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

Abstract 3199

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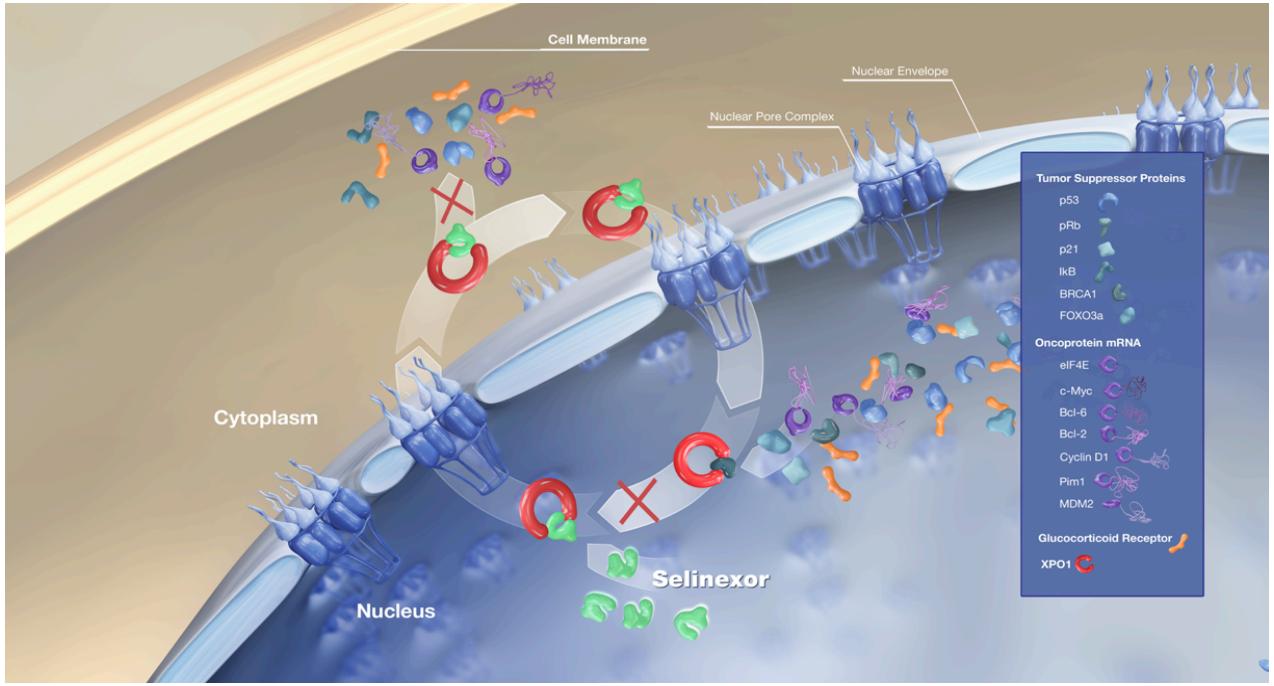
Selinexor Mechanism of Action



Exportin 1 (XPO1) is the major nuclear exporter 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 demonstrate that selinexor:

- Reactivates multiple TSPs relevant to MM, inhibits NF-κB signaling and reduces c-Myc levels
- Reactivates GR signaling in combination with dexamethasone (dex)
- Demonstrates synergistic activity in combination with pomalidomide (Pom) and lenalidomide (Len) *in vitro* and *in vivo*

STOMP Study Design

Selinexor 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 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) Was Determined 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
- G3 nausea, vomiting, dehydration, diarrhea, or fatigue lasting >3 days despite optimal supportive medications
- G4 neutropenia lasting >7 days or G≥3 thrombocytopenia with clinically significant bleeding, petechiae, purpura

STOMP Study Design (SPd)

- **Patient Population SPd:** Patients with MM who received ≥2 prior therapies, including Len and a proteasome inhibitor (separate or same regimens) with progression during or within 60 days of last therapy; prior 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 daily (QD).

STOMP Agents	SVd ARM	SPd ARM	SRd ARM	SDd ARM	SKd Arm	SRd – Newly Diagnosed Patients
Selinexor, PO	60 – 80 mg BIW 80 – 100 mg QW	60 – 80 mg BIW 60 – 100 mg QW	60 – 80 mg BIW 80 – 100 mg QW	60 mg BIW 100 mg QW	80 – 100 mg QW	60 – 80 mg, QW
Bortezomib, SC	1.3 mg/m^2 – QW/BIW	--	--	--	--	--
Pomalidomide, PO	--	2 – 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, PO	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 (dex) will be dosed on selinexor dosing days.

SPd Arm - Patient Characteristics

SPd Patient Characteristics	N
Enrolled as May 1, 2019	**45**
Median Age, Years (range)	63 (43 – 83)
Males : Females	23 (51%) : 22 (49%)
Median Years from Diagnosis to SPd Treatment, Years (range)	5 (<1 – 23)
Median Prior Regimens (range)	**4 (2–9)**
-Refractory to Lenalidomide	41 (91%)
-Refractory to Lenalidomide & Pomalidomide	14 (31%)
-Proteasome Inhibitor Therapy (Treated : Refractory)	45 (100%) : 26 (58%)
-Prior Carfilzomib Therapy	15 (33%)
-Stem Cell transplant	36 (80%)

SPd Treatment-Related Adverse Events ≥10% Patients

AE Term	60/80 mg Sel BIW + 3/4 Pom QD				60/80/100 mg Sel QW + 2/3/4 Pom QD			
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=18)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=27)**
Neutropenia	--	6 (33.3)	3 (16.7)	**9 (50.0)**	3 (11.1)	6 (22.2)	10 (37.0)	**19 (70.4)**
Thrombocytopenia	2 (11.1)	3 (16.7)	5 (27.8)	**10 (55.6)**	8 (29.6)	5 (18.5)	1 (3.7)	**14 (51.9)**
Anemia	2 (11.1)	8 (44.4)	--	**10 (55.6)**	6 (22.2)	6 (22.2)	--	**12 (44.4)**
Leukopenia	--	1 (5.6)	1 (5.6)	**2 (11.1)**	6 (22.2)	3 (11.1)	2 (7.4)	**11 (40.7)**
Lymphopenia	--	1 (5.6)	--	**1 (5.6)**	1 (3.7)	4 (14.8)	1 (3.7)	**6 (22.2)**
Febrile Neutropenia*	--	2 (11.1)	--	**3 (16.7)**	--	3 (11.1)	1 (3.7)	**4 (14.8)**
Gastrointestinal								
Nausea	12 (66.7)	--	--	**12 (66.7)**	13 (48.1)	--	--	**13 (48.1)**
Anorexia	11 (61.1)	--	--	**11 (61.1)**	11 (40.7)	--	--	**11 (40.7)**
Diarrhea	6 (33.3)	--	--	**6 (33.3)**	7 (25.9)	--	--	**7 (25.9)**
Vomiting	2 (11.1)	1 (5.6)	--	**3 (16.7)**	8 (29.6)	--	--	**8 (29.6)**
Altered Taste	4 (22.2)	--	--	**4 (22.2)**	5 (18.5)	--	--	**5 (18.5)**
Constitutional								
Fatigue	9 (50.0)	2 (11.1)	--	**11 (61.1)**	10 (37.0)	3 (11.1)	--	**13 (48.1)**
Asthenia	3 (16.7)	1 (5.6)	--	**4 (22.2)**	1 (3.7)	--	--	**1 (3.7)**
Weight Loss	7 (38.9)	--	--	**7 (38.9)**	9 (33.3)	--	--	**9 (33.3)**
Dizziness	2 (11.1)	--	--	**2 (11.1)**	5 (18.5)	--	--	**5 (18.5)**
Dehydration	5 (27.8)	--	--	**5 (27.8)**	1 (3.7)	--	--	**1 (3.7)**
Other								
Hyponatremia	--	1 (5.6)	--	**1 (5.6)**	3 (11.1)	2 (7.4)	1 (3.7)	**6 (22.2)**
Muscle Spasms	3 (16.7)	--	--	**3 (16.7)**	4 (14.8)	--	--	**4 (14.8)**
Hypokalemia	--	1 (5.6)	--	**1 (5.6)**	4 (14.8)	1 (3.7)	--	**5 (18.5)**
Insomnia	2 (11.1)	--	--	**2 (11.1)**	4 (14.8)	--	--	**4 (14.8)**
Edema Peripheral	4 (22.2)	--	--	**4 (22.2)**	2 (7.4)	--	--	**2 (7.4)**
Hyperglycemia	1 (5.6)	1 (5.6)	--	**2 (11.1)**	3 (11.1)	--	--	**3 (11.1)**
Blurred Vision	1 (5.6)	--	--	**1 (5.6)**	4 (14.8)	--	--	**4 (14.8)**

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

Treatment-Related Adverse Events as of May 1, 2019

SPd DLTs

Selinexor Dose	Pom Dose	Patients Enrolled	Patients with DLT	Dose Limiting Toxicity
60 mg BIW	4 mg QD	6	1	Grade 3 Fatigue
60 mg BIW	3 mg QD	6	1	Grade 3 Febrile Neutropenia
80 mg BIW	4 mg QD	6	--	No DLT
***60 mg QW**	**4 mg QD**	**3**	**--**	**No DLT and Enrollment is Ongoing**
80 mg QW	4 mg QD	7	2	Grade 3 Febrile Neutropenia Grade 4 Neutropenia
80 mg QW	3 mg QD	6	2	Pom Dose Reduction for Grade 2 Neutropenia Grade 3 Thrombocytopenia (re-escalated and maintained at 3 mg) Grade 3 Febrile Neutropenia
***80 mg QW**	**2 mg QD**	**7**	**--**	**No DLT and Enrollment is Ongoing**
100 mg QW	4 mg QD	4	--	No DLT

- ***Enrollment is ongoing: once-weekly Sel (80 mg) / Pom (2 mg) and once-weekly Sel (60 mg) / Pom (4 mg)**

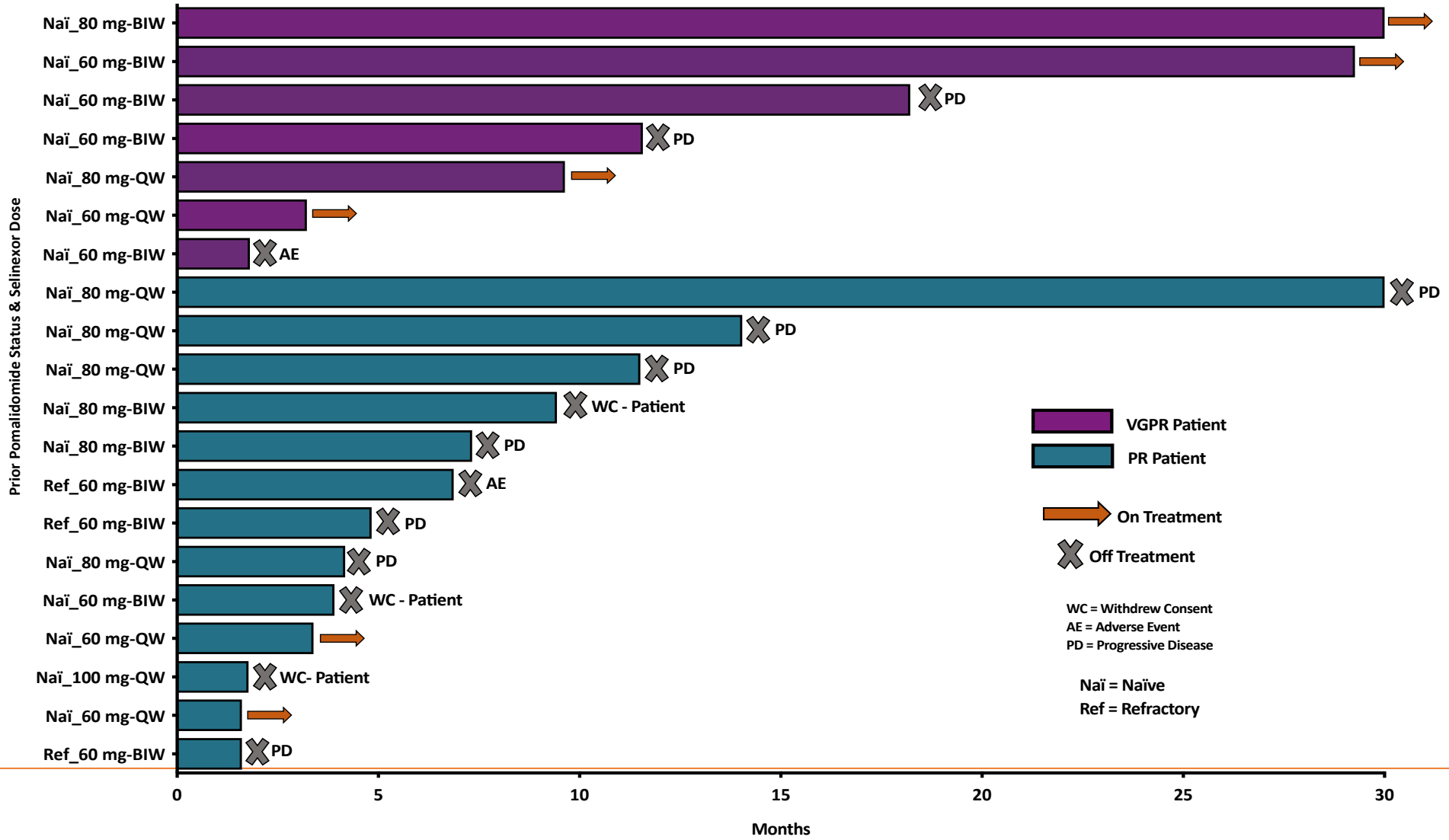
BIW, Twice-Weekly; DLT, dose limiting toxicity; QD, Once-Daily; QW, Once-Weekly.

SPd Efficacy

Best Responses† in Evaluable Patients Treated with SPd as of May 1, 2019									
Category	**N***	**ORR (%)**	**CBR (%)**	**CR (%)**	**VGPR (%)**	**PR‡ (%)**	**MR‡ (%)**	**SD (%)**	**PD (%)**
All	40	**20 (50%)**	**27 (68%)**	--	7 (18%)	13 (33%)	7 (18%)	12 (30%)	1 (3%)
Pom Naïve & Len-Refractory or Relapsed	30	**17 (57%)**	**22 (73%)**	--	7 (23%)	10 (33%)	5 (17%)	7 (23%)	1 (3%)
Pom & Len-Refractory	10	**3 (30%)**	**5 (50%)**	--	--	3 (30%)	2 (20%)	5 (50%)	--

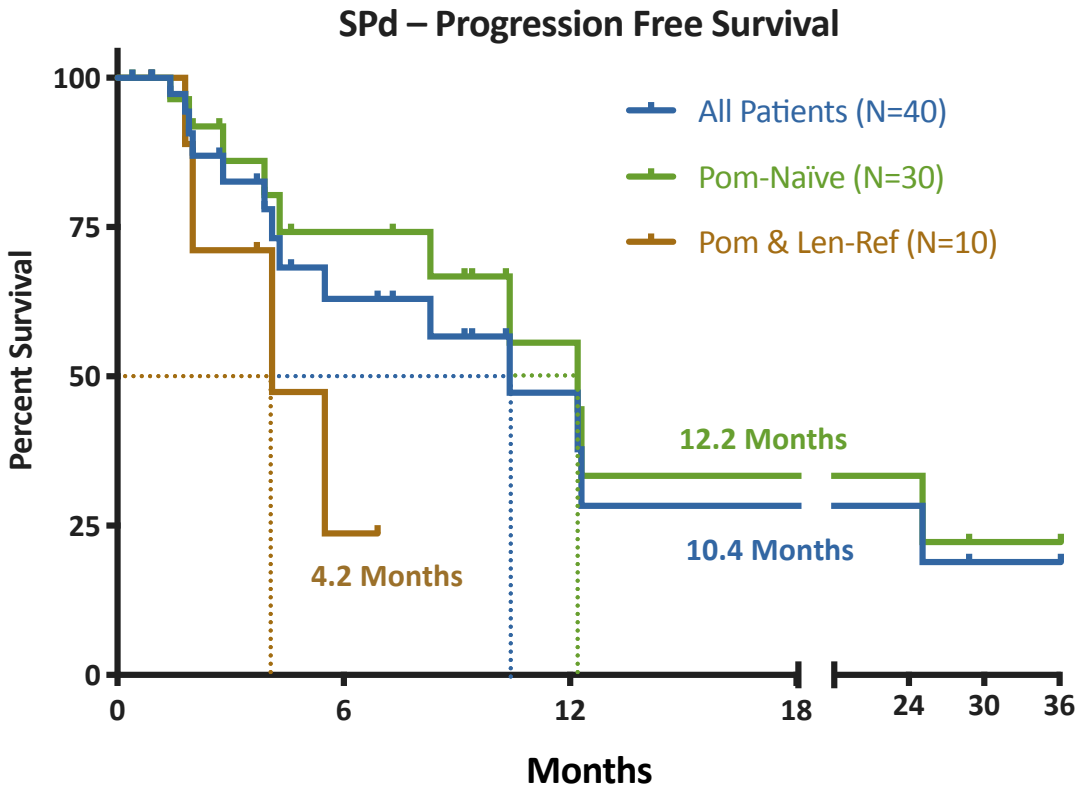
†Responses were adjudicated according to the International Myeloma Working Group criteria, *five patients not evaluable for response: one death unrelated to myeloma, one non-compliance with study procedures, two withdrawal of consent before disease follow up, one patient on treatment pending response evaluation. ‡one unconfirmed PR, one unconfirmed MR. ORR=Overall Response Rate (CR+VGPR+PR), CBR=Clinical Benefit Rate (ORR+MR), CR=Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response, SD=Stable Disease, PD=Progressive Disease. Responses as of May 1, 2019 based on interim unaudited data.

SPd Time on Study and Response (Responders)



A) Among patients with a PR or better (N=20) the median time on treatment was **7.1** months. Responses were rapid in onset with a median time to response of **1** month.

SPd Progression Free Survival



Patients at Risk	Months	0	2.0	5.5	7.0	9.2	10.4	12.2	25.1	28.8	36.1
	All Patients	40	24	13	12	9	6	5	3	2	1
	Pom-Naï & Len-Ref	30	19	--	--	9	6	5	3	2	1
	Pom & Len-Ref	10	5	2	1	--	--	--	--	--	--

B) Median PFS among evaluable patients was **10.4** months. Median PFS in Pom-naïve and Len-refractory or relapsed MM was **12.2** months (versus ~4 months expected for the standard Pd regimen).

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: nausea, anorexia, fatigue, and G3/4 neutropenia, anemia, thrombocytopenia; which are expected and can be managed with appropriate supportive care and/or dose modifications**
- **Determination of the RP2D of SPd is ongoing with Sel 60 mg QW / Pom 4 mg QD / Dex 40 mg QW and Sel 80 mg QW / Pom 2 mg QD / Dex 40 mg QW regimens**

The all oral SPd combination rapidly (typically within 1 cycle) produces responses, which are durable

- **ORR of 57% in Pom-naïve patients (compared to expected ORR of ≤ 30% for Pom + Dex)[1] and 23% of patients achieving a VGPR**
- **CBR was 68% across all patients, and 73% in Pom-naïve patients**
- **PFS in Pom-naïve patients was 12.2 months (compared to expected PFS of ~4 months for Pom + Dex)[1]**

[1] Pomalyst Package Insert; Initial US Approval 2013; Celgene Corporation