# Selinexor Plus Pomalidomide and Low Dose Dexamethasone (SPd) in Patients with Relapsed or Refractory Multiple Myeloma

Abstract 1993

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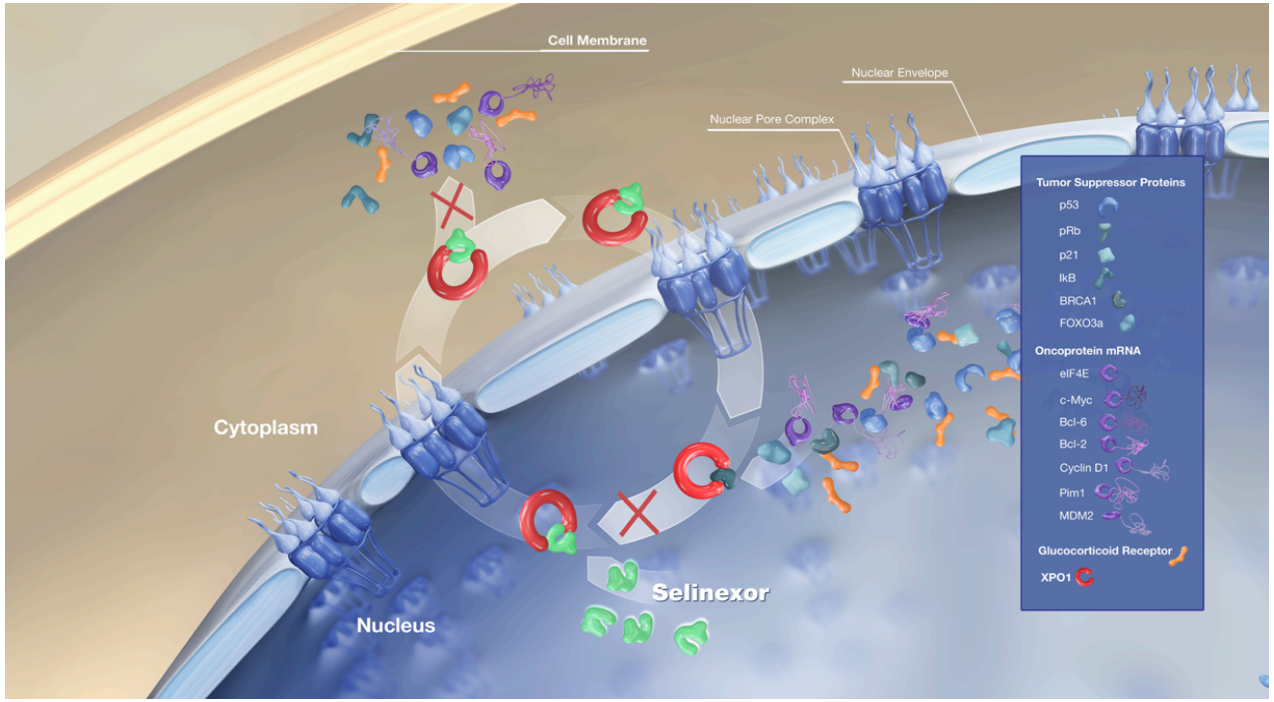
# Selinexor Mechanism of Action




**Exportin 1 (XPO1)** is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, MDM2, cyclins)

**XPO1** is overexpressed in MM:

- High XPO1 levels enable cancer cells to escape TSP mediated cell cycle arrest and induction of apoptosis
- XPO1 levels correlate with poor prognosis and drug resistance

**Selinexor** is an oral selective XPO1 inhibitor; preclinical data supports that selinexor:

- Reactivates multiple TSPs relevant to MM, inhibits NF-kB signaling and reduces c-Myc levels
- Reactivates GR signaling in combination with dexamethasone (dex)
- Selinexor demonstrates synergistic activity in combination with pomalidomide and lenalidomide in vitro and in vivo

# STOMP Study Design

**S**elinexor and backbone **T**reatments **O**f multiple **M**yeloma **P**atients (**STOMP**) is an open-label, dose escalation (Phase 1) and expansion (Phase 2) study in patients evaluating selinexor in combination with other anti-myeloma therapies in patients with newly diagnosed and relapsed/refractory multiple myeloma (MM)

**Objectives:**

- Primary Endpoint: maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
- Secondary Endpoint: overall response rate (ORR) and duration of response (DOR) for each arm independently

**Dose Limiting Toxicity (DLT) Definition: Evaluable in Dose Escalation Cycle 1 Only**

- >1 missed dose (out of 4 doses – once-weekly selinexor dose schedules), or >2 missed doses (out of 6 doses – twice-weekly dose schedules) of selinexor during a cycle due to study-drug related toxicity
- Discontinuation of a patient before completing Cycle 1, due to study-drug related toxicity
- Grade 3 nausea, vomiting, dehydration, diarrhea, or fatigue lasting >3 days despite optimal supportive medications
- Grade 4 neutropenia lasting >7 days or Grade ≥3 thrombocytopenia with clinically significant bleeding, petechiae, or purpura

# STOMP Study Design (Cont.)

- **Patient Population SPd:** Patients with MM who received ≥2 prior therapies, including lenalidomide (Len) and a proteasome inhibitor (separate or same regimens) with progression during or within 60 days of last therapy; prior pomalidomide (Pom) allowed
- **SPd Dose Escalation Scheme:** A standard 3 + 3 design will be used for all dose escalations and include 2 Cohorts to evaluate Once-Weekly (QW) vs. Twice-Weekly (BIW) selinexor dosing. Pom dosing will be evaluated at 2, 3, or 4 mg QD.

| Drug | SVd ARM | SPd ARM | SRd ARM | SDd ARM | SKd Arm | SRd – Newly Diagnosed Patients |
|---|---|---|---|---|---|---|
| **Selinexor, Oral** | 60 – 80 mg BIW<br>80 – 100 mg QW | 60 – 80 mg BIW<br>80 – 100 mg QW | 60 – 80 mg BIW<br>80 – 100 mg QW | 60 mg BIW<br>100 mg QW | 100 mg QW | 60 – 80 mg, QW |
| **Bortezomib, SC** | 1.3 mg/m$^2$ – QW/BIW | -- | -- | -- | -- | -- |
| **Pomalidomide, PO** | -- | 3 – 4 mg, QD | -- | -- | -- | -- |
| **Lenalidomide, PO** | -- | -- | 25 mg, QD | -- | -- | 25 mg, QD |
| **Daratumumab, IV** | -- | -- | -- | 16 mg/kg, QW | -- | -- |
| **Carfilzomib, IV** | -- | -- | -- | -- | 56 – 70 mg/m$^2$, QW | -- |
| **Dexamethasone, Oral** | 20 mg BIW or 40 mg QW | 20 mg BIW or 40 mg QW | 20 mg BIW or 40 mg QW | 20 mg BIW or 40 mg QW | 20 mg BIW or 40 mg QW | 20 mg BIW or 40 mg QW |

**Data presented will focus on the SPd arm. Dexamethasone will be dosed on selinexor dosing days.**

SVd, selinexor + bortezomib + dexamethasone; SPd selinexor + pomalidomide + dexamethasone; SDd, selinexor + daratumumab + dexamethasone; SKd selinexor + carfilzomib + dexamethasone; SRd, selinexor + lenalidomide + dexamethasone; BIW, Twice-Weekly; QD, Once-Daily; QW, Once-Weekly;

# SPd Patient Characteristics

| SPd Patient Characteristics | N |
|---|---|
| **Enrolled as November 1, 2018** | **38** |
| Median Age, Years (range) | 62 (43–83) |
| Males: Females | 19 M: 19 F |
| Median Years from Diagnosis to SPd Treatment, Years (range) | 5.9 (<1 – 22.3) |
| **Median Prior Regimens (range)** | **4 (2–9)** |
| -Refractory to Lenalidomide | 35 (92%) |
| -Refractory to Lenalidomide & Pomalidomide | 11 (29%) |
| -Proteasome Inhibitor Therapy (Refractory: Exposed) | 20 (53%): 38 (100%) |
| -Carfilzomib Therapy | 11 (29%) |
| -Stem Cell transplant | 30 (79%) |
| **International Staging System (ISS) at Diagnosis** | |
| Stage I | 9 (24%) |
| Stage II | 11 (29%) |
| Stage III | 8 (21%) |
| Stage Unknown | 10 (26%) |

BIW, Twice-Weekly; QD, Once-Daily; QW, Once-Weekly.

# SPd Treament Related Adverse Events ≥ 10% Patients

| AE Term | 60/80 mg Sel BIW + 3/4 mg Pom QD | | | | 80/100 mg Sel QW + 2/3/4 mg Pom QD | | | |
|---|---|---|---|---|---|---|---|---|
| **Hematologic** | **Grade 1/2** | **Grade 3** | **Grade 4** | **Total (N=18)** | **Grade 1/2** | **Grade 3** | **Grade 4** | **Total (N=20)** |
| Neutropenia | -- | 6 (33.3%) | 3 (16.7%) | **9 (50.0%)** | 2 (10.0%) | 3 (15.0%) | 9 (45.0%) | **14 (70.0%)** |
| Thrombocytopenia | 2 (11.1%) | 3 (16.7%) | 5 (27.8%) | **10 (55.6%)** | 7 (35.0%) | 4 (20.0%) | 1 (5.0%) | **12 (60.0%)** |
| Anemia | 3 (16.7%) | 7 (38.9%) | -- | **10 (55.6%)** | 5 (25.0%) | 4 (20.0%) | -- | **9 (45.0%)** |
| Leukopenia | -- | 1 (5.6%) | 1 (5.6%) | **2 (11.1%)** | 5 (25.0%) | 3 (15.0%) | 2 (10.0%) | **10 (50.0%)** |
| Lymphopenia | -- | 1 (5.6%) | -- | **1 (5.6%)** | 1 (5.0%) | 4 (20.0%) | 1 (5.0%) | **6 (30.0%)** |
| Febrile Neutropenia | -- | 2 (11.1%) | -- | **3 (16.7%)*** | -- | 3 (15.0%) | -- | **3 (15.0%)** |
| **Gastrointestinal** | | | | | | | | |
| Nausea | 12 (66.7%) | -- | -- | **12 (66.7%)** | 8 (40.0%) | -- | -- | **8 (40.0%)** |
| Anorexia | 11 (61.1%) | -- | -- | **11 (61.1%)** | 5 (25.0%) | -- | -- | **5 (25.0%)** |
| Vomiting | 2 (11.1%) | 1 (5.6%) | -- | **3 (16.7%)** | 7 (35.0%) | -- | -- | **7 (35.0%)** |
| Diarrhea | 6 (33.3%) | -- | -- | **6 (33.3%)** | 3 (15.0%) | -- | -- | **3 (15.0%)** |
| Altered Taste | 4 (22.2%) | -- | -- | **4 (22.2%)** | 5 (25.0%) | -- | -- | **5 (25.0%)** |
| Constipation | 2 (11.1%) | -- | -- | **2 (11.1%)** | 2 (10.0%) | -- | -- | **2 (10.0%)** |
| **Constitutional** | | | | | | | | |
| Fatigue | 9 (50.0%) | 2 (11.1%) | -- | **11 (61.1%)** | 6 (30.0%) | 2 (10.0%) | -- | **8 (40.0%)** |
| Asthenia | 3 (16.7%) | 1 (5.6%) | -- | **4 (22.2%)** | 1 (5.0%) | -- | -- | **1 (5.0%)** |
| Weight Loss | 7 (38.9%) | -- | -- | **7 (38.9%)** | 6 (30.0%) | -- | -- | **6 (30.0%)** |
| Dehydration | 5 (27.8%) | -- | -- | **5 (27.8%)** | -- | -- | -- | **--** |
| Dizziness | 2 (11.1%) | -- | -- | **2 (11.1%)** | 4 (20.0%) | -- | -- | **4 (20.0%)** |
| **Other** | | | | | | | | |
| Edema | 4 (22.2%) | -- | -- | **4 (22.2%)** | 3 (15.0%) | -- | -- | **3 (15.0%)** |
| Muscle spasms | 3 (16.7%) | -- | -- | **3 (16.7%)** | 4 (20.0%) | -- | -- | **4 (20.0%)** |
| Hyponatremia | -- | 1 (5.6%) | -- | **1 (5.6%)** | 3 (15.0%) | 1 (5.0%) | 1 (5.0%) | **5 (25.0%)** |
| Insomnia | 2 (11.1%) | -- | -- | **2 (11.1%)** | 3 (15.0%) | -- | -- | **3 (15.0%)** |
| Hyperglycemia | 1 (5.6%) | 1 (5.6%) | -- | **2 (11.1%)** | 3 (15.0%) | -- | -- | **3 (15.0%)** |
| Hypokalemia | -- | 1 (5.6%) | -- | **1 (5.6%)** | 3 (15.0%) | 1 (5.0%) | -- | **4 (20.0%)** |
| Hypoalbuminemia | -- | -- | -- | **--** | 4 (20.0%) | -- | -- | **4 (20.0%)** |

- Three Grade 5 related events occurred (*febrile neutropenia, intracranial hemorrhage, pneumonia)

**Treatment Related Adverse Events as of November 1, 2018**

AE, adverse event; BIW, Twice-Weekly; Pom, pomalidomide; QD, Once-Daily; QW, Once-Weekly; RP2D, phase 2 dose; Sel, selinexor.

# SPd DLTs

| Selinexor Dose | Pomalidomide Dose | Patients Enrolled | Dose Limiting Toxicity |
|---|---|---|---|
| 60 mg BIW | 4 mg QD | 6 | Grade 3 Fatigue |
| 60 mg BIW | 3 mg QD | 6 | Grade 3 Febrile Neutropenia |
| 80 mg BIW | 4 mg QD | 6 | No DLT |
| 80 mg QW | 4 mg QD | 7 | Grade 3 Febrile Neutropenia<br>Grade 4 Neutropenia |
| 80 mg QW | 3 mg QD | 6 | Pom Dose Reduction for Grade 2 Neutropenia Grade 3 Thrombocytopenia (re-escalated and maintained at 3 mg)<br>Grade 3 Febrile Neutropenia |
| 80 mg QW | 2 mg QD | 3 | No DLT and enrollment is ongoing |
| 100 mg QW | 4 mg QD | 4 | No DLT |

- Enrollment is ongoing: once weekly selinexor (80 mg) / pom (2 mg) and once weekly selinexor (60 mg) / pom (4 mg)

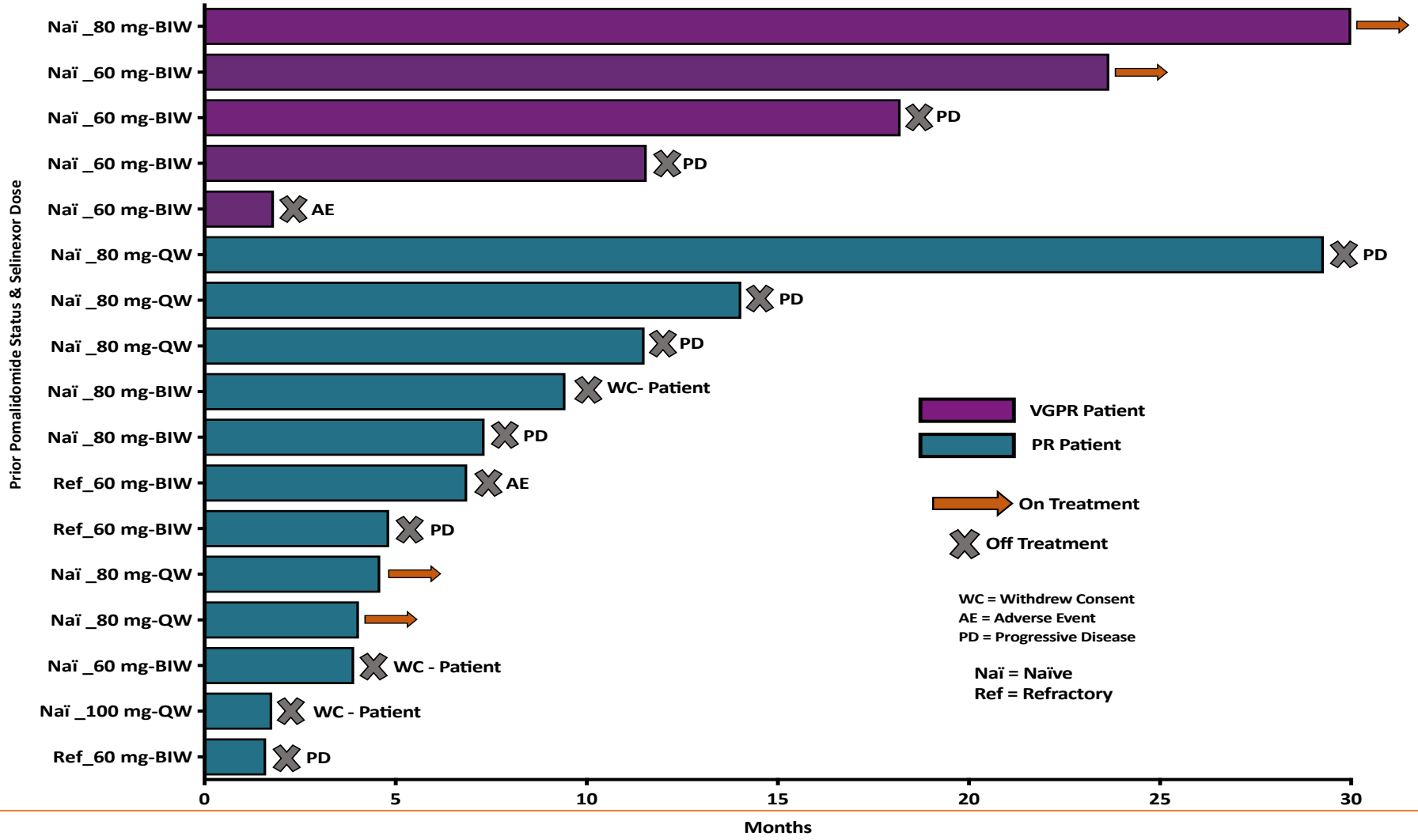
BIW, Twice-Weekly; DLT, dose limiting toxicity; QD, Once-Daily; QW, Once-Weekly.

# SPd Efficacy

| Best Responses† in Evaluable SPd Patients as of November 15, 2018 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Category** | **N*** | **ORR (%)** | **CBR (%)** | **VGPR (%)** | **PR‡ (%)** | **MR (%)** | **SD (%)** | **PD (%)** |
| **All** | 34 | **17 (50%)** | **23 (68%)** | 5 (15%) | 12 (35%) | 6 (18%) | 11 (32%) | -- |
| **Pom Naïve & Len-Refractory or Relapsed** | 26 | **14 (54%)** | **19 (73%)** | 5 (19%) | 9 (35%) | 5 (19%) | 7 (27%) | -- |
| **Pom & Len-Refractory** | 8 | **3 (38%)** | **4 (50%)** | -- | 3 (38%) | 1 (12%) | 4 (50%) | -- |

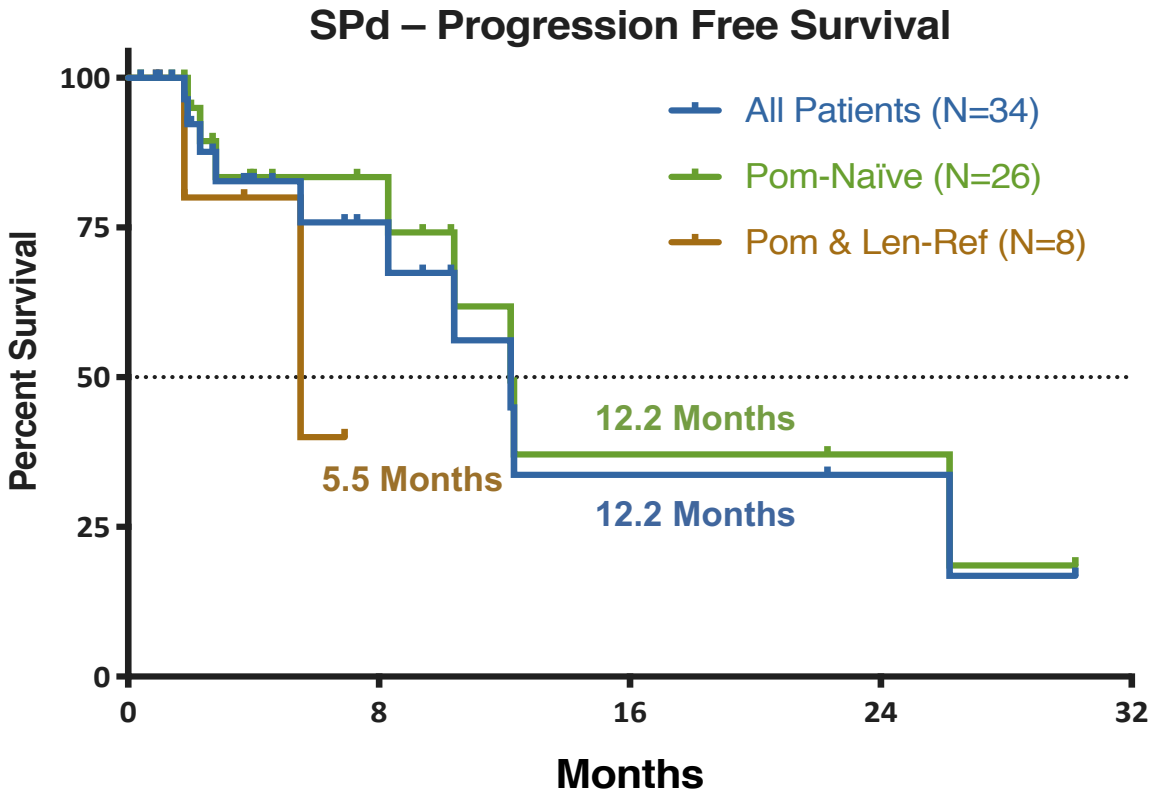
†Responses were adjudicated according to the International Myeloma Working Group criteria, *four patients not evaluable for response: one death unrelated to myeloma, one non-compliance with study procedures, two withdrawal of consent before disease follow up. ‡one unconfirmed PR. ORR=Overall Response Rate (VGPR+PR), VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response, SD=Stable Disease, PD=Progressive Disease, CBR=Clinical Benefit Rate (ORR+MR). Responses as of November 15, 2018 based on interim unaudited data.

# SPd Time on Study and Response (Responders)




**A**) Among patients with a PR or better (N=17) the median time on treatment was **9.4** months. Responses were rapid in onset with a median time to response of 1 month.

# SPd Progression Free Survival




| Patients at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Months | 0 | 1.8 | 3.7 | 4.6 | 5.5 | 6.9 | 7.3 | 9.4 | 12.2 | 22.3 | 26.2 | 30.2 |
| All Patients | 34 | 28 | 17 | 13 | 12 | 11 | 10 | 8 | 5 | 3 | 2 | 1 |
| Pom-Naï & Len-Ref | 26 | 23 | -- | 11 | -- | -- | 10 | 8 | 5 | 3 | 2 | 1 |
| Pom & Len-Ref | 8 | 5 | 3 | -- | 2 | 1 | -- | -- | -- | -- | -- | -- |

**B)** Median PFS among evaluable patients was **12.2** months. Median PFS in Pom-naïve and Len-refractory or relapsed MM was **12.2** months, and in Pom & Len-refractory MM was **5.5** months.

POM, Pomalidomide; LEN, lenalidomide.

# Summary and Conclusions

**Selinexor, once weekly, plus pomalidomide and low-dose dexamethasone (SPd) is being evaluated in an ongoing phase 1 study in patients with heavily pretreated MM**

- **The most common AEs are: anorexia, nausea, fatigue, and G3/4 neutropenia and thrombocytopenia**
- **Determination of the recommended phase 2 dose of SPd is ongoing with once-weekly selinexor and pomalidomide once-daily**

**The combination of SPd appears active and durable, and responses typically occur within 1 cycle of treatment**

- **ORR of 54% in pomalidomide-naïve patients (compared to expected ORR of ≤ 30% of pomalidomide + dex based on pomalidomide approval) and 19% of patients achieving a VGPR**
- **CBR was 68% in all patients, and 73% in pomalidomide naïve patients**
- **PFS in pomalidomide-naïve patients was 12.2 months (compared to expected PFS of ~4 months for pomalidomide + dex)**