# Phase 1 MMRC Trial of Selinexor, Carfilzomib (CFZ), and Dexamethasone (DEX) in Relapsed and Relapsed/Refractory Multiple Myeloma

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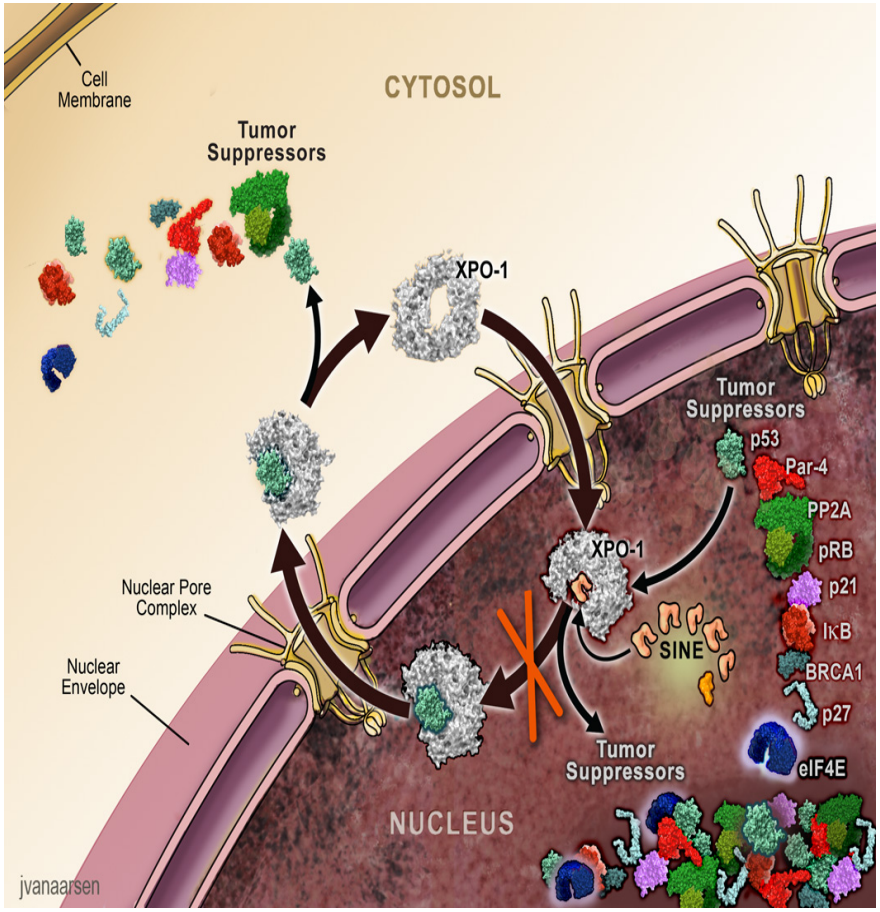
MM RF SM MULTIPLE MYELOMA Research Foundation

# Selinexor Mechanism of Action



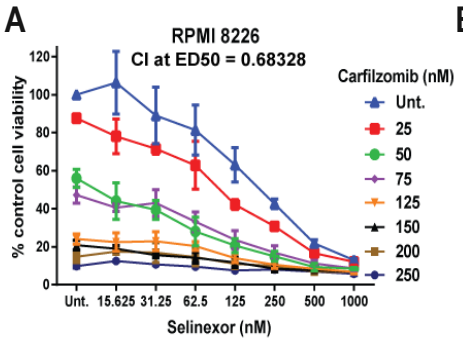

- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs) and eIF4E-bound oncoprotein mRNAs (c-myc, cyclins)
- SINE compounds inhibit XPO1 → nuclear reactivation of TSPs and retention of oncoprotein mRNAs → reduced c-myc and cyclin D1 levels and induction of apoptosis selectively in tumor cells
- Selinexor is a novel oral SINE compound currently being evaluated in solid and hematological cancers including multiple myeloma (MM)
- MM is a rationale indication for selinexor
  - XPO1 is overexpressed in MM and other hematological malignancies and its levels often correlate with poor prognosis
  - Selinexor reactivates multiple TSPs relevant to MM including p53 and FOXO and overcomes MDM2-mediated p53 degradation
  - Selinexor increases IκB, which inhibits the overactive NF-κB commonly found in MM
  - By trapping mRNAs bound to eIF4E, selinexor reduces expression of c-myc, cyclin D, MDM2 and survivin – frequently overexpressed in MM

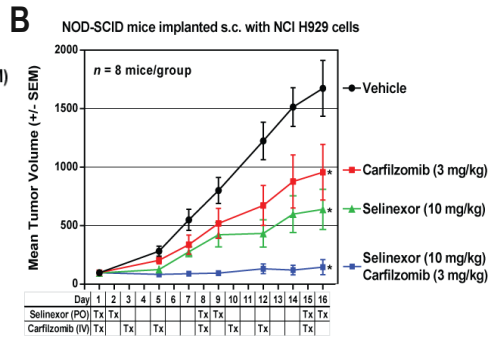
# Carfilzomib Background

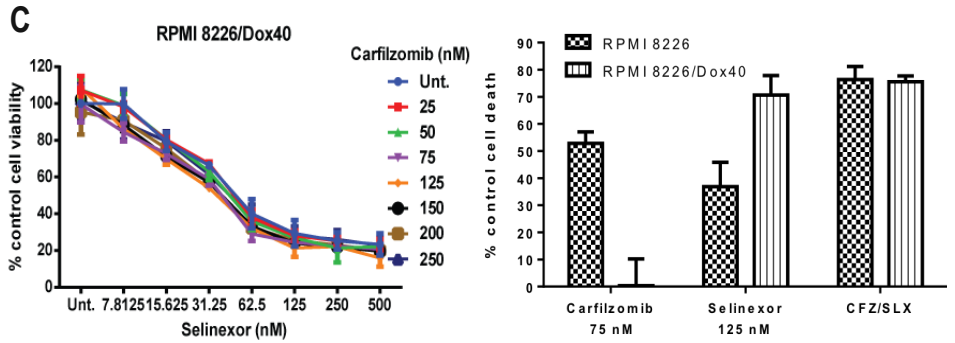
- Carfilzomib is a tetrapeptide ketoepoxide-based proteasome inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib. In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib.

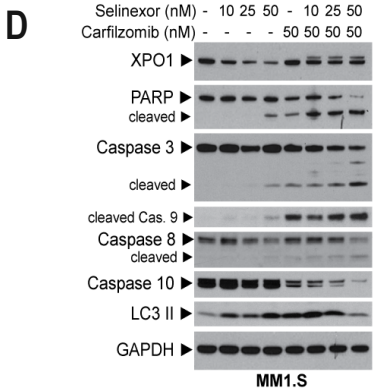
- Carfilzomib received approval from the Food and Drug Administration (FDA) in July 2012 for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (IMiD) and have demonstrated disease progression on or within 60 days of completion of the last therapy.

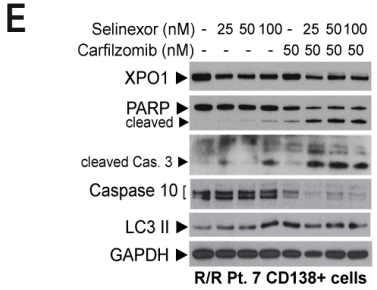
# Synergistic Activity in Pre-Clinical Models

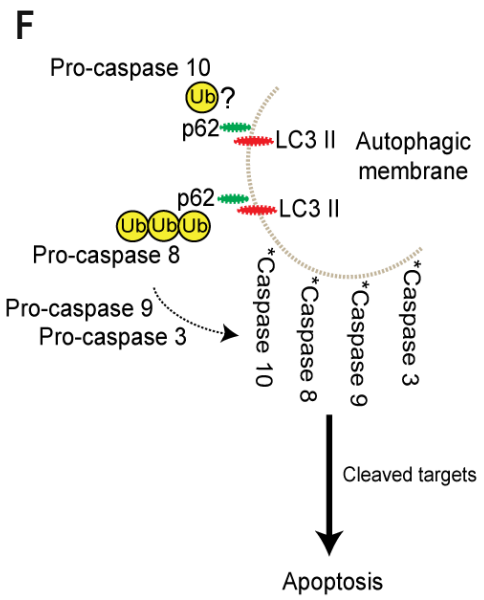



**Synergistic myeloma cell death after treatment with selinexor – carfilzomib combination:** **(A)** Dose responses of HMCL treated with selinexor and carfilzomib for 72 hours determined by MTT assay. Combination index (CI) values at ED50 are indicated; values less than 1 indicate synergy. **(B)** Effects of single agent and combination treatment in tumor-bearing NOD-SCID mice implanted with NCI H929 cells subcutaneously (s.c). Treatment schedule is depicted below. (*p<0.0001) **Activity of selinexor–carfilzomib combination in carfilzomib-refractory cells: (C)** Two depictions of the same data: as in (A), combination dose responses in carfilzomib-resistant Dox40 cells. Selinexor is active in these cells which are cross-resistant to both bortezomib and carfilzomib. **Increased cell death by engagement of both apoptosis and autophagy: (D)** Western blot analysis of MM1.S cells treated as indicated for 24 hours detecting synergistic induction of markers of both apoptosis and autophagy. **(E)** Western blot analysis of PC from a R/R MM patient (pt. was treated previously with BORT/Dex and LEN/Dex, transplant, then LEN maintenance; progressed; treated with and progressed on MLN, progressed on PdC Jan. 2014) treated as indicated for 24 hours. **(F)** Possible mechanism of caspase 10 involvement in the apoptotic machinery.

# Selinexor + Carfilzomib + Dexamethasone Combination Phase I Study Design

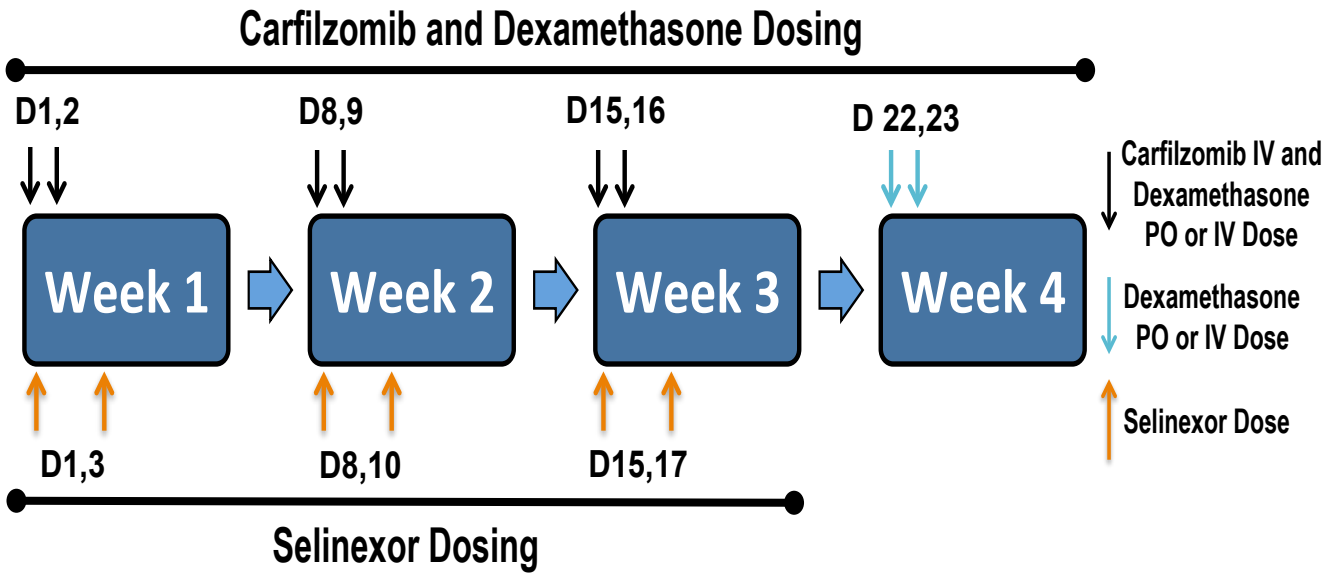
- **Selinexor + Carfilzomib + Dexamethasone Combination**
  - Open label, first in human evaluation of the combination of selinexor + carfilzomib + dexamethasone: dose escalation in patients with relapsed or relapsed/refractory advanced MM
  - Modified "3+3" design, 28 day cycle
  - Starting dose of selinexor 30 mg/m$^2$ (~50 mg flat) twice weekly for three weeks (6 doses), starting dose of carfilzomib 20/27 mg/m$^2$ twice weekly for three weeks (6 doses), 20 mg of dexamethasone given twice weekly for four weeks (8 doses)

- **Primary Objective**
  - Determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of the combination of selinexor, carfilzomib, and dexamethasone in patients with relapsed/refractory MM

- **Key Eligibility Criteria**
  - Relapsed +/– Refractory MM with progressive disease at study entry with ≥2 prior therapies including a proteasome inhibitor and an immunomodulatory drug (IMiD)
  - MM refractory to carfilzomib is allowed in the escalation cohorts and is required in expansion
  - Measurable MM disease by IMWG Criteria
  - Absolute neutrophil count (ANC) ≥ 1.0 × 10$^9$/L; Hemoglobin ≥ 8 g/dL; Platelet count ≥50,000 mm$^3$
  - Adequate renal function within 14 days prior to C1D1: estimated creatinine clearance of ≥ 30 mL/min

# Selinexor + Carfilzomib + Dexamethasone Combination Dosing Scheme

A




**(A)** Dosing scheme for selinexor, carfilzomib, and dexamethasone combination

B

| Dose Level | Carfilzomib ($mg/m^2$) | Selinexor ($mg/m^2$) | Dex (mg) | Patients Enrolled | Patients with DLTs |
|---|---|---|---|---|---|
| 1 | 20/27 | 30 | 20/10 | 5 | 0 |
| 2a | 20/36 | 30 | 20/10 | 3 | 0 |
| 2b | 20/27 | 60* | 20/10 | 1 | 0 |
| 3 | 20/36 | 60* | 20/10 | | |
| 4 | 20/45 | 60* | 20/10 | | |
| 5 | 20/56 | 60* | 20/10 | | |

*Patients enrolled in these cohorts will receive a 60 mg flat dose of selinexor

**(B)** Dose levels for selinexor, carfilzomib and dexamethasone and number of patients enrolled per cohort as of 30-September-2015

# Selinexor + Carfilzomib + Dexamethasone Combination Patient Characteristics

| Patient Characteristic | N |
|---|---|
| Patients Enrolled[1] | 9 |
| Median Age (Range) | 67 (55 – 73) |
| Patients ≥65 years (%) | 56% |
| ECOG Performance Status, 0-1 (%) | 100% |
| Median Years from Diagnosis (Range) | 3.6 (1.6 – 8.6) |
| Median Prior Regimens (Range) | 4 (2 – 5) |
| Refractory to Carfilzomib Combinations on Last Prior Therapy | 7 |
| Refractory to Carfilzomib, Pom, and Dex | 5 |
| Cytogenetic risk by FISH, High : Standard (%) | 44% : 56% |
| Serum $\beta_2$-microglobulin ≥3.5 mg/L (%) | 44% |

| Patient Characteristic | N |
|---|---|
| Patients evaluable for DLT[2] | 7 |
| Patients with a DLT | 0 |
| Median Treatment Selinexor+Carfilzomib Cycles (Range) | 4 (0.5–13) |
| Patients Discontinued, N (%) | 6 (67%) |
| Discontinued due to Disease progression | 6 |
| Discontinued due to Adverse Event | 0 |
| Discontinued due to Patient/Investigator Preference | 0 |

Data cut-off as of 30-September-2015. [1]All patients were refractory carfilzomib. [2]Two patients required replacement for DLT evaluation (1 patient had dex reduced in cycle 1 not due to DLT; 1 patient did not receive all scheduled cycle 1 doses due to progressive disease), both are evaluable for efficacy

# Selinexor + Carfilzomib + Dexamethasone Combination Patient Prior Therapies

| Selinexor + Carfilzomib + Dexamethasone Combination Patient Prior Therapies | | | | |
|---|---|---|---|---|
| Patient ID | Age | Sex | # Prior Tx | Prior Therapies |
| 1 | 59 | F | 4 | Len-Dex-Transplant, Bort-Dex, Len-Dex, Carfil-Panob |
| 2 | 73 | F | 2 | Bort-Len-Dex-Tansplant+Len Maint., Pom-Carfil-Dex |
| 3 | 64 | F | 5 | Vinc-Dox-Dex, Bort-Dex, Thal-Dex-Transplant, Len-Dex, Pom-Carfil-Dex |
| 5 | 70 | M | 5 | Ixaz-Len-Dex-Transplant, Carfil-Cyclo-Dex, Carfil-Dox-Cyclo-Etop-Dex, Pom-Carfil-Dex, Carfil-Dox-Cyclo-Etop-Dex-Radiation |
| 6 | 63 | M | 5 | Melp-Bort-Pred, Cyclo-Bort-Dex, Len-Dex, Carfil, Pom-Dex |
| 7 | 67 | M | 2 | Cyclo-Bort-Pom-Dex-Transplant, Pom-Carfil-Dex |
| 8 | 68 | F | 5 | Len-Bort-Dex-Len Maint., Len-Bort-Dex-Transplant+Bort Maint., Carfil-Bort-Dex-Radiation, Carfil-Dex, ACY-1215-Pom-Dex |
| 9 | 55 | M | 2 | Len-Bort-Dex-Bort-Carfil-Dex-HdC-ASCR-Transplant, Pom-Carfil-Dex |
| 10 | 68 | F | 3 | Carfil-Len-Dex, VDT-PACE-Transplant-Cyclo-Bort-Dex+Bort-Dex Maint., Investigational-Carfil-Pom-Dex |

Patient prior therapies listed by patient and treatment regimen. All patients have received prior carfilzomib – based treatment (and their disease became refractory to it). 7 of 9 patients were refractory to carfilzomib combinations on their last line of therapy at the time of enrollment.

# Adverse Events (AE's)

| All Adverse Events N=9 | | |
|---|---|---|
| **AE Term** | **All Grades** | **Grade ≥3** |
| **Hematologic** | | |
| Anemia | 5 (56%) | 2 (22%) |
| Lymphopenia | 3 (33%) | 2 (22%) |
| Thrombocytopenia | 6 (67%) | 6 (67%) |
| Neutropenia | 4 (44%) | 4 (44%) |
| **Non Hematologic** | | |
| Fatigue | 7 (78%) | 2 (22%) |
| Infection | 1 (11%) | 1 (11%) |
| Edema | 2 (22%) | 1 (11%) |
| Muscular Disorders | 3 (33%) | 0 (0%) |
| Peripheral Neuropathy | 2 (22%) | 0 (0%) |
| Dyspnea | 4 (44%) | 1 (11%) |
| Headache | 2 (22%) | 0 (0%) |
| GI Tract Disorders | 8 (89%) | 0 (0%) |
| Eye Disorders | 5 (56%) | 0 (0%) |
| Confusion | 1 (11%) | 1 (11%) |
| Elevated Liver Enzymes | 4 (44%) | 1 (11%) |
| Elevated Pancreatic Enzymes | 2 (22%) | 0 (0%) |
| Hyponatremia | 1 (11%) | 1 (11%) |
| Psychosis | 1 (11%) | 1 (11%) |

All grade adverse events (AEs) recorded that were related to at least one of the treatment drugs for at least 20% of the patient population and all Grade 3 and Grade 4 AE's as of 30-September-2015 are shown for the nine patients enrolled. The most common AEs reported are fatigue, gastrointestinal tract (GI) disorders, and cytopenias, as anticipated in this patient population. Cytopenias were generally observed beyond cycle 1, however only a minority of patients (2/9) required dose modifications due to cytopenias. No unexpected AEs were observed to date. AEs were reversible and managed with supportive therapy and/or dose adjustments.

# Clinical Activity

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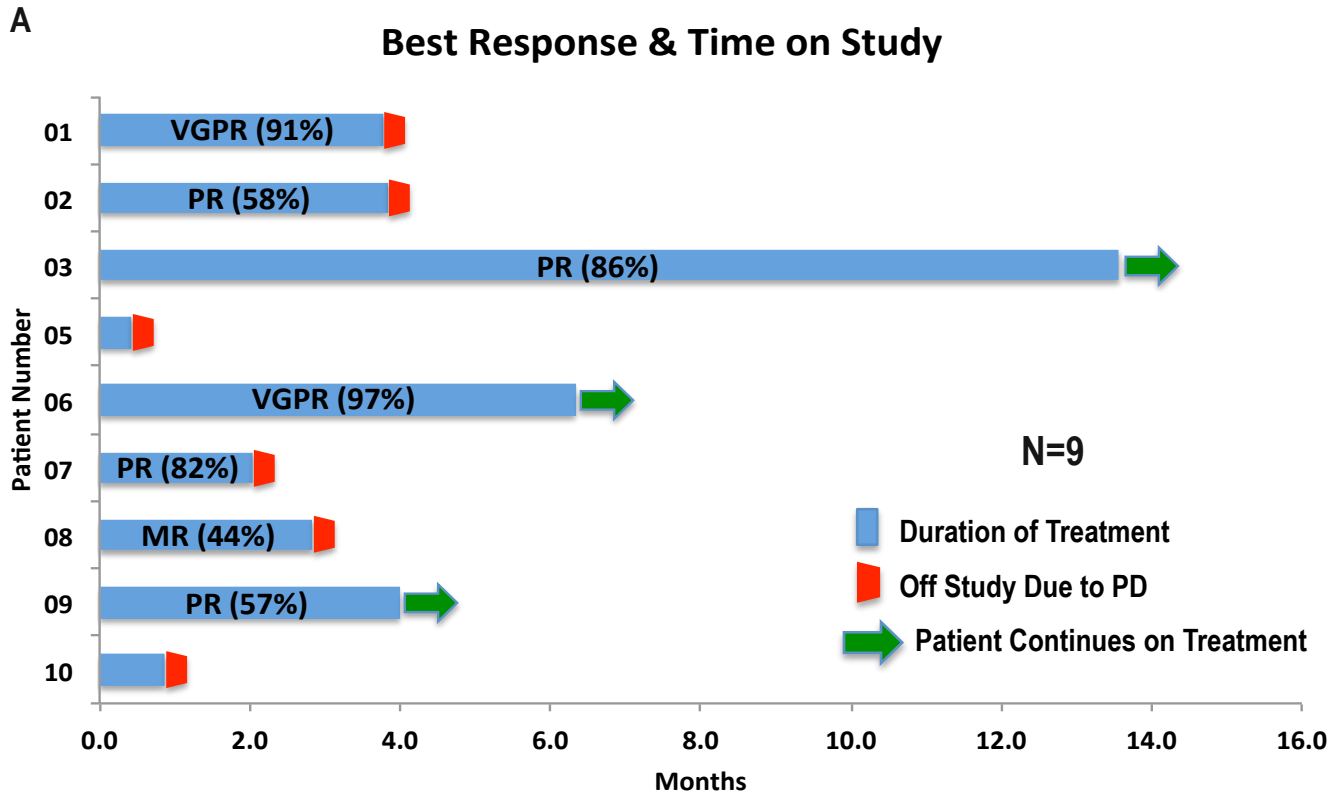


(**A**) Best response and time on study (in months) for each patient. Median time on study was 4 months with a range of 0.5 – 13+ months.

**B** Best Responses in Evaluable (N=9) Patients (as of 30-Sept-2015)

| | N | CBR | ORR | VGPR | PR | MR | PD |
|---|---|---|---|---|---|---|---|
| Selinexor + Carfilzomib + Dexamethasone Combination | 9 | 7 (78%) | 6 (67%) | 2 (22%) | 4 (44%) | 1 (11%) | 2 (22%) |

CBR=Clinical Benefit Response (VGPR+PR+MR), ORR=Overall Response Rate (VGPR+PR), VGPR=Very Good Partial Response, PR=Partial Response, MR=Minor Response, PD=Progressive Disease. Responses as of 30-Sep-2015 based on interim unaudited data. Responses were adjudicated according to the *International Myeloma Working Group* criteria.

(**B**) Best responses as of 30-Sep-2015 (IMWG criteria). The ORR (overall response rate) is 67% in these patients, all of whom had carfilzomib/dexamethasone refractory MM.

# Summary and Conclusions

Although still early, the combination of selinexor, carfilzomib, and dexamethasone, demonstrates encouraging activity in these heavily pretreated patients :

- 67% (6 out of 9) reached PR or better as their best response
- 71% (5 out of 7) patients refractory to carfilzomib *in their last prior therapy* responded to this combination of selinexor-carfilzomib-dexamethasone
- Most patients achieved clinically meaningful duration of response (up to 12+ months)

- There were no unexpected toxicities
- Responses in patients with MM refractory to highly active carfilzomib combinations in the last line of therapy (e.g., Pom-Carfil-Dex) suggest that this regimen can overcome carfilzomib resistance
- The study continues to enroll to determine MTD and better define tolerability and efficacy at MTD
- Based on these results, further evaluation of this combination in randomized setting is warranted

## Acknowledgements


- We would like to thank all of the patients who have participated in this study, the investigators, nursing staff, and research support staff in participating institutions, the Multiple Myeloma Research Consortium, under whom this multi-site trial is conducted, Onyx Pharmaceuticals, Inc, an Amgen subsidiary, and Karyopharm Therapeutics for supporting the study


## References


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