Carfilzomib, Lenalidomide, and Dexamethasone (CRd) in Newly Diagnosed Myeloma: Initial Results of Phase I/II MMRC Trial

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Background

- **The aim of novel combinations in front-line MM is to further improve depth of response and tolerability**
  - TTP or PFS are prolonged in patients who achieve CR or VGPR in non-transplant and transplant candidates[1, 2]
- **Regimens containing Thalidomide or Lenalidomide (R) + bortezomib (V) + dexamethasone, e.g. (RVD) have emerged as potentially the best initial treatments**
  - Best Response to RVD (all patients): ≥ PR 100%, ≥ VGPR 67%, CR/nCR 39%[3]
  - Best Response to RVD (MTD): ≥ PR 100%, ≥ VGPR 74%, CR/nCR 57%[3]
- **The depth of response to novel agents and their combinations improves over time**
  - Responses to RVD at 4 cycles: ≥ PR 75%, ≥ VGPR 11%, CR/nCR 6%
- **Extended treatment at optimal doses can be limited by emerging toxicities including peripheral neuropathy**

1. Harousseau et al. Blood. 2010 Nov 11;116(19):3743-50. Epub 2010 Jul 13
2. Jakubowiak et al. J Clin Oncol, 2009 Oct 20;27(30):5015-22. Epub 2009 Sep 8.
3. Richardson et al, Blood 2010;116;679-686.

Rationale

- **Carfilzomib (Cfz) is a novel, irreversible proteasome inhibitor:**
  - Proven efficacy[1]
  - Favorable toxicity profile[1], including no significant neurotoxicity after prolonged treatment [2]
- **Based on these characteristics, combining Cfz with Lenalidomide (Len) and Dexamethasone (Dex) was a next logical step**
- **Cfz + Len + Dex (CRd) has shown synergy in preclinical studies and promising activity and tolerability in relapsed/refractory MM[3,4]**
  - At maximum planned doses, 78% response rate (≥ PR) and 40% VGPR
  - Prolonged administration (14 + months)
- **We hypothesized that the CRd combination has potential for even higher activity in newly diagnosed MM and could produce better CR/nCR rates than currently available regimens**

1. Siegel et al, ASH 2009, Abstract #303
2. Vij et al, ASH 2009, Abstract #430
3. Niesvizky et al, ASH 2009, Abstract #304
4. Martin et al, Lymphoma and Myeloma 2010, New York, NY

Objectives

Primary

- Phase I : Determine the MTD of CRd
- Phase I/II: Determine the rate of CR/nCR

Secondary

- Determine the overall response rate ≥ PR
- Evaluate TTP, DOR, PFS, and OS
- Evaluate the tolerability and toxicity
- For transplant candidates, evaluate the impact of CRd on stem cell mobilization
- Evaluate prognostic factors and markers of response

Eligibility

Key inclusion criteria:

- Newly diagnosed MM requiring first line therapy[1]
  - transplant eligible and ineligible
- Measurable disease as per IMWG Criteria[1]
- Karnofsky/ECOG performance status ≥60/0-2

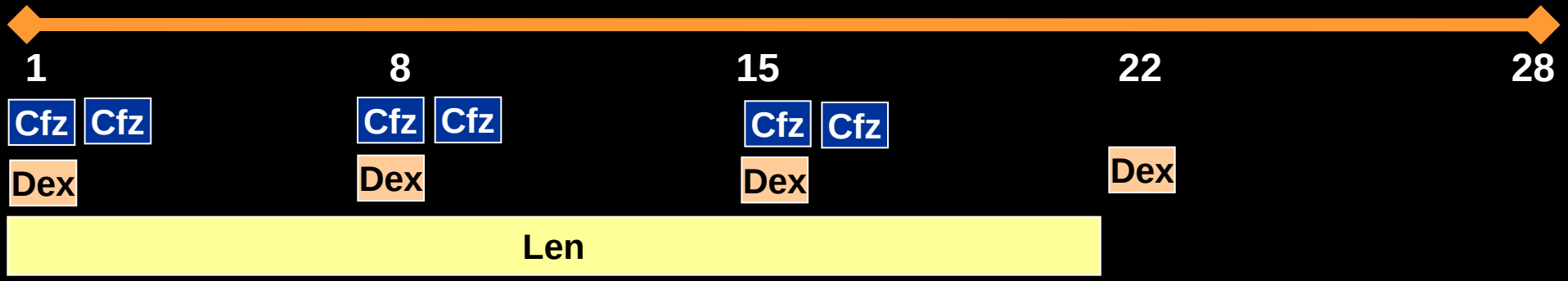
Key exclusion criteria:

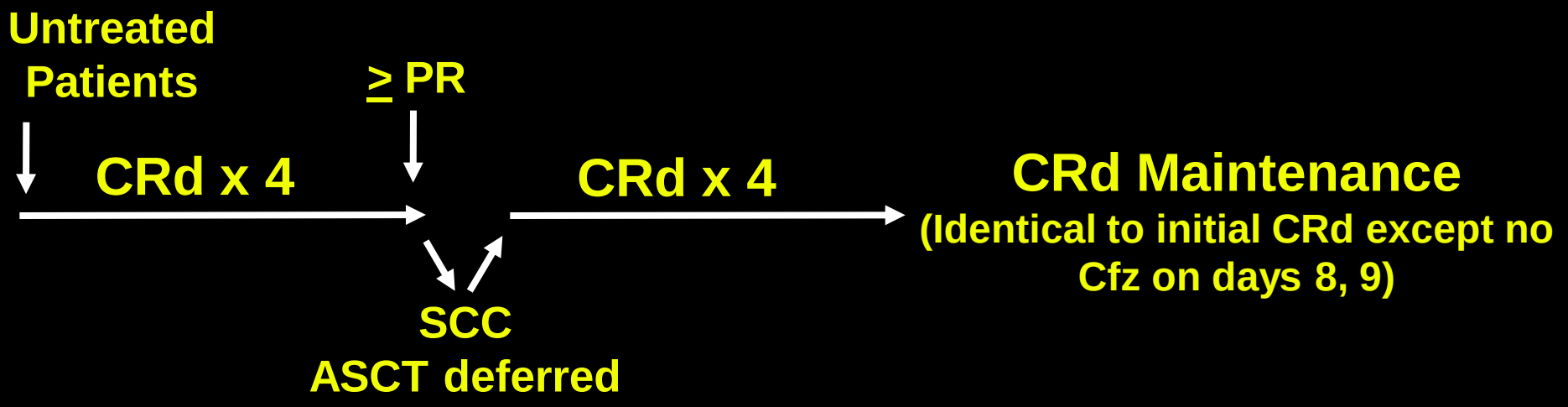
- Grade > 2 peripheral neuropathy
- ANC < 1.0, Hgb < 8.0 g/dl, platelets < 75,000
- Creatinine Clearance < 60 ml/min
- Serious co-morbidities

1. Durie et al. Leukemia 2006;20;1467-73.

Treatment Schema

Initial Treatment: 28-day cycles





Dex, 40 mg/day days 1, 8, 15, and 22; 20 mg, cycles 5–8, and maintenance

Assessments

- Toxicities are graded by NCI CTCAE v3.0
- Responses assessed by modified IMWG Uniform Criteria[1,2] with an addition of nCR[3]
- Assessments with each cycle[2]

1. Bladé et al. Br J Haematol 1998;102:1115-23.
2. Durie et al. Leukemia 2006;20;1467-73.
3. Richardson et al., Blood. 2005 Nov 1;106(9):2977-81

Phase I Dose Levels

Dose level	Cfz	Len	Dex Cycles 1-4 / 5-8
-1	15 mg/m^2	25 mg/day	40/20 mg
1	20 mg/m^2	25 mg/day	40/20 mg
2	27 mg/m^{2*}	25 mg/day	40/20 mg
3	36 mg/m^{2**}	25 mg/day	40/20 mg

* CFZ 20 mg/m^2 on Days 1 and 2 of Cycle 1, followed by 27 mg/m^2

** CFZ 20 mg/m^2 on Days 1 and 2 of Cycle 1, followed by 36 mg/m^2

Patient Characteristics (Phase I)

Characteristic	N=31
Median age, years (range)	59 (35-81)
Male, n (%)	25 (80)
Myeloma type, n (%)	
IgG	24 (77)
IgA	6 (19)
κ light chain	24 (75)
λ light chain	7 (23)
ISS stage II/III, n (%)	18 (58)
Durie-Salmon stage II/III, n (%)	29 (93)
13q del or t(4;14) or t(14;16) or 17p	13 (48)

Enrollment and DLTs

TITE-CRM Design:

- Continued enrollment of a total of 35 patients
- MTD: DLT <20%

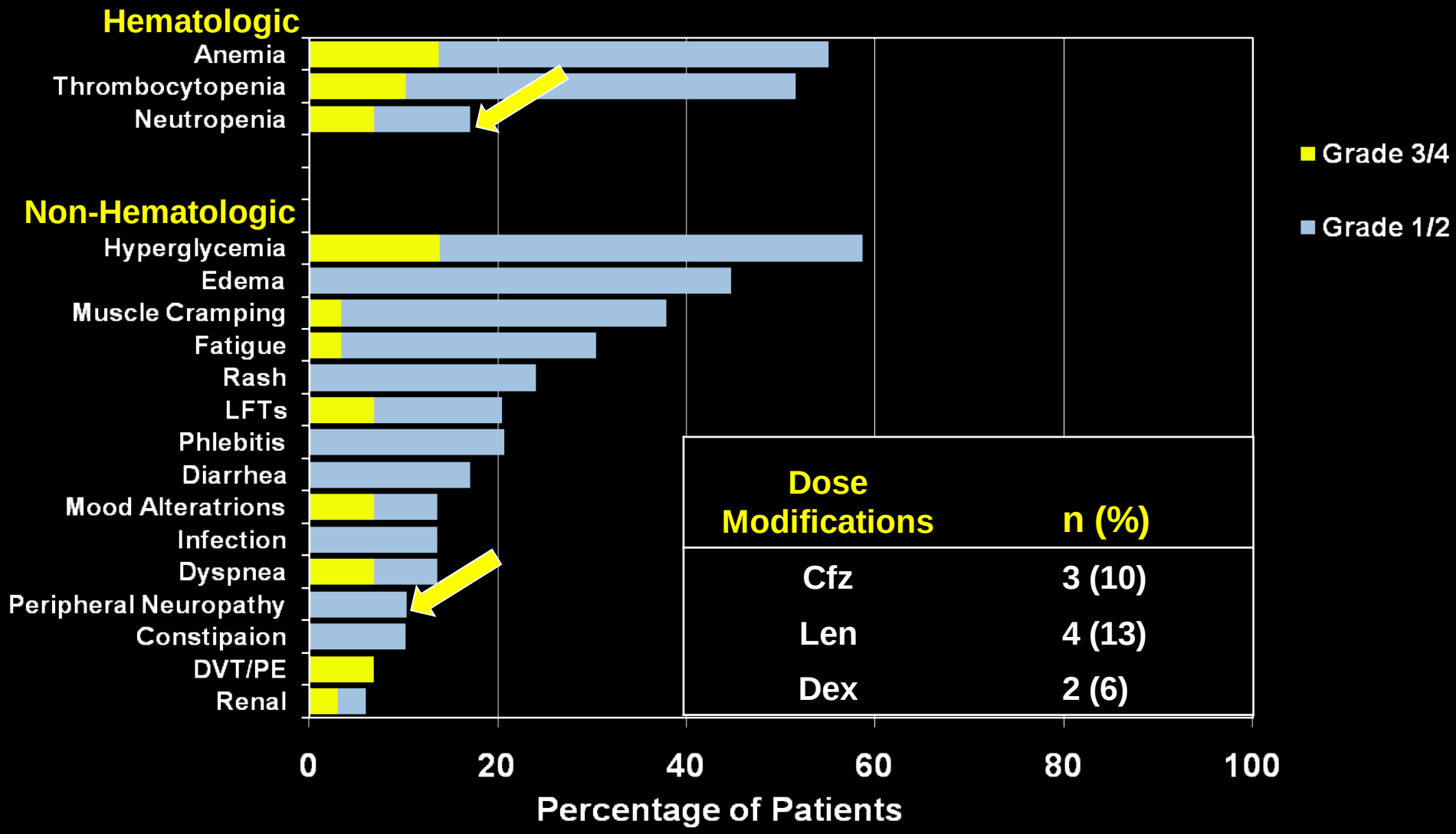
Dose level	Cfz mg/m^2	N=31*	DLT	Probability estimates
-1	15	-	-	-
1	20	4	0	7.3%
2	27	13	1	9.9%
3	36	14	2	14.3%

MTD Not Reached: DLT < 20%

Data cutoff 12 November 2010

*One patient at level 2 not evaluable for DLT and replaced

Toxicities



Dose Modifications	n (%)
Cfz	3 (10)
Len	4 (13)
Dex	2 (6)

- No neutropenic fevers
- No significant decline of ANC or platelets in consecutive cycles
- No treatment-related mortality

Treatment Duration

Median treatment duration, cycles (range)	6 (1-13)
Completed 4 cycles, n (%)	22 (71)
Completed 8 cycles, n (%)	12 (39)
Remain on treatment , n (%)	29 (93)
Discontinued/completed treatment, n (%)	
Proceeded to ASCT, n (%)	1 (3)
Pt choice (prior to completion)	1 (3)
Progressive disease, n (%)	0
Toxicities, n (%)	1 (3)

Data cutoff 12 November 2010

Best Response to Date

Response, %	(N=27*)
sCR/CR/nCR	**55**
sCR	22
CR/nCR	33
≥VGPR	**70**
≥PR	**96**

*As of data cutoff date: 12 November 2010,
4 patients not evaluable for response
(2 did not complete 1 cycle, 2 response not yet confirmed)

Responses by Cycle

Response, %	2 cycles (n=25)	4 cycles (n=22)	8 cycles (n=12)
sCR/CR/nCR	24	36	67
≥ VGPR	40	59	83
≥ PR	96	100	100

Stem Cell Harvest and Transplantation

- **Successful stem cell harvest in 14/14 patients**
  - Harvest after median 4 cycles (range 4-6)
  - Median days of harvest 3 (range 1-7)
  - Median 6.15 x 10^6 CD34+ cells/kg (range 4.1-8.5)
- **One patient completed single stem cell transplant with no unexpected toxicities**

Time to Event

- **At a median follow-up of 6 months**
  - 100% of patients are free of progression
  - 100% alive
- **After 8 cycles, patients continue CRd maintenance**
  - Most with no dose modification

Conclusions

- **The CRd regimen is highly active, demonstrating rapid and deep responses in newly diagnosed MM**
  - At completion of 4 cycles: ≥ PR 100%, ≥ VGPR 59%, CR/nCR 36%
  - At completion of 8 cycles: ≥ PR 100%, ≥ VGPR 83%, CR/nCR 67%
  - At 6 months median follow-up, all patients are alive and progression free
- **Response rates compare favorably to the current best regimens in newly diagnosed MM**
- **The CRd regimen is well tolerated allowing for extended treatment**
  - Dose modifications rarely required
  - No emergent neuropathy or myelosuppression observed

Future Directions

- Completion of Phase I and initiation of Phase II
- Present study provides additional support for recently initiated Phase III ASPIRE trial of CRd vs. Rd in relapsed MM
- Evaluation of prognostic markers and predictors of response by proteomics and GEP
- Investigation of other Cfz combination regimens ongoing
- Additional studies of CRd in newly diagnosed MM are warranted

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