Weekly Carfilzomib, Cyclophosphamide and Dexamethasone (wCCd) in Newly Diagnosed Multiple Myeloma Patients: A Phase I-II Study

Abstract 175

Palumbo A, Rossi D, Bringhen S, Larocca A, Gentilini F, De Paoli L, Omedé P, Ballanti S, Cavallo F, Passera R, Liberati AM, Boccadoro M, Gaidano G, Sonneveld P, Corradini P

Rationale

	Bortezomib Twice Weekly	Bortezomib Once Weekly	*P* value
CR	35%	30%	.27
PR	32%	30%	.66
PFS @ 3 years	47%	50%	1.00
OS @ 3 years	89%	88%	.54
Hematologic AEs	45%	44%	.83
Nonhematologic AEs	51%	35%	.003
PNP	28%	8%	<.001
Gastrointestinal AEs	11%	6%	.08
Median dose intensity	59%	84%	<.001
Median delivered dose – mg/m^2	39.4	40.1	
Dose reduction	41%	17%	<.001
Discontinuation	15%	5%	<.001

CR, complete response; PR, partial response; PFS, progression-free survival; OS, overall survival; AE, adverse event; PNP, peripheral neuropathy

Bringhen S, et al. *Blood*. 2010;116(23):4745-4753.

Palumbo A, et al. *Blood*. 2014;124: Abstract 175.

Key Objectives

- **Primary:**
  - Phase I: maximum tolerated dose (MTD) of weekly carfilzomib
  - Phase II: response rate
- **Secondary:**
  - Safety
  - Progression-free survival (PFS)
  - Time to progression (TTP)
  - Duration of response (DOR)
  - Time to next therapy (TTNT)
  - Outcome in subgroups with different prognosis according to: β2-microglobulin, C-reactive protein (CRP), FISH, gene expression profile
  - PFS and OS of maintenance

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Patient Eligibility

- **Key inclusion criteria:**
  - Symptomatic *newly diagnosed MM*
  - *≥65-years-of-age or ineligible for autologous stem cell transplantation*
  - Measurable disease (≥0.5 g/dL of M-protein or urine light-chain excretion of >200 mg/24 hours)
  - ECOG 0-2
  - Adequate hepatic function (ALT ≤3.5 times the upper limit of normal and serum direct bilirubin ≤2 mg/dL)
  - *Creatinine clearance (CrCl) ≥15 mL/min*

- **Key exclusion criteria:**
  - Prior systemic MM therapy
  - Relapsed or refractory MM
  - History of severe heart disease
  - Uncontrolled hypertension or congestive heart failure (CHF)

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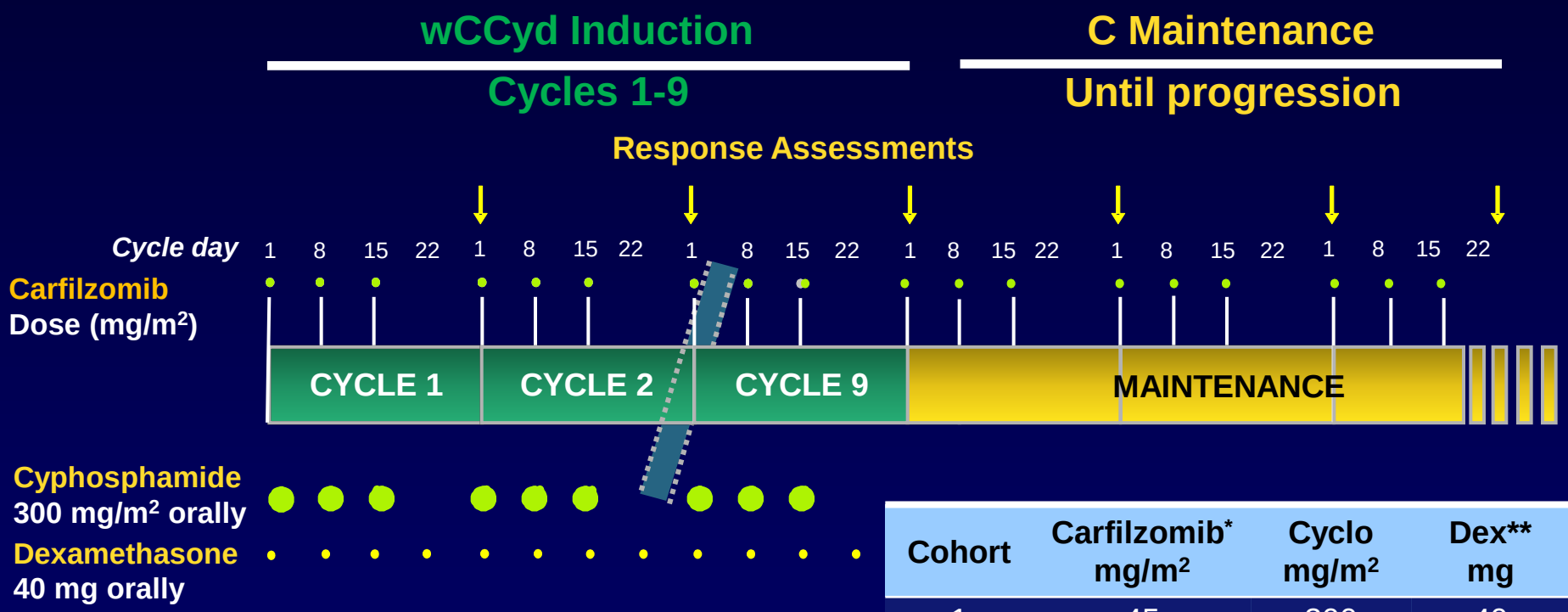
Study Design

Phase I/II - Multicenter (8 centers)



Cohort	Carfilzomib* mg/m²	Cyclo mg/m²	Dex** mg
1	45	300	40
2	56	300	40
3	70	300	40

*All patients received 20 mg/m² carfilzomib on D1 of cycle 1; subsequent doses were escalated to the indicated levels
**or 20 mg of dexamethasone on days 1,2,8,9,15,16,22,23.

wCCyd, weekly carfilzomib-cyclophosphamide-dexamethasone; C maintenance, carfilzomib maintenance.

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Enrollment

- From April 2013 to data cutoff (September 2014), 30 patients have been enrolled
- Phase I (April 2013 and October 2013)
  - 12 patients
  - Carfilzomib dose cohorts:

	45 mg/m^2	56 mg/m^2	70 mg/m^2
No. of patients	3	6	3
DLT	0	1	0
Type of DLT	-	Creatinine increase	-

  - MTD: 70 mg/m^2
- Phase II
- Stage I (November 2013 – June 2014): 16 patients

  Stage II (July 2014 – ongoing): 2 patients
- 21 patients treated at the MTD
  - 3 from dose escalation, 18 from phase II

DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

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Patient Characteristics

	Phase I, n = 12	Phase II, n = 18	Total, N = 30
Median age, years (range)	73 (65–79)	74 (64–79)	74 (64–79)
Age ≥75 years, n (%)	4 (33)	5 (28)	9 (30)
Male, n (%)	5 (42)	8 (44)	13 (43)
ISS stage at diagnosis, n (%)			
I	4 (33)	8 (44)	12 (40)
II	4 (33)	3 (17)	7 (23)
III	4 (33)	7 (39)	11 (37)
Unfavorable profile*, n (%)	3/9 (40)	4/12 (33)	7/21 (33)
del 17	3 (33)	4 (33)	7 (33)
t(4;14)	0	0	0
t(14;16)	1 (11)	0	1 (5)
Creatinine clearance, n (%)			
>60 mL/min	7 (58)	14 (78)	21 (70)
30-60 mL/min	4 (33)	3 (17)	7 (23)
<30 mL/min	1 (9)	1 (5)	2 (7)

*Unfavorable profile was assessed by FISH and included del 17, t(4;14) or t(14;16). ISS, International Staging System

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Treatment Exposure

	Phase I, n = 12	MTD, n = 21	Total, N = 30
Median cycles of wCCyd received, n (range)	9 (1–9)	4 (1–9)	8 (1–9)
Patients treated with … cycles of CCyd, n (%)			
≥4	11 (92)	11 (52)	23 (77)
≥8	10 (83)	7 (33)	15 (50)
Patients started maintenance, n (%)	9 (75)	3 (14)	10 (33)
Median relative dose intensity*, %			
Carfilzomib	100	100	100
Cyclophosphamide	100	100	100
Dexamethasone	85	92	96
Patients remaining on treatment,† n (%)	8 (67)	17 (81)	24 (80)
Reasons for going off treatment, n (%)			
Adverse events	2 (17)	2 (9)	3 (10)
Progressive disease	1 (8)	1 (5)	2 (7)
Other	1 (8)	1 (5)	2 (7)

*Dose taken/dose prescribed. †At data cut-off of September 30, 2014.

wCCyd, weekly carfilzomib-cyclophosphamide-dexamethasone

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Summary of Safety Profile

AE, n (%)	Phase I N = 12	MTD N = 21	Total N = 30
Any serious AE* (SAE)	1 (8)	4 (19)	5 (17)
Any drug-related SAE†	1 (8)	4 (19)	4 (13)
Dose reduction due to AE	3 (25)	0	3 (10)
On-study death	0	1 (5)	1 (3)

AE, adverse event. *AEs graded using NCI-CTCAE v4.02. †Drug-related defined as related to any drug in the combination

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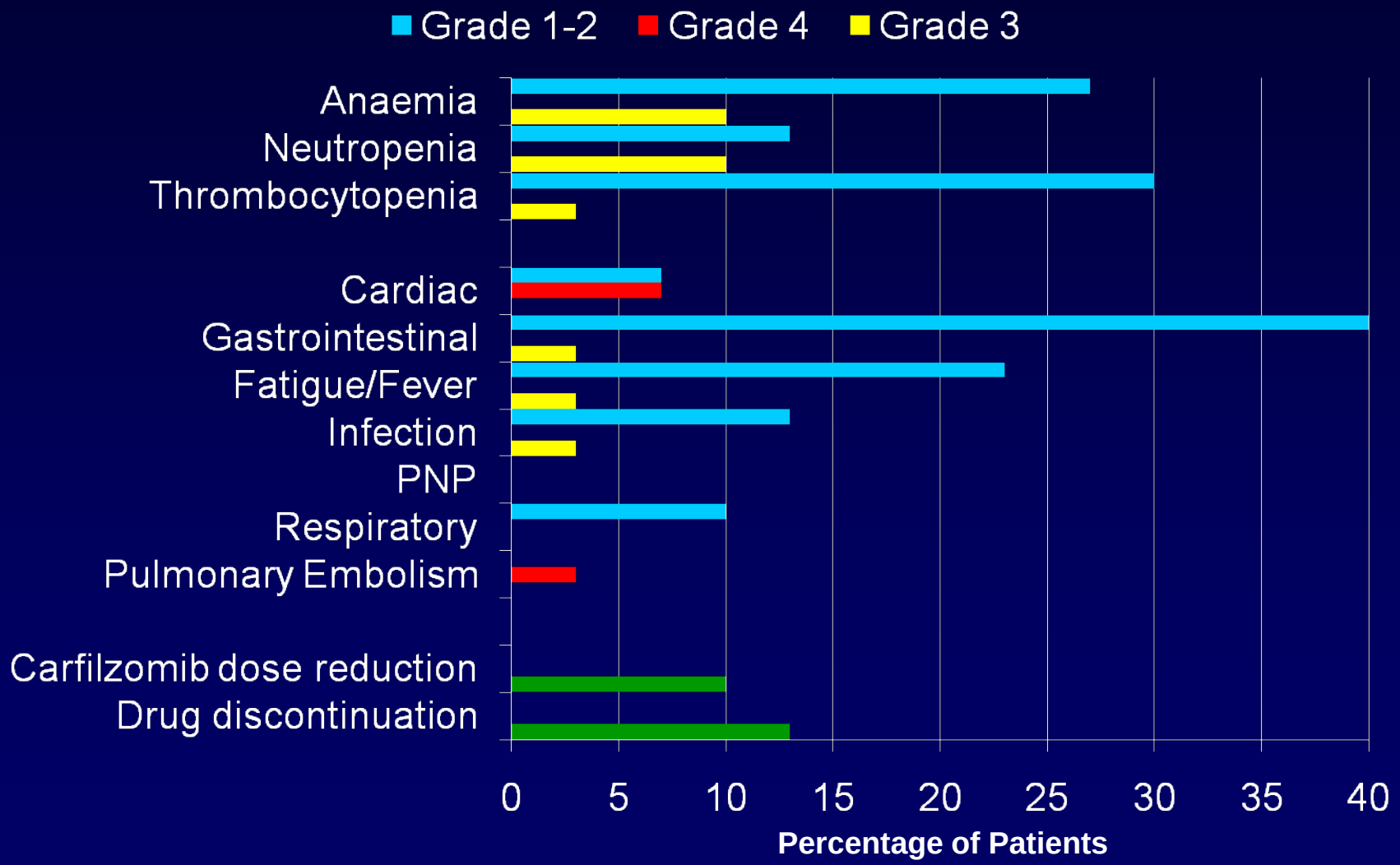
Adverse Events – All Grades, All Patients



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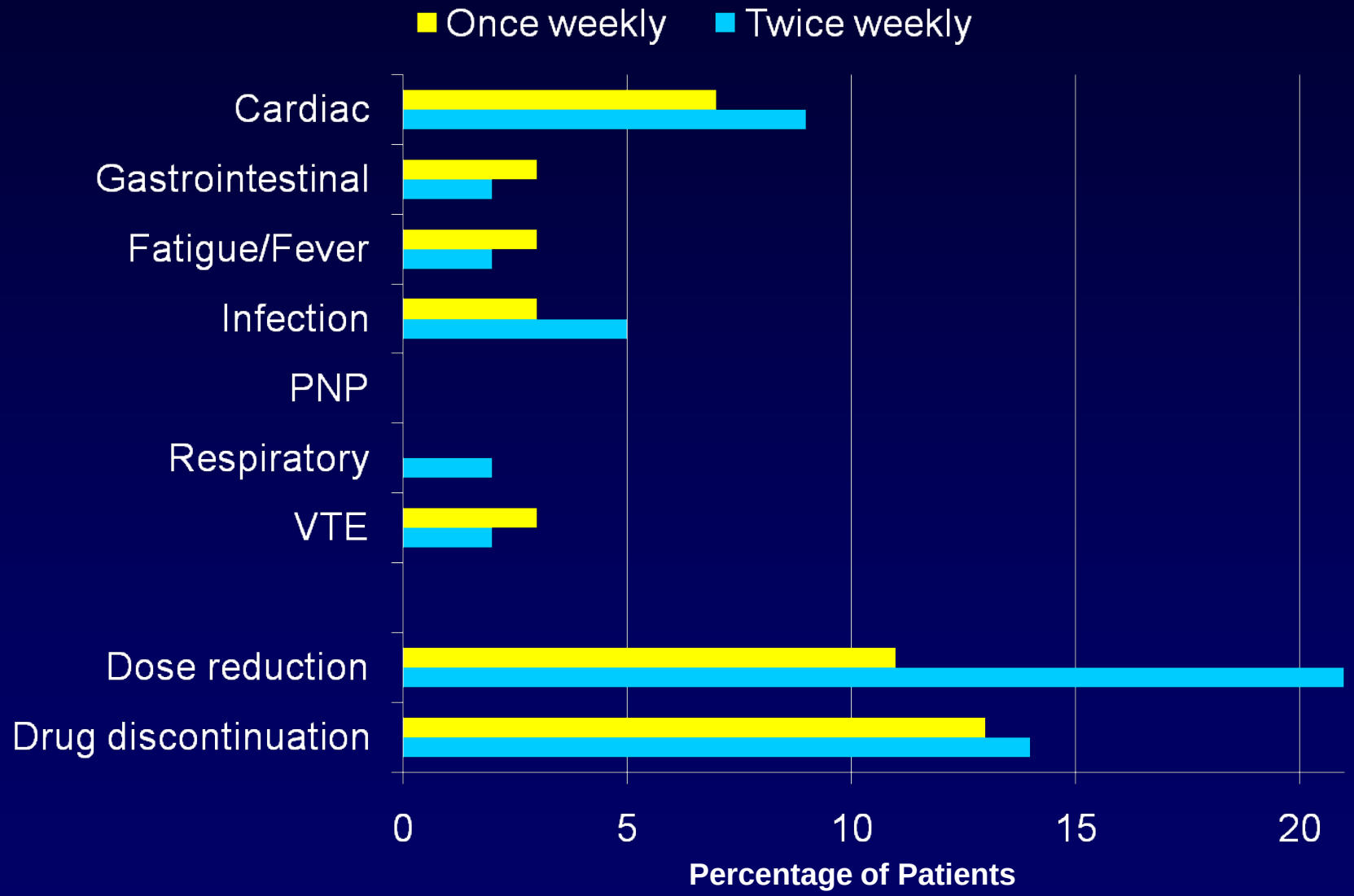
PNP, peripheral neuropathy

Adverse Events – Grade 3-4
Weekly vs Twice Weekly



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PNP, peripheral neuropathy; VTE, venous thromboembolism

Preliminary Response Data

- 28 of 30 patients were evaluable for response (2 patients not evaluable for response due to early discontinuation [pulmonary edema] and 1st cycle ongoing)
- Median time to first response (≥PR) was 1 month
- Median duration of response not reached

	Phase I n = 12	MTD n = 19	Total N = 28
Median cycles received, n (range)	9 (1–9)	4 (1–9)	8 (1–9)
ORR (≥PR), n (%)	11 (92)	15 (79)	24 (86)
≥VGPR, n (%)	9 (75)	11 (58)	18 (64)
sCR + CR + nCR, n (%)	4 (33)	4 (21)	7(25)

PR, partial response; ORR, overall response rate; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; nCR, near complete response; MTD, maximum tolerated dose.

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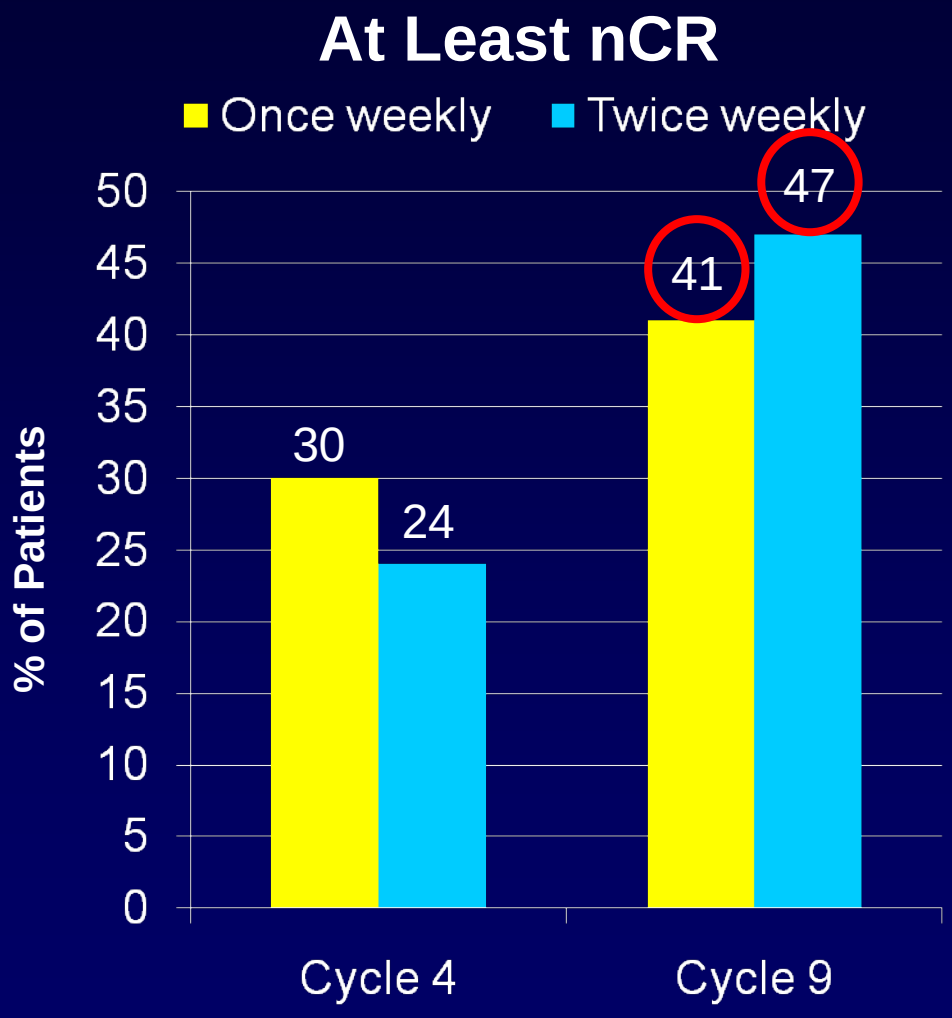
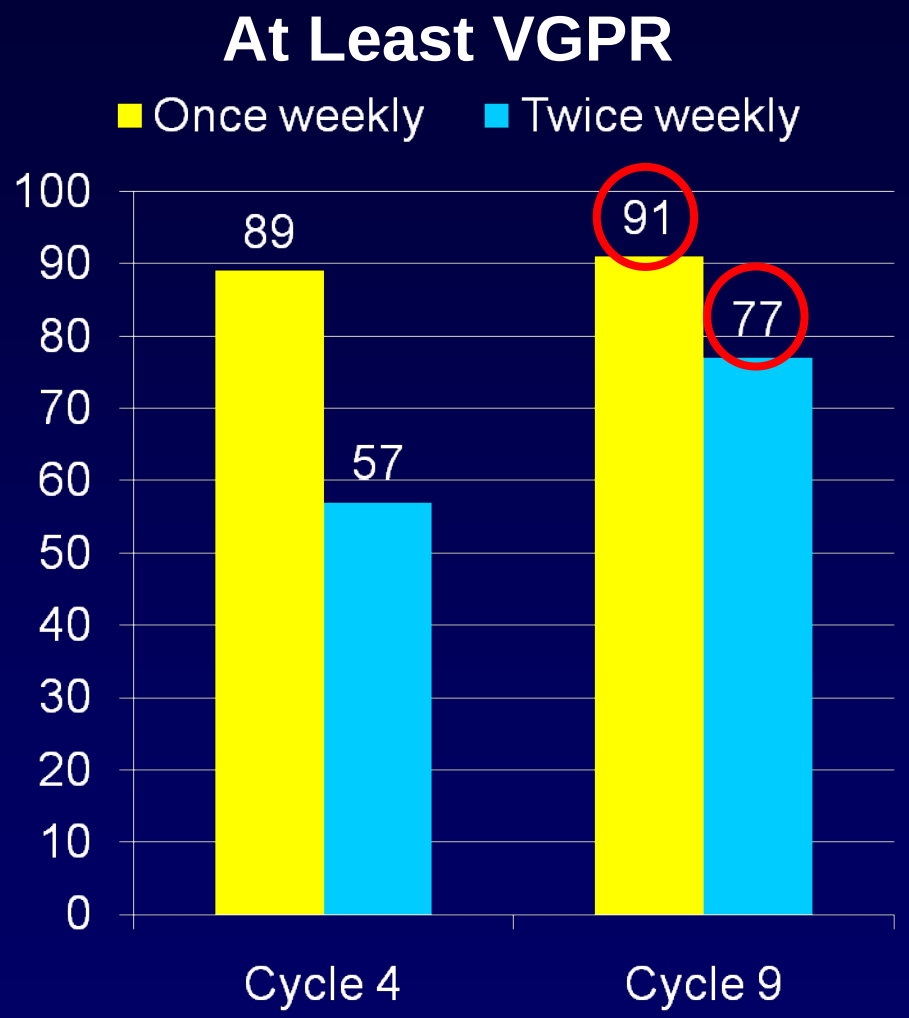
Response Rate By Treatment Duration
Weekly vs Twice Weekly





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nCR, near complete response; VGPR, very good partial response.

Conclusions

	CCyd once weekly	CCyd twice weekly
≥ nCR*	41%	47%
PR*	99%	91%
Grade 3-4 hematologic	23%	27%
Grade 3-4 nonhematologic	30%	29%
Median delivered carfilzomib dose, mg*	3534	2904
Dose reduction	10%	21%
Discontinuation	13%	14%

* After 9 cycles of Ccyd

CCyd, carfilzomib-cyclophosphamide-dexamethasone; PR, partial response; nCR, near complete response; PFS, progression-free survival.

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