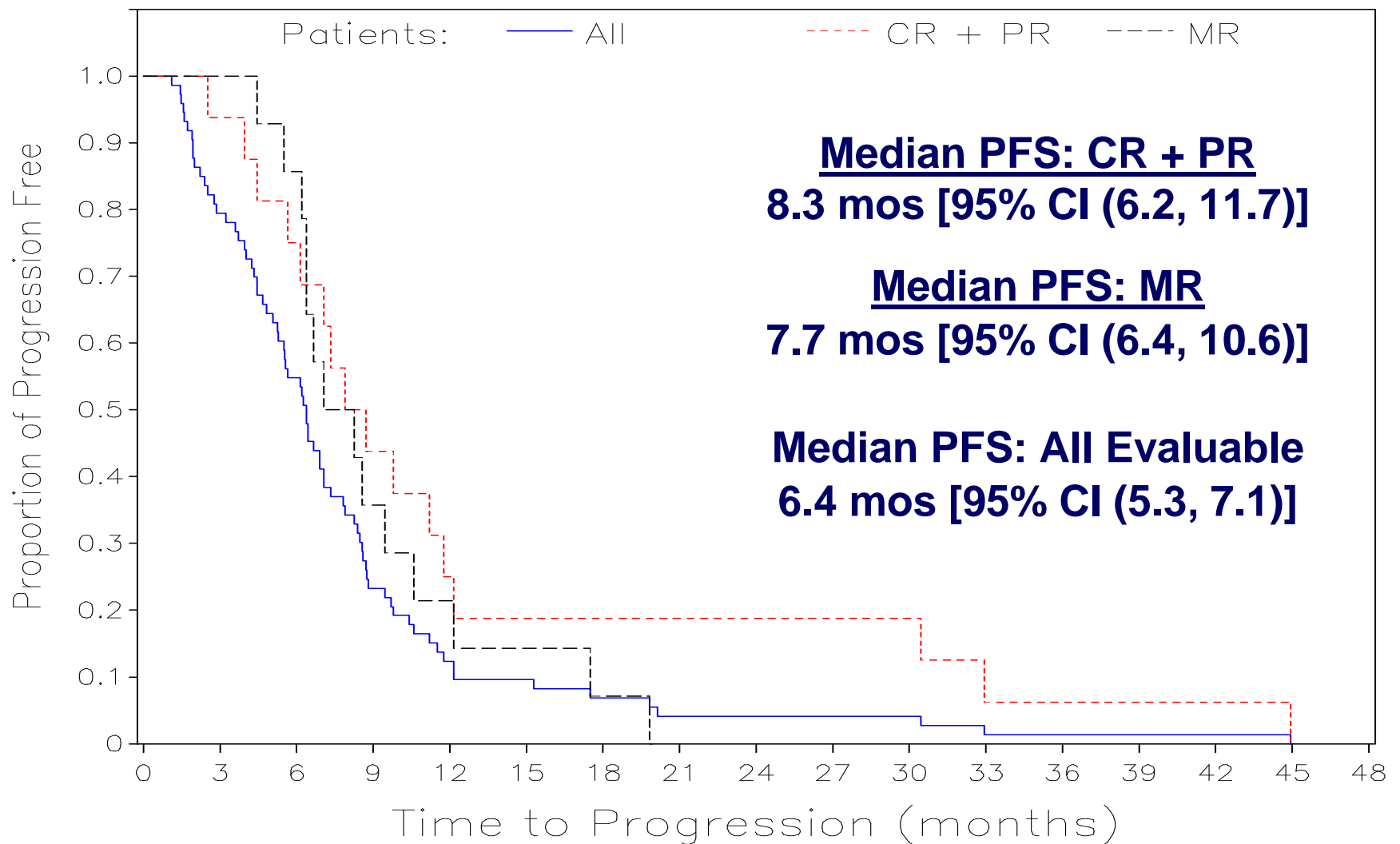
Efficacy: Overall Response (n = 73)

Median # of Treatment Cycles Received: 8

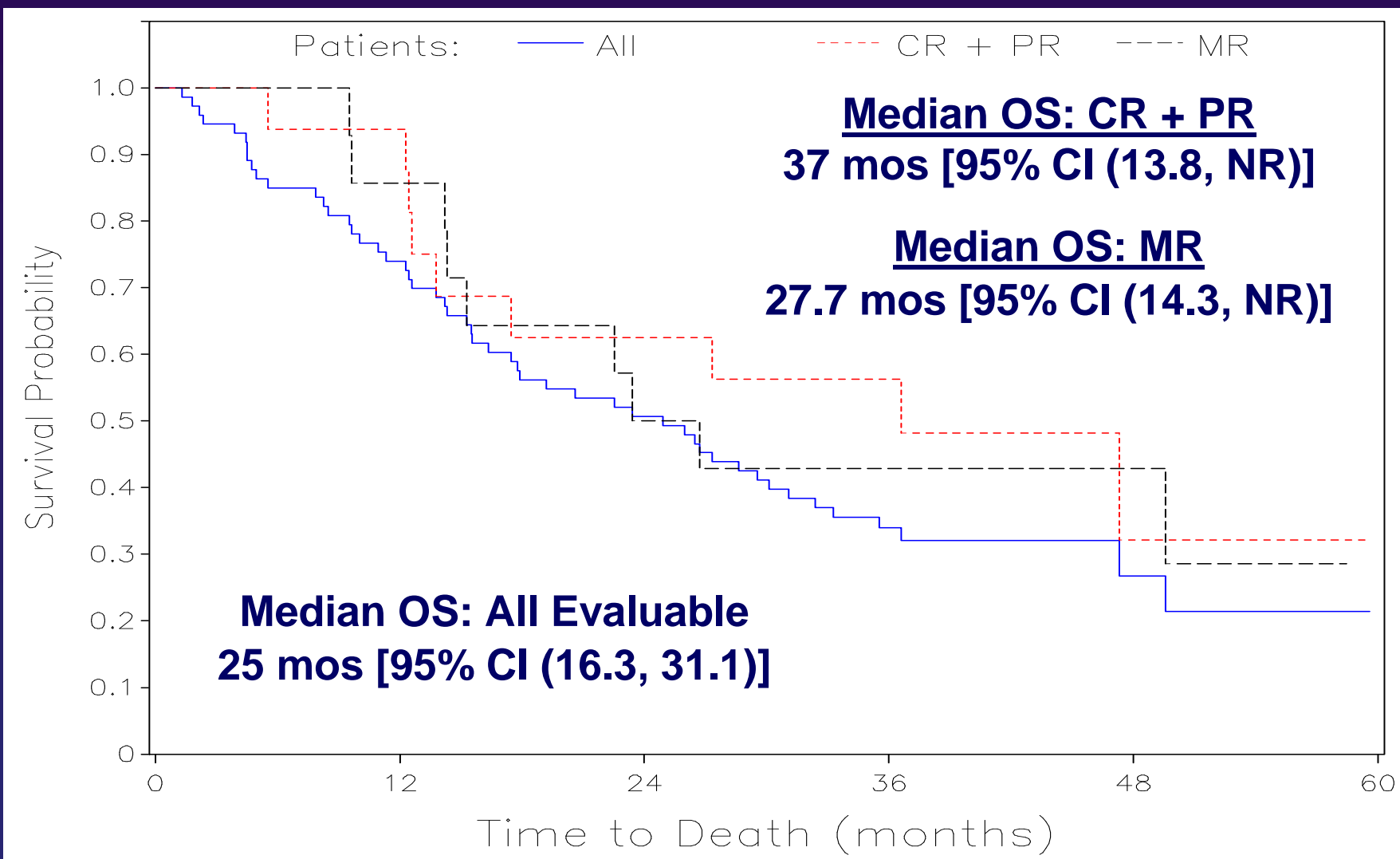
Evaluable Patients	CR/nCR		PR		MR		ORR		SD > 3 mos	
	n	%	n	%	n	%	n	%	n	%
All Evaluable Patients (n=73)	3	4%	13	18%	14	19%	30	41%	30	41%
Bortezomib Relapsed (n=20)	2	10%	7	35%	4	20%	13	65%	7	35%
Bortezomib Refractory (n=53)	1	2%	6	11%	10	19%	17	32%	23	43%
Median time to first response: 4 cycles (1 – 9)					Median time to best response: 6.5 cycles (2 – 11)					

- Median prior Rx in Bz refractory pts: 6
- Median prior Bz in Bz refractory pts: 2
- 45/84 pts (54%) had Dex added to Peri/Vel
- Median prior Rx in Bz relapsed pts: 4
- Median prior Bz in Bz relapsed pts: 1
- 39/84 (46%) pts had Peri/Vel only

Median PFS: CR/PR vs. MR



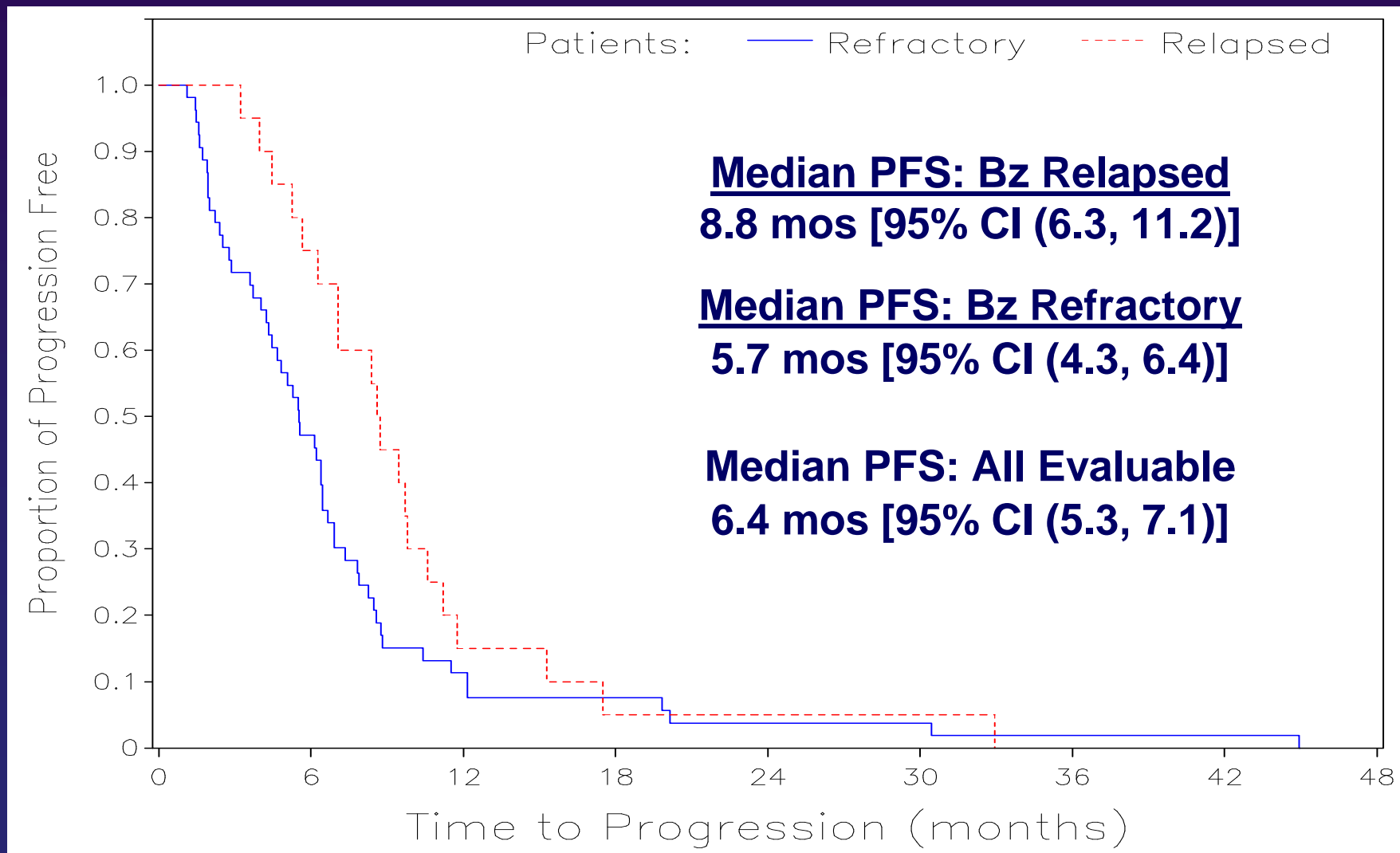
Median OS: CR/PR vs. MR



NR: Not Reached

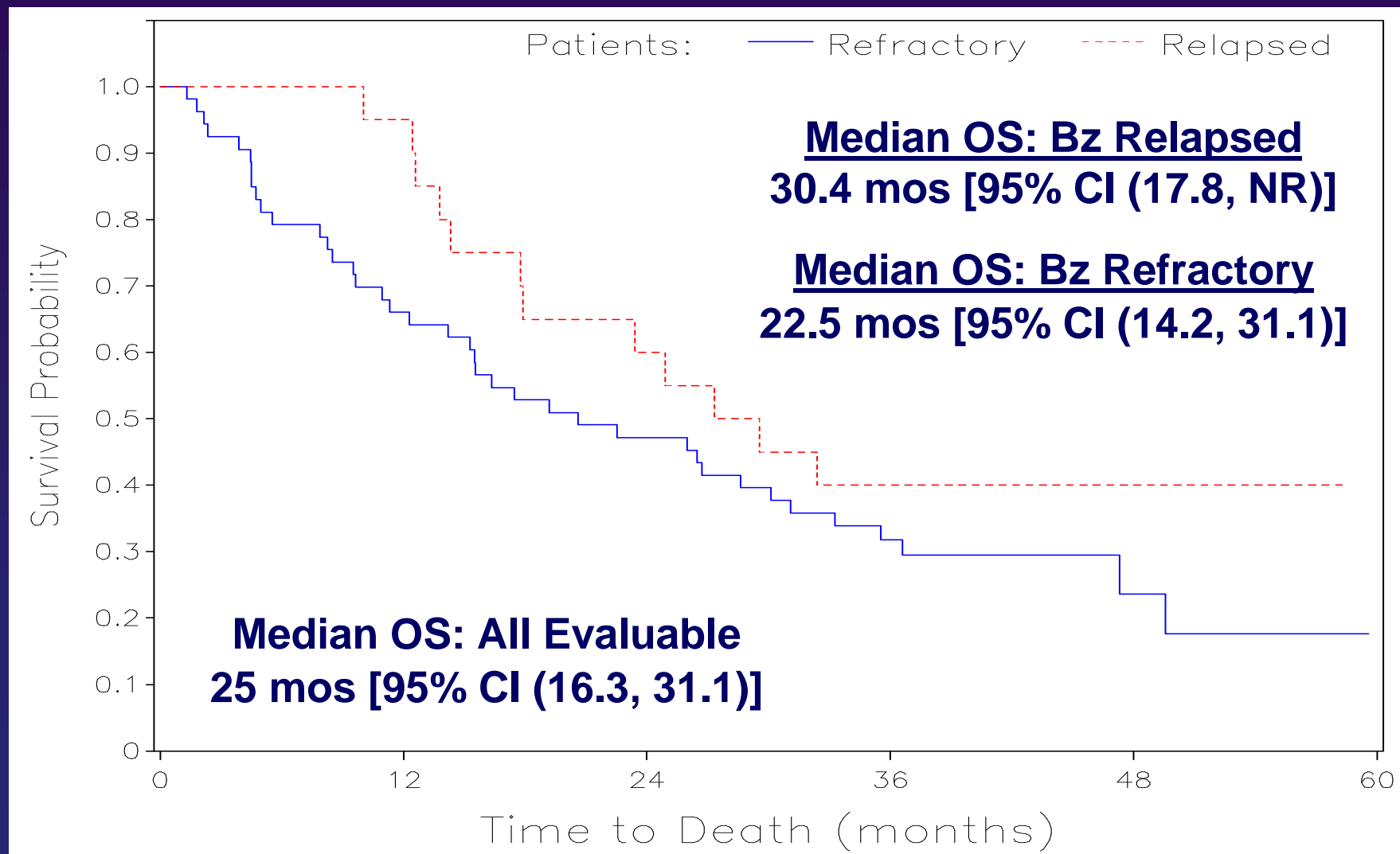
Kaplan–Meier method used to calculate OS

Median PFS: Bz Refractory vs. Relapsed



Kaplan–Meier method used to calculate PFS

Median OS: Bz Refractory vs. Relapsed



NR: Not Reached

Kaplan–Meier method used to calculate OS

Conclusions

- **Peri + Bz + Dex is active and well tolerated in previously Bz treated pts with advanced MM**
 - Median 5 prior lines of treatment
 - Median # of prior Bz lines of Rx: 2 (including prior Bz + Dex)
- **All Evaluable Study Pts (n = 73)**
 - Overall Response Rate: 41%
 - Median PFS: 6.4 mos Median OS: 25 mos
- **Bortezomib Refractory vs. Relapsed Pts**
 - Refractory: ORR (32%), PFS (5.7 mos), OS (22.5 mos)
 - Relapsed: ORR (65%), PFS (8.8 mos), OS (30.4 mos)
- **Toxicities have been manageable, with dose reduction and supportive care**
- **Ph III randomized trial under SPA – ACTIVELY RECRUITING (US/EU/CANADA/ISRAEL/SOUTH KOREA)**

Multiple Myeloma Ph III Global Trial

REQUIRED

Prior Velcade-based Rx (relapsed)
Prior Revlimid and/or Thal Rx (relapsed and refractory)
1 – 4 prior lines of Rx

Randomize

