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Results From the Phase II Dose Expansion of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) in Patients with Newly Diagnosed Multiple Myeloma

J. Mikhael, C. Reeder, E. Libby, L. Costa, A. Mayo, L. Bergsagel, F. Buadi, N. Pirooz, J. Lubben, AC. Dueck, AK. Stewart

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

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Rationale for Study Design

Carfilzomib

- proteasome inhibitor that irreversibly binds its target in upfront therapy
- Favorable toxicity profile (especially with minimal neuropathy)

Cyclophosphamide

- Success of addition to bortezomib in CyBorD regimen
- Well tolerated orally

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Rationale contd.

Thalidomide

- Evidence for adding IMiD to proteasome inhibitor pre-transplant
- Worldwide access for use in front line
- Minimal stem cell toxicity
- Minimal neuropathy at lower dose for only 4 cycles

Dexamethasone

- Standard of care given weekly

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Overall Combination - Rationale

- **Adding carfilzomib to international standard of CTD (cyclo-thal-dex)**
- **Optimize a 4 drug combination without overlapping toxicities**
- **Rapid and deep response after 4 cycles followed by stem cell transplant**
- **Combination does not utilize bortezomib and lenalidomide initially**
  - **such highly effective drugs can be added if required in consolidation, maintenance or at relapse**

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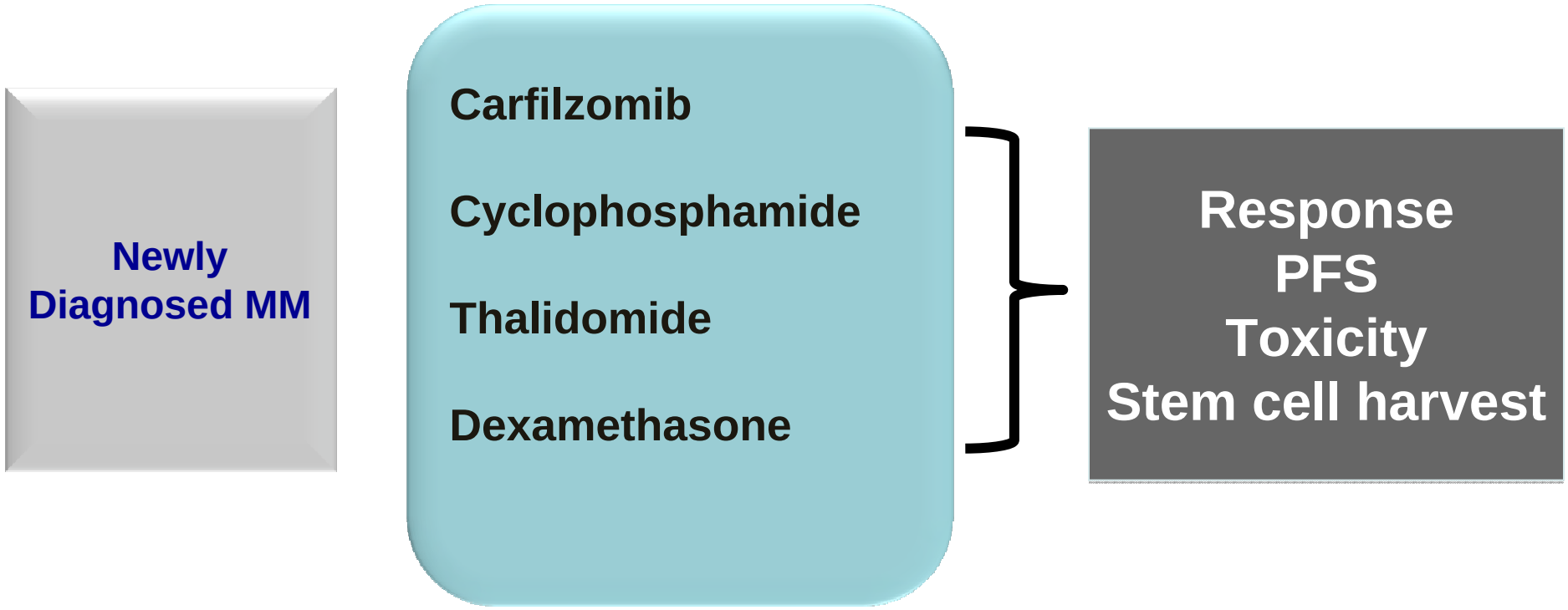
Newly Diagnosed: CYCLONE Phase I/II



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Study Goals

Primary Goals

- **Phase I: Establish the MTD of carfilzomib given in combination with CTD**
- **Phase II: Evaluate the response rate (CR, VGPR) to CYCLONE**

Secondary Goals

- **Determine overall response rate (≥PR)**
- **Duration of PFS and OS**
- **Evaluate toxicity**
- **Assess ability to successfully collect stem cells**

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Treatment Plan

Agent	*Dose Level*	*Route*	*Day*	*Rx*
Carfilzomib	**See Phase I and II dosing (15-45 mg/m^2)**	**IV**	**1,2,8,9,15,16**	**Every 28 days**
Thalidomide	**100mg**	**PO**	**1-28**	**Every 28 days**
Cyclophosphamide	**300mg/m^2**	**PO**	**1,8,15**	**Every 28 days**
Dexamethasone	**40mg**	**PO**	**1,8,15,22**	**Every 28 days**

All patients given herpes zoster prophylasis and ASA daily

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Carfilzomib Dosing

Dose Level	Cycle 1	Cycle 1 Day 8 and beyond
-1*	15 mg/m^2	20 mg/m^2
0	20 mg/m^2	27 mg/m^2
1**	20 mg/m^2	36 mg/m^2
2	20 mg/m^2	45 mg/m^2

* STARTING Dose Original Phase I

** Dose EXPANSION cohort

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Accrual Order

- **Phase I:**
  - **3 pts at 15/20 – no DLT**
  - **3 pts at 20/27 - no DLT**
- **Original Phase II:**
  - **22 pts at 20/27**
- **Dose increase expansion**
  - **3 pts at 20/36 – no DLT**
  - **7 pts at 20/45 – 3 DLTs**
  - **2 pts at 20/36 – accruing**

38 Total included in this report

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Baseline Characteristics n=38

Median Age - 62 (27-74)

Gender – 53% female

ECOG PS

- **0 - 63%**
- **1 - 29%**
- **2 – 8%**

ISS Stage

- **I – 44%**
- **II – 38%**
- **III – 19%**

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Results

38 patients in this analysis

- **Median follow up 11.6 months (0.9-29.3)**
- **37/38 patients still alive**
  - **One died during cycle 3 of pneumonia**
- **35/38 have not progressed**

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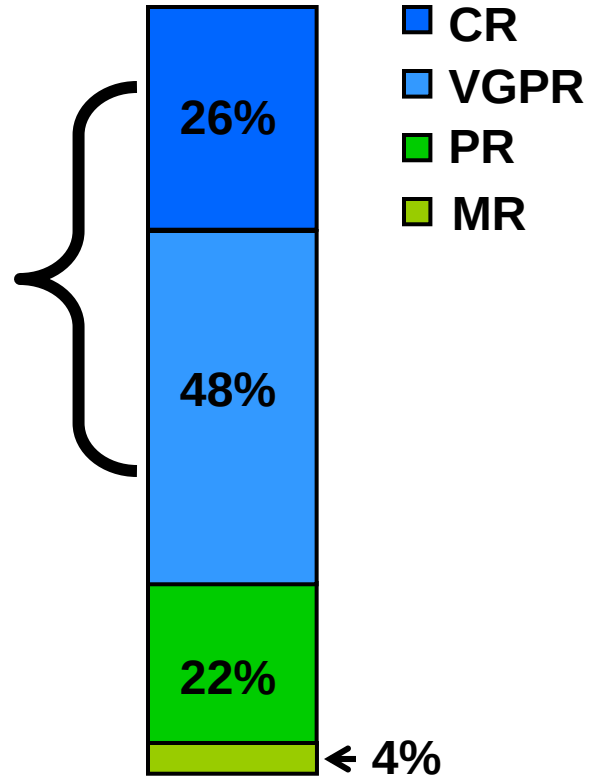
Results Levels 0 and 1 – Response n=27

- **Overall Response 96%**

CR	7
VGPR	13
PR	6
MR	1

≥ VGPR 74%



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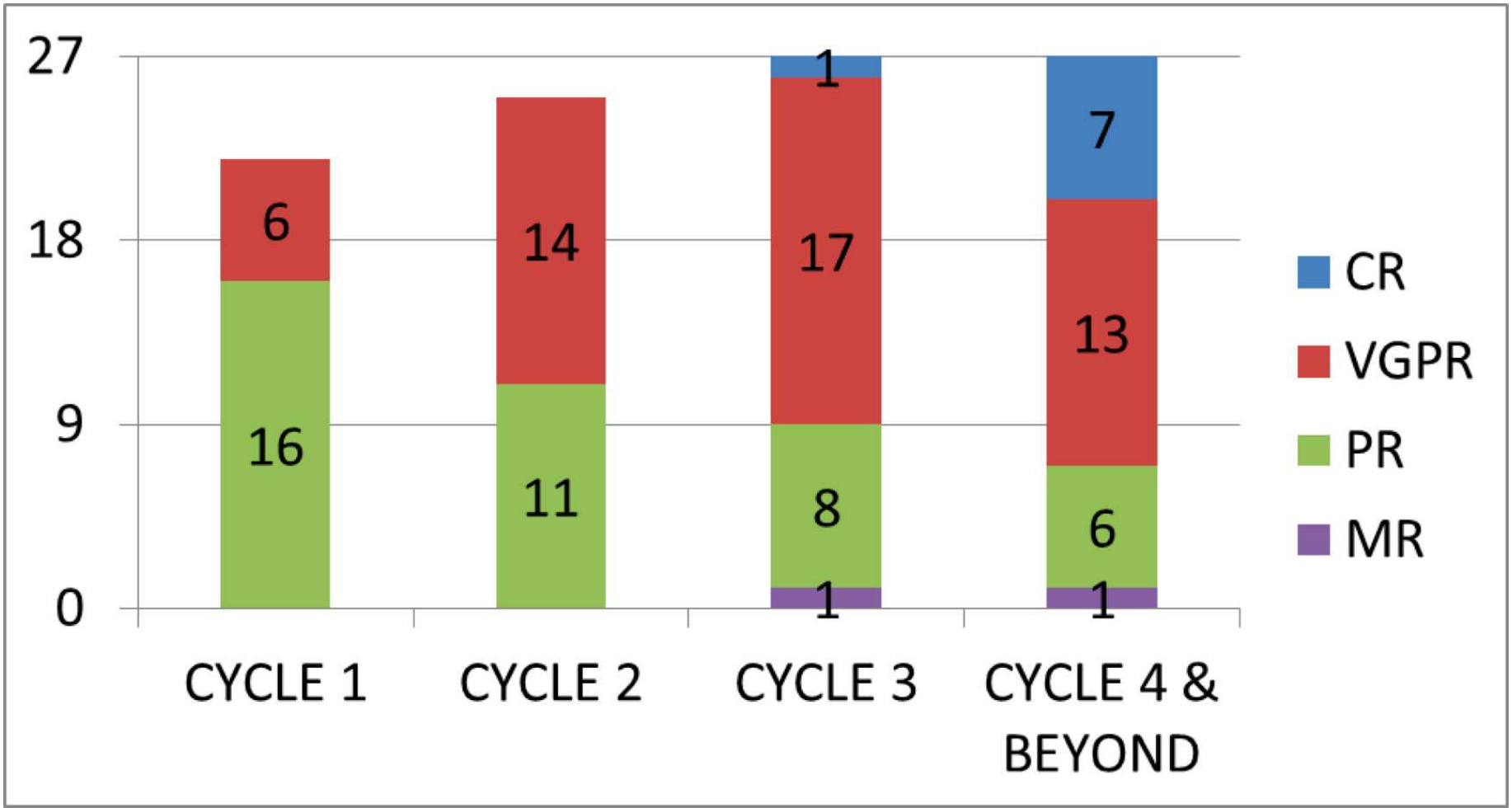
Response by Cycle

ORR **81%** **93%** **96%** **96%**



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Adverse Events (n=38) – possibly related

Overall

Grade 3 events in 16 (42%) of patients

Grade 4 events in 6 (16%) of patients

Non Hematological

Grade 3 events occurred in 12 (32%) patients

Events that occurred in more than once:

- **Arrhythmia (4)**
- **Increased LFTs (2)**
- **Fatigue (2)**
- **Muscle weakness (2)**

Grade 4 events in 3 (8%) patients

- **Thrombosis (2)**

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Adverse Events – possibly related contd.

Hematological

- **Grade 3 events occurred in 7 pts (18%):**

  Events that occurred in more than once:
  - **Lymphopenia (2)**
  - **Neutropenia (1)**

- **Grade 4 events occurred in 5 pts (13%):**

  Events that occurred in more than once:
  - **Neutropenia (5)**
  - **Lymphopenia (1)**

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Adverse Events - Notable

- **Sensory Peripheral Neuropathy**
  - **9 cases of grade 1, no ≥ grade 2**
- **Tumor Lysis Syndrome**
  - **None grade 3 or higher**
- **Most common low grade AEs were fatigue, constipation and lethargy**
- **Most common heme AE was grade 1 thrombocytopenia**

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Dose Modification

By Cycle (n=133)

Dose reduction for at least one drug 21 (16%)

- **Carfilzomib** 8 (5%)
- **Thalidomide** 8 (5%)
- **Dexamethasone** 7 (4%)
- **Cyclophosphamide** 4 (3%)

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Dose Limiting Toxicities

3/7 pts experienced DLT in 20/45 mg/m2 group (all Grade 3 Non Hematological)

- **Pt 1:**
  - **Grade 3 infusion reaction (probably)**
- **Pt 2:**
  - **Grade 4 heart failure (possibly related)**
  - **Grade 3 dyspnea (possibly)**
  - **Grade 3 afib (possibly)**
  - **Grade 3 fatigue (possibly)**
- **Pt 3:**
  - **Grade 3 ALT increase (probably)**

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Stem Cell Mobilization/Collection

- **All attempted collections successful in Phase I and Phase II**
  - **3 patients in Phase I**
  - **18 patients in Phase II (3 not attempted)**

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Future plans

- **Complete MTD cohort at 20/36 mg/m^2 with at least another 20 patients**

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Conclusions

1. CYCLONE (carfilzomib, cyclophosphamide, thalidomide and dexamethasone) is highly effective with ORR 96% and ≥ VGPR 74% in only 4 cycles
2. CYCLONE is well tolerated, with manageable myelosuppression and no > Grade 1 neuropathy
3. Patients can successfully collect stem cells
4. This upfront strategy allows the use of lenalidomide and bortezomib combinations subsequently
5. MTD has been reached at carfilzomib 20/36 mg/m^2

Acknowledgements

Sponsor

ONYX PHARMACEUTICALS

Consultants at Mayo Clinic Arizona:

A Keith Stewart – co chair

Craig Reeder – co chair

Rafael Fonseca

Leif Bergsagel

Other Site Investigators:

Francis Buadi – Mayo Rochester

Edward Libby – University of New Mexico/University of Washington

Luciano Costa – Medical University of South Carolina

Statistician

Amylou Dueck

Trial Coordinators

Nick Pirooz, JR Singh, Jade Lubben, Cassandra Wolf

Lisa Stewart – protocol specialist