Results of PX-171-003-A1, an Open-label, Single-arm, Phase 2 Study of Carfilzomib in Patients with Relapsed/Refractory Multiple Myeloma

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Rationale for Use of Carfilzomib in Relapsed and Refractory MM

- **Significant advances in MM treatment have occurred in the past decade, including approval of several novel agents and use of highly active combination regimens.**

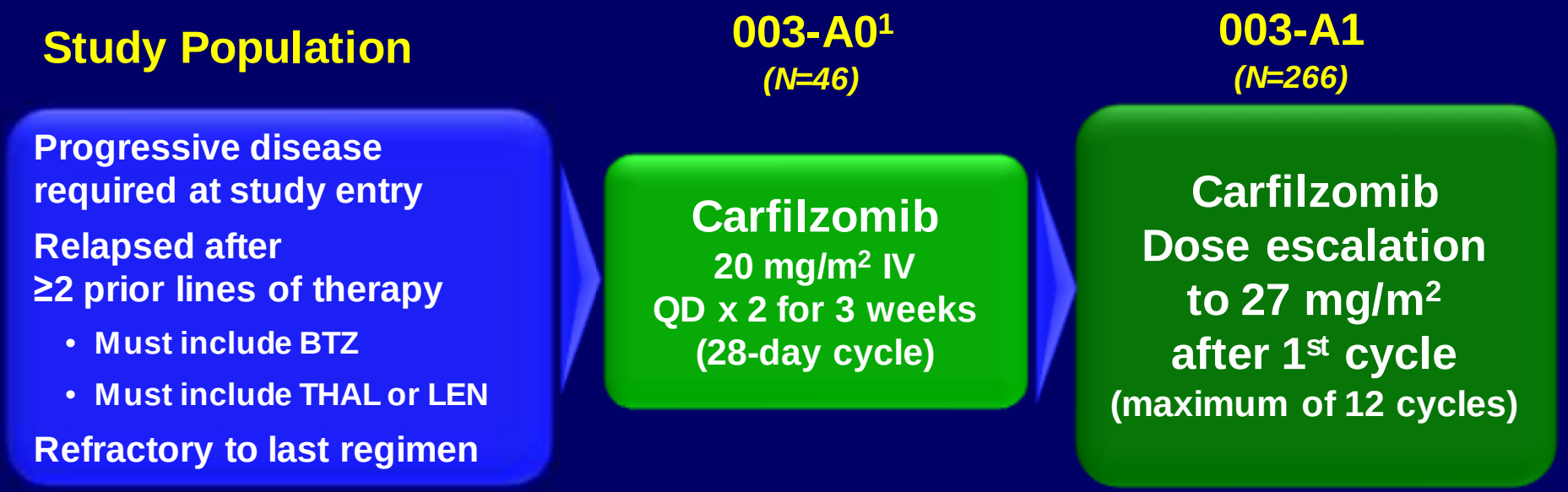
- **The majority of patients will eventually relapse following successive treatment regimens with progressively shorter response durations.[1]**

- **Outcomes are poor for patients who have received multiple therapies and whose disease is relapsed and refractory following BTZ and LEN:**
  - Estimated median survival of ~9 months[2]
  - Unmet medical need for new agents in this heavily pretreated patient population

- **Carfilzomib is a novel epoxyketone proteasome inhibitor:**
  - Highly selective for proteasome N-terminal threonine active sites
  - Sustained binding, potent inhibition, and minimal off-target activity

1. Richardson PG, et al. *Blood*. 2007; 110(10):3557-60. 2. Kumar S. *et al*. *Haematologica*. 2010;95:Abstract 0376.

003 Study Design



Primary endpoint: ORR

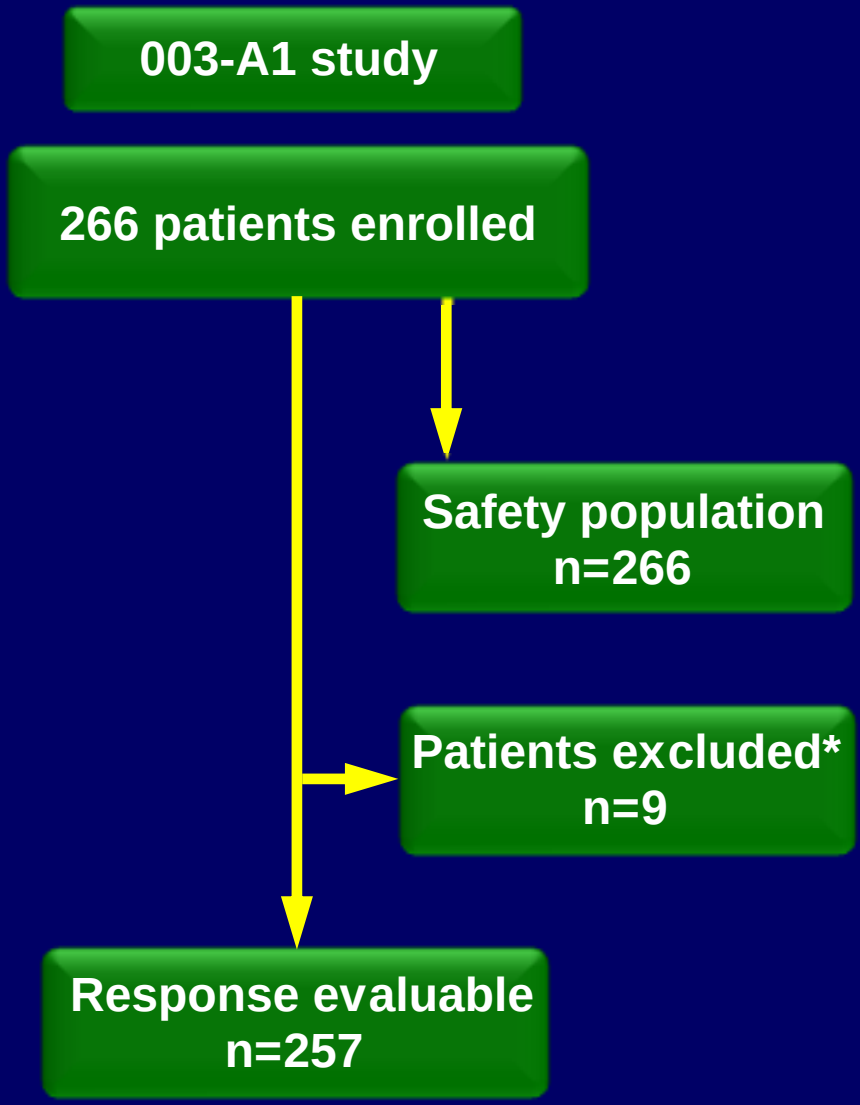
- IMWG response criteria (IRC assessed)

Secondary endpoints

- CBR (ORR+MR), DOR, OS, PFS, TTP, safety

1. Jagannath S, et al. ASH 2009 *J Clin Oncol*. 2009; 27: Abstract 8504.

003-A1 Patient Disposition



*Missing baseline or post-baseline disease assessment

Patient Baseline Characteristics (N=266)

Median age, years (range)	63 (37–87)
Median time since diagnosis, years (range)	5.4 (0.5–22.3)
ECOG ≤1, %	87
Immunoglobulin class, %	
IgG	73
IgA	17
IgD	1
Cytogenetics or FISH, %	
Normal/favorable	60
Unfavorable	28
Unknown or not done	12
ISS stage I / II / III, %	29 / 38 / 31
Baseline evaluation, %	
Grade 1/2 neuropathy*	77
CrCl <50 ml/min	25

*Based on physical assessment at screening (NCI-CTC scale)

Prior Therapies (N=266)

Prior lines of therapy, median #	5 (range 1–20)
≥4 prior lines of therapy	82%
Prior anti-MM agents, median #	13
Progressive disease at study entry	100%
Refractory to last line of therapy	95%
PD on therapy	74%
PD within 60 days	15%
≤25% Response (PD at study entry)	6%
Specific prior therapies	%
Bortezomib	99.6
Immunomodulatory agent	100
Lenalidomide	94
Thalidomide	75
Corticosteroid	98
Alkylating agents	93
Stem cell transplant	74
Anthracycline	64

Prior Bortezomib Treatment (N=266)

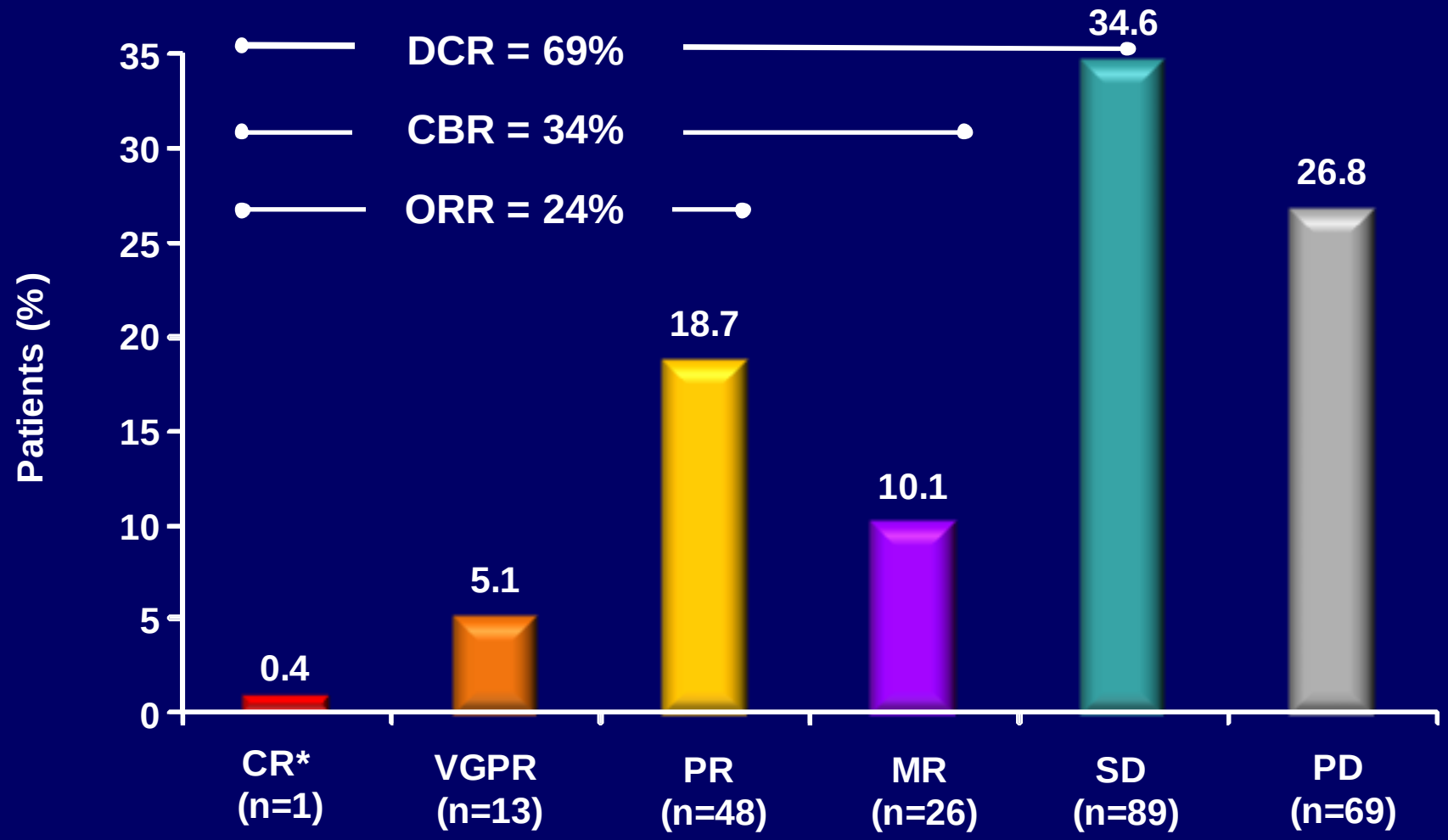
Prior bortezomib, median (range)	2 (1*–10)
Received bortezomib, % (n)	99.6 (265)*
Bortezomib refractory, % (n)	
In line prior to study entry	44 (116)
In line any prior line	73 (193)
Not refractory but intolerant to bortezomib, % (n)	15 (40)

88%

*1 patient did not receive prior bortezomib

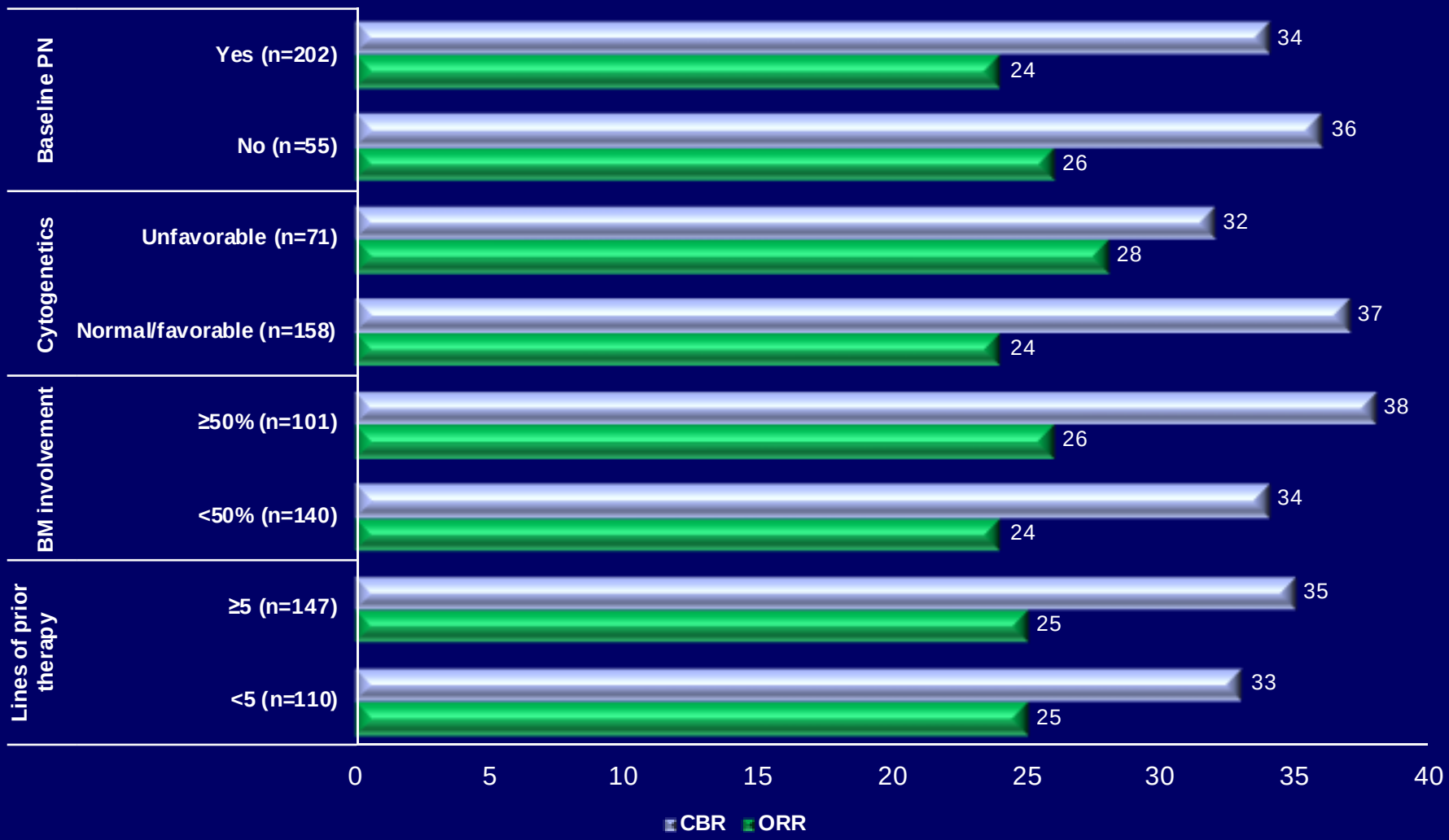
Responses
(Response-evaluable Population, N=257)

DOR (≥ PR) and (≥ MR) = 8.3 mo



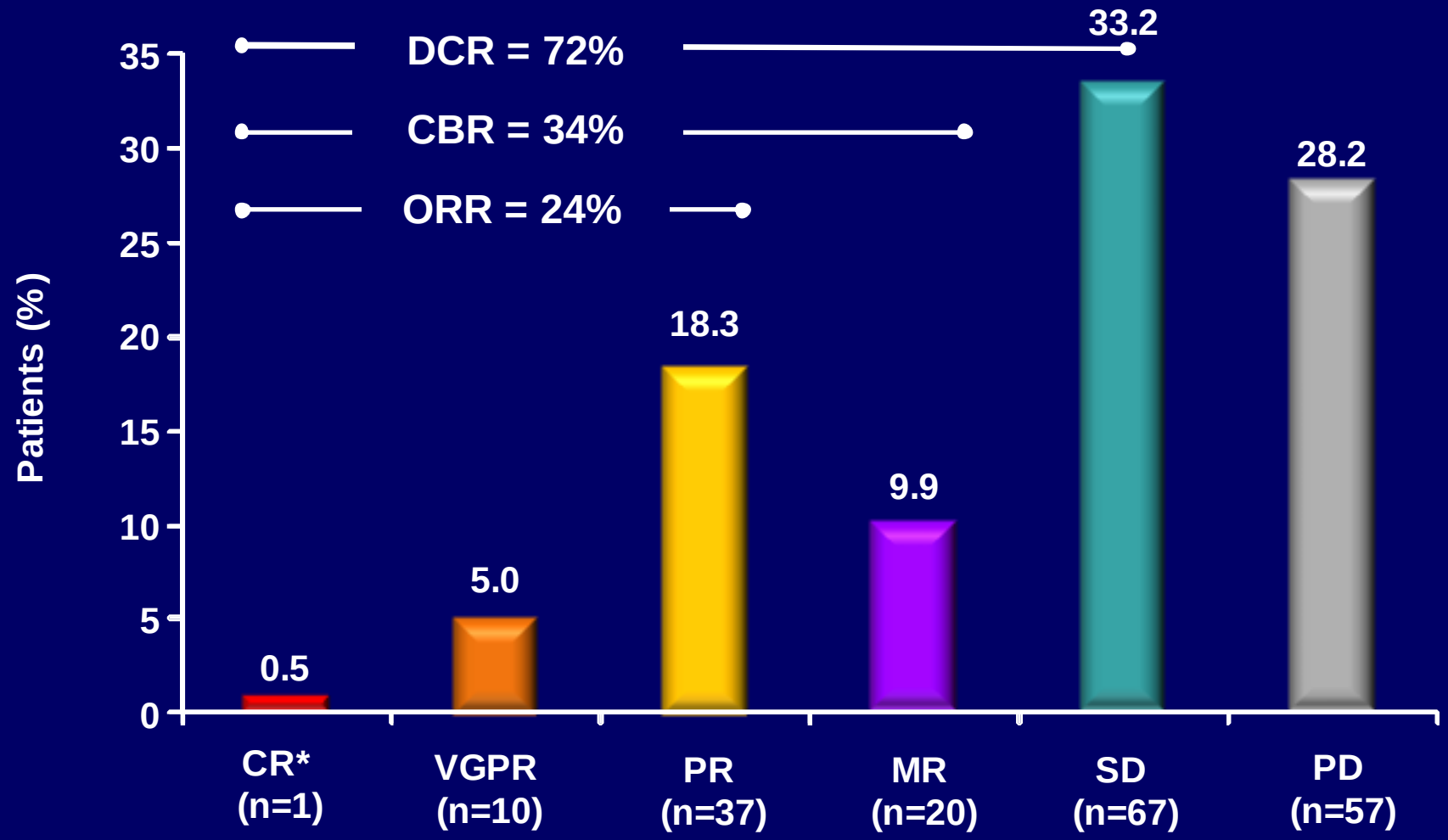
*CR IRC determined; 11 patients did not have a response that could be confirmed

Responses
(Higher-risk Subsets)



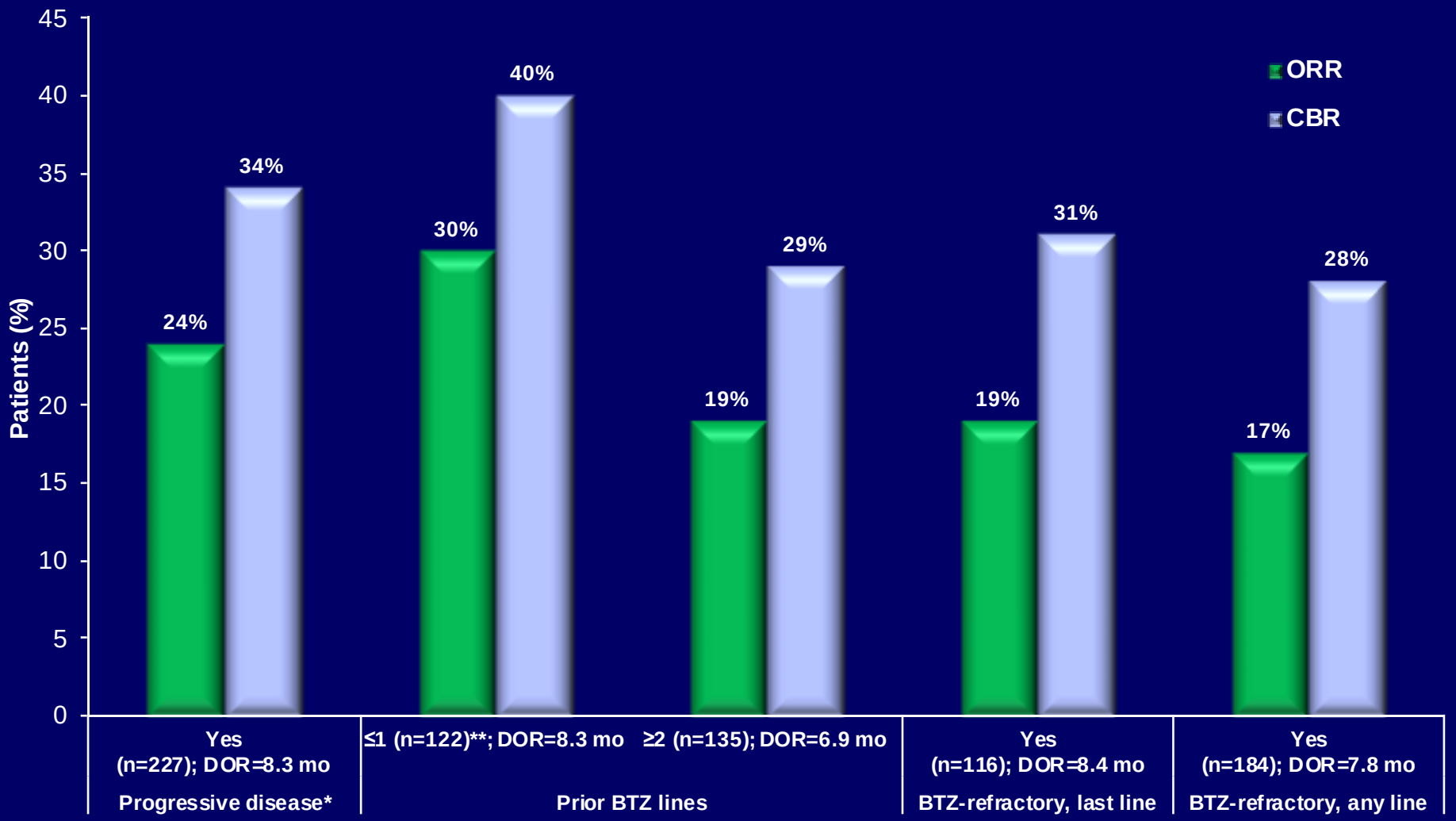
Responses
(Baseline PN Population, N=202)

DOR (≥ PR) and (≥ MR) = 8.3 mo



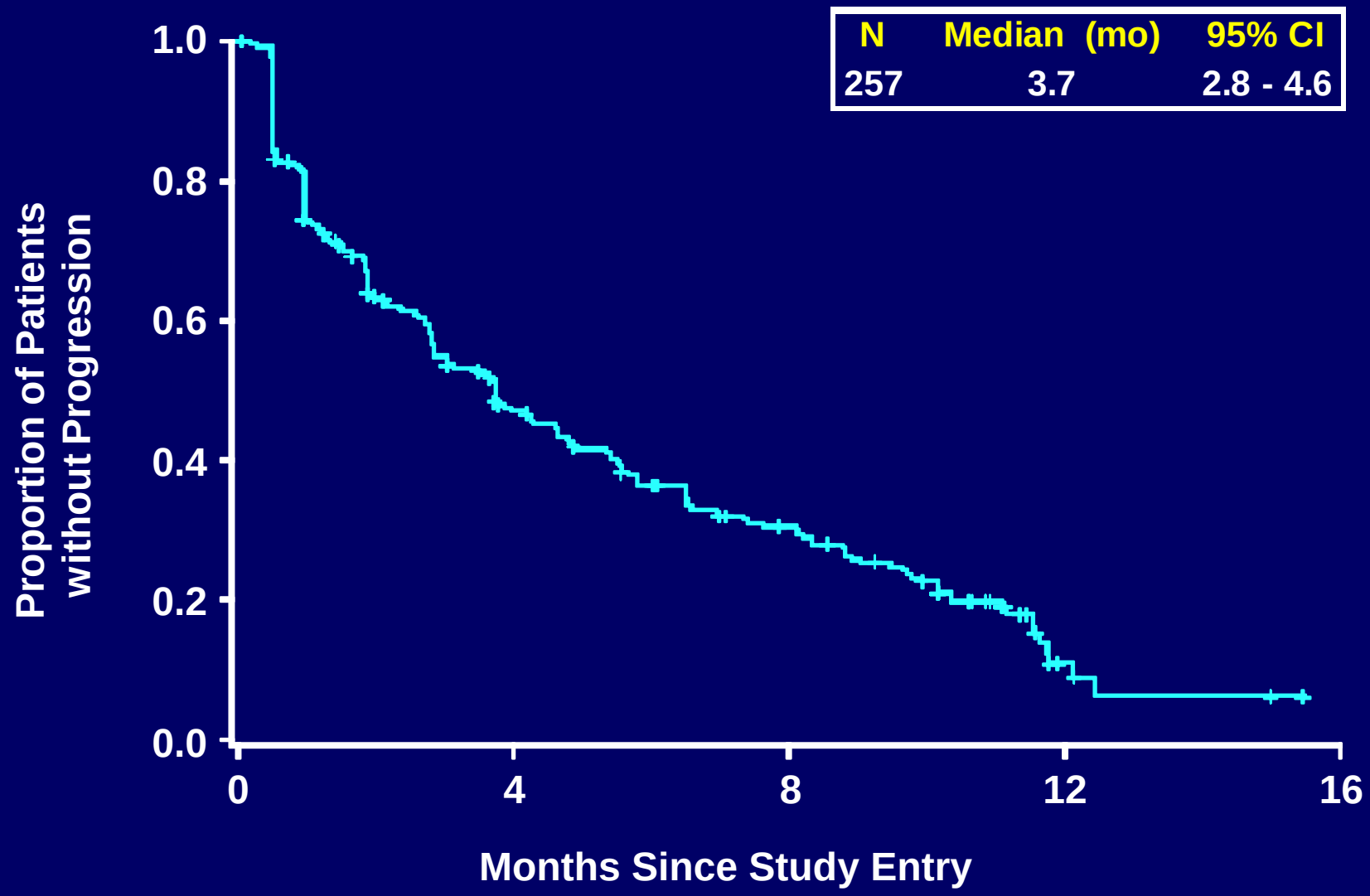
*CR IRC determined; 11 patients did not have a response that could be confirmed

Responses
(Subsets of Interest)

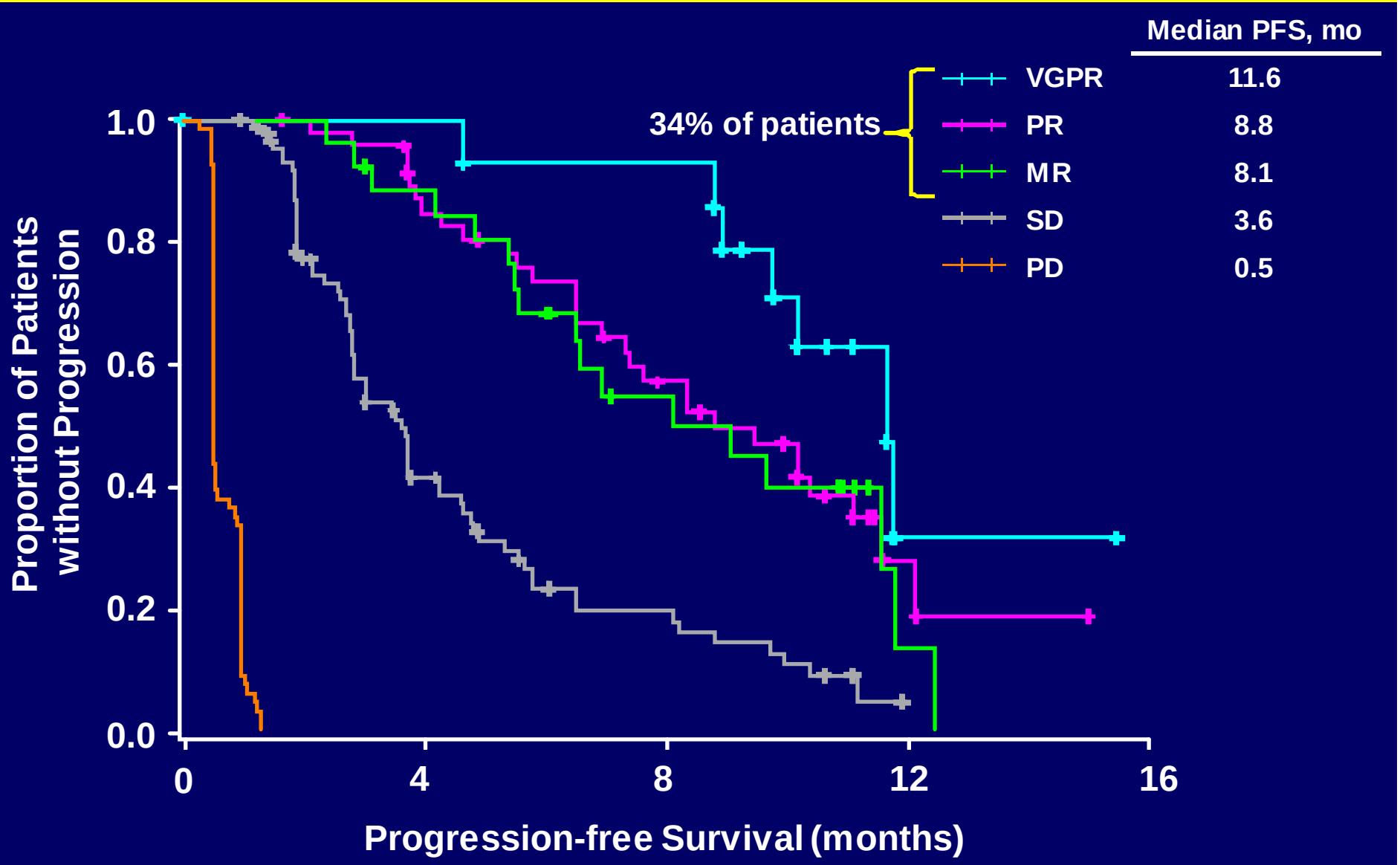


* On or within 60 days of last therapy; ** 1 patient did not receive prior bortezomib

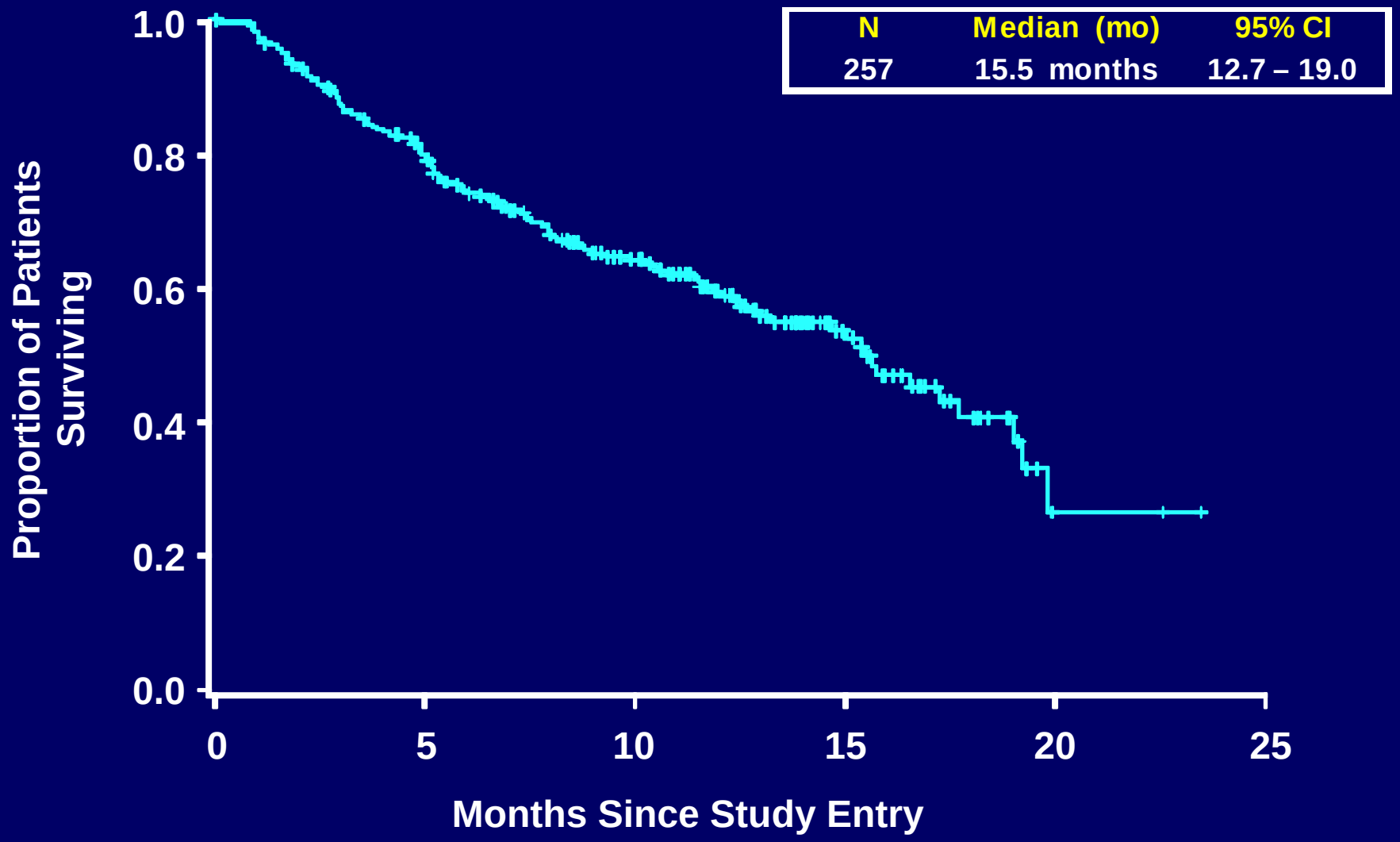
Progression-free Survival



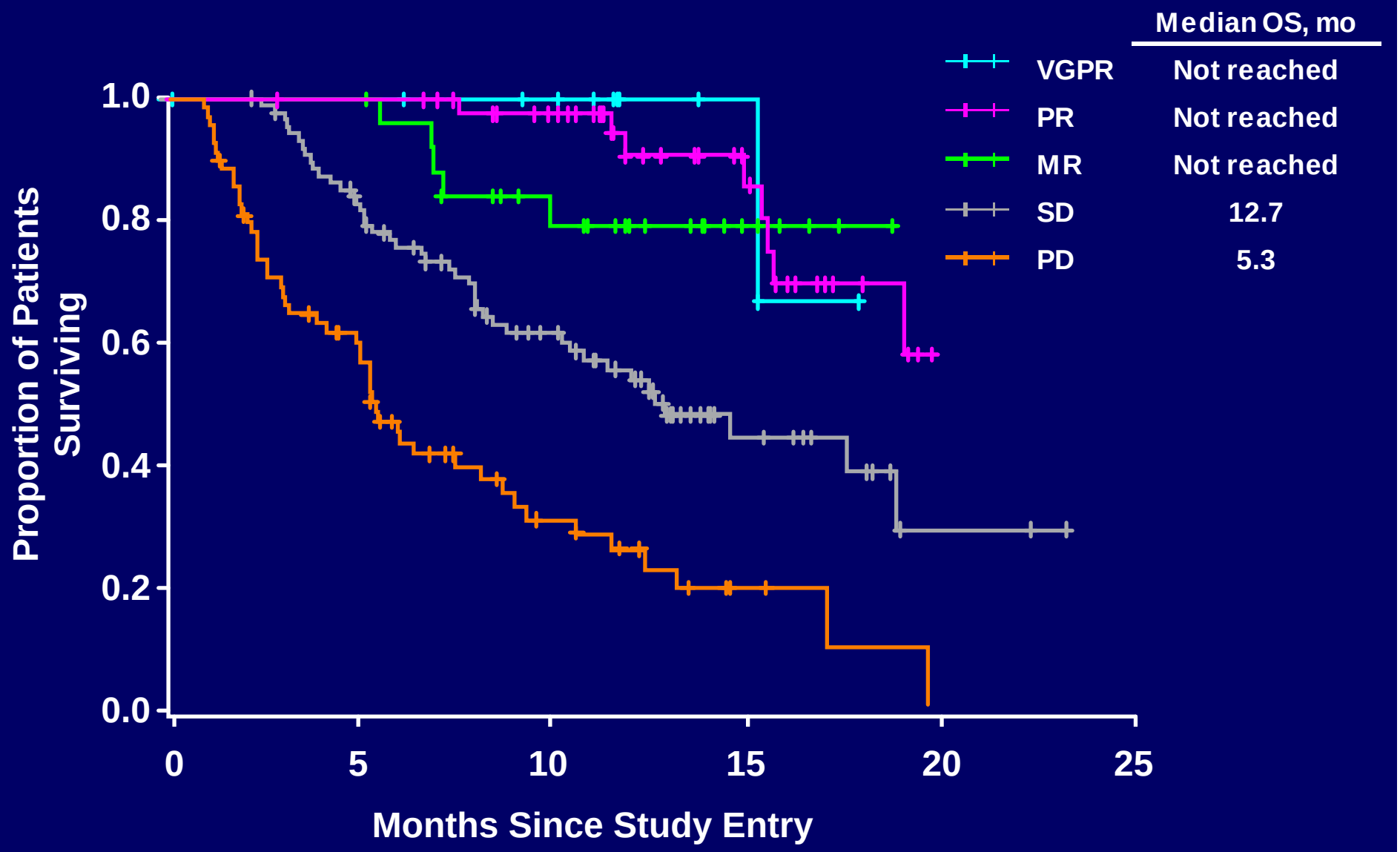
PFS by Response



Overall Survival



OS by Response



Treatment-emergent Adverse Events* (N=266)

	Any Grade, %	Grade 3/4, %
Hematologic (≥15%)		
Anemia	44	22
Thrombocytopenia	38	27
Lymphopenia	23	18
Neutropenia	17	10
Non-hematologic (≥25%)		
Fatigue	46	7.1
Nausea	41	1.5
Dyspnea	31	3.0
Diarrhea	29	0
Pyrexia	29	1.1
Upper respiratory tract infection	26	4.1
Headache	25	1.9
Other AEs of interest		
Febrile neutropenia	0.8	0.8
Peripheral neuropathy†	12	0.8
Tumor lysis syndrome	0.4	0

*Any cause

† includes: neuropathy, peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy

Additional Safety Data (N=266)

Endpoint	%
Discontinuations	**8.2**
Due to disease progression	5.7
Due to AE	1.2
• PN related	0
On study deaths	**9.0**
Due to AE	3.3
Due to disease progression	5.3
Due to AE *(considered possibly or probably related to study drug)*	1.9
Patients completing 12 cycles of treatment*†	**1.6**

*Patients completing the study (12 cycles, 11 months) were eligible to receive long-term extended therapy on study PX-171-010.
†No evidence of cumulative toxicity in patients from 003-A1 completing >6–12 additional months of therapy on the extension study.

Conclusions

- **Single-agent carfilzomib is active in heavily pretreated MM patients whose disease was refractory to their last line of therapy**
  - 24.1% ORR; 34.2% CBR
  - Median DOR of 8.3 months (both ≥PR *and* ≥MR populations)
- **Overall Survival is impressive in this patient population**
  - 15.5 months
- **34% of patients (≥MR) treated with carfilzomib had improved PFS and OS relative to non-responders**
- **Carfilzomib is well-tolerated in heavily pretreated patients**
  - Very low rate of neuropathy — Grade 3/4 0.8% (2 patients)
  - Low rates of neutropenia
  - 16% of patients completed 12 cycles

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MMRC Multiple Myeloma Research Consortium

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