A Phase 2, Open-Label, Single-Arm Study of Selinexor in Combination with Clarithromycin, Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (NCT04843579)

IRB Protocol #: 20-12023093

IND/IDE #: 154930

Version Date: 07/08/2021

Funding Source: Karyopharm Therapeutics, Inc. (IST-343)

Principal Investigator: Jorge Monge, M.D.
425 East 61st Street, 8th Floor
New York, NY 10065
T: 646.962.6500
F: 212.746.8961
E: jum9127@med.cornell.edu

Protocol Cover Page

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Jorge Monge, M.D.
425 East 61st Street, 8th Floor
New York, NY 10065
T: 646.962.6500
F: 212.746.8961
E: jum9127@med.cornell.edu

Co-Investigators:

Ruben Niesvizky, M.D.
425 East 61st Street, 8th Floor
New York, NY 10065
T: 646.962.6500
F: 212.746.8961
E: run9001@med.cornell.edu

Roger Pearse, M.D., Ph.D.
425 East 61st Street, 8th Floor
New York, NY 10065
T: 646.962.6500
F: 212.746.8961
E: rnp2001@med.cornell.edu

Cara Rosenbaum, M.D.
425 East 61st Street, 8th Floor
New York, NY 10065
T: 646.962.6500
F: 212.746.8961
E: car9156@med.cornell.edu

Perry Cook, MD
506 6th Street, Wesley House #3C
Brooklyn, NY 11215
T: 718.780.5541
E: pec9040@nyp.org

Andy Huang, MD
506 6th St
Brooklyn, NY 11215
T: 718.780.5246
E: anh9107@nyp.org

Statistician:

Paul Christos, Dr.PH, MS
1300 York Ave, Box 65
New York, NY 10065
T: 212.746.6565
F: 212.746.5981
pac2001@med.cornell.edu

Participating Network Site:
NewYork Presbyterian-Brooklyn Methodist Hospital
Perry Cook, MD and Andy Huang, MD
515 6th Street, 6th floor
Brooklyn, NY 11215
pec9040@nyp.org and anh9107@nyp.org

Participating Sites:

TBD

PROTOCOL VERSION AND DATE:
Original, April 19th, 2021
Amendment 1, July 8th, 2021

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Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

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Institution Name

_____	_____	_____
Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

AE	Adverse Event
C	Cycle
CFR	Code of Federal Regulations
ClaSPd	Clarithromycin, selinexor, pomalidomide and dexamethasone
CrCl	Creatinine Clearance
CRF	Case Report Form
CTSC	Clinical Translational Science Center
CYP	Cytochrome
D	Day
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
ECOG PS	Eastern cooperative oncology group performance status
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
MM	Multiple Myeloma
N	Number of patients
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PHI	Protected Health Information
PI	Principal Investigator
PO	Oral
Pts	Patients
QD	Daily
QOL	Quality of life
REDCap	Research Electronic Data Capture
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	Serious Adverse Event

SINE	Selective inhibitor of nuclear export
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

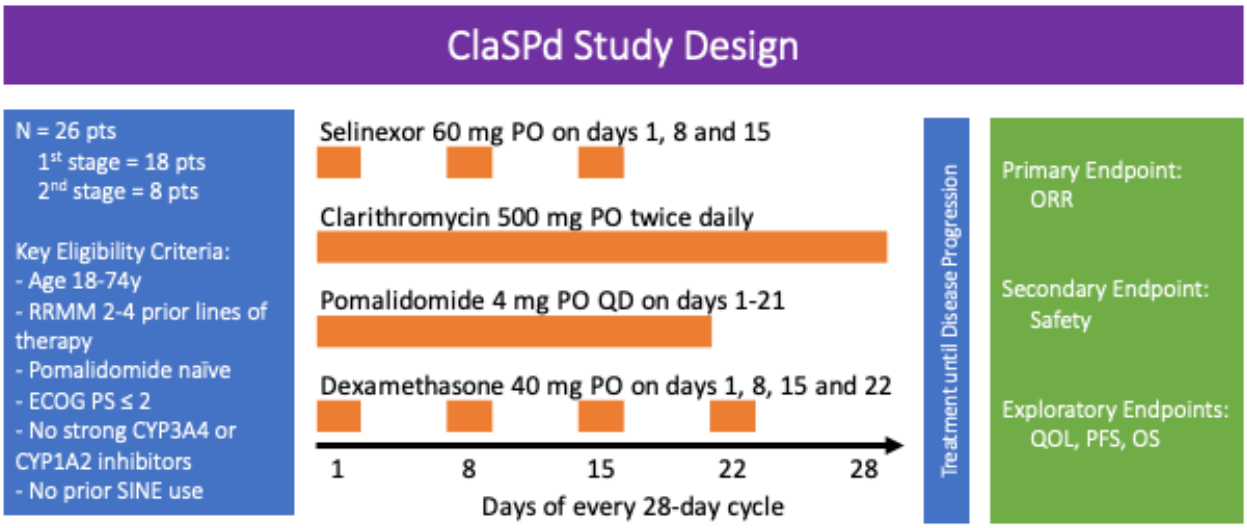
Full Title:	A Phase 2, Open-Label, Single-Arm Study of Selinexor in Combination with Clarithromycin, Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma
Short Title:	ClaSPd in patients with RRMM
Clinical Phase:	II
Principal Investigator:	Jorge Monge, MD
Study Description:	This study will assess the efficacy and safety of combination therapy with Selinexor, Clarithromycin, Pomalidomide and Dexamethasone (ClaSPd) for the treatment of patients with relapsed/refractory multiple myeloma (RRMM).
Sample Size:	N = 26 in a two-stage design; $n_1 = 18$, $n_2 = 8$.
Enrollment:	This study will enroll 26 subjects and screen up to 50 subjects.
Study Population:	Patients over 18 and under 75 years of age with RRMM previously treated with two to four prior lines of therapy.
Enrollment Period:	13 months
Study Design:	This is a phase 2, open-label, single-arm study to assess the efficacy and safety of ClaSPd in patients with RRMM previously treated with two to four prior lines of therapy. A Simon's two-stage design will be used. In the first stage, 18 patients will be accrued. If there are 6 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 26. The null hypothesis will be rejected if 14 or more responses are observed in 26 patients. The study treatment is an all-oral regimen given in 28-day cycles until progression of disease, death, toxicity that cannot be managed by standard care or study withdrawal: Selinexor 60 mg PO on days 1, 8, and 15. Clarithromycin 500 mg PO twice a day on days 1-28. Pomalidomide 4 mg PO daily on days 1-21. Dexamethasone 40 mg PO on days 1, 8, 15 and 22.

Description of Sites/ Facilities Enrolling Participants:	Subjects will be screened and enrolled at Weill Cornell Medicine and NewYork Presbyterian-Brooklyn Methodist Hospital in New York, NY. There is no intention to include sites outside of the United States.
Study Duration:	The projected total study duration is 40 months (13 months to complete enrollment, 24 months of median study treatment duration for the last enrolled participant, and 3 months for data analysis).
Participant Duration:	Participants are estimated to receive study treatment for approximately 10 months, undergo a follow-up assessment 1 month later, and four duration-of-response/survival follow-up assessments every 3 months, for approximately 24 months on study.
Study Agent/Device Name Intervention Description:	Selinexor 60 mg PO on days 1, 8, and 15, Clarithromycin 500 mg PO twice a day on days 1-28, Pomalidomide 4 mg PO daily on days 1-21, and Dexamethasone 40 mg PO on days 1, 8, 15 and 22 of a 28-day cycle, until progression of disease, death, toxicity that cannot be managed by standard care or study withdrawal.
Primary Objective:	To determine the efficacy of combination therapy with ClaSPd for the treatment of patients with RRMM.
Secondary Objectives*:*	To evaluate the safety of combination therapy with ClaSPd for *the* treatment of patients with RRMM.
Exploratory Objectives:	To determine the duration of response of combination therapy with ClaSPd for the treatment of patients with RRMM. To determine the clinical benefit rate of combination therapy with ClaSPd for the treatment of patients with RRMM. To determine the disease control rate of combination therapy with ClaSPd for the treatment of patients with RRMM. To determine the progression-free survival of combination therapy with ClaSPd for the treatment of patients with RRMM. To determine the overall survival of combination therapy with ClaSPd for the treatment of patients with RRMM. To determine the relative dose intensity of combination therapy with ClaSPd for the treatment of patients with RRMM.

	To assess quality of life during combination therapy with ClaSPd for the treatment of patients with RRMM.
Primary Endpoints:	Overall response rate, which includes a partial response or better according to the International Myeloma Working Group response criteria, assessed at the completion of every cycle of study treatment.
Secondary Endpoints:	Frequency of participants with Adverse Events as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

1.1 Schema

Figure 1. ClaSPd Study Design



Abbreviations: ClaSPd = selinexor + clarithromycin + pomalidomide + dexamethasone; CYP = cytochrome; ECOG PS = eastern cooperative oncology group performance status; N = number of patients; ORR = overall response rate; OS = overall survival; pts = patients; PFS = progression-free survival; PO = by mouth; QD = once daily; QOL = quality of life; RRMM = relapsed/refractory multiple myeloma; SINE = selective inhibitor of nuclear export.

Table 1. ClaSPd Dosing Schedule

	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D2	D2	D2	D2	D2	D2	D2	D2	D2
Sel	X							X							X													
Cla	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pom	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Dex	X							X							X							X						

Abbreviations: Cla = clarithromycin; ClaSPd = selinexor + clarithromycin + pomalidomide + dexamethasone; D = day; Dex = dexamethasone; Pom = pomalidomide; Sel = selinexor; X = dosing day.

1.2 Study Objectives and End Points

This study will explore the efficacy and safety of selinexor in combination with clarithromycin, pomalidomide and dexamethasone (ClaSPd) for the treatment of patients with relapsed/refractory multiple myeloma (RRMM) previously treated with two to four prior lines of therapy.

1.2.1 Primary Objectives

To determine the efficacy of combination therapy with ClaSPd for the treatment of patients with RRMM.

1.2.2 Secondary Objectives

To evaluate the safety of combination therapy with ClaSPd for the treatment of patients with RRMM.

1.2.3 Exploratory Objectives

- To determine the duration of response of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To determine the time to maximum response of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To determine the clinical benefit rate of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To determine the disease control rate of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To determine the progression-free survival of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To determine the overall survival of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To determine the relative dose intensity of combination therapy with ClaSPd for the treatment of patients with RRMM.
- To assess quality of life during combination therapy with ClaSPd for the treatment of patients with RRMM.

1.2.4 Primary Endpoints

Overall response rate, which includes a partial response or better according to the International Myeloma Working Group response criteria, assessed at the completion of every cycle of study treatment.

1.2.5 Secondary Endpoints

Frequency of participants with Adverse Events as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

2. Background

2.1 Disease

Multiple myeloma (MM) is the second most common hematological malignancy, representing 1.8% of all cancers. In 2020, there are an estimated 140,779 people living with myeloma in the United States, and it is estimated that there will be 32,270 new cases of myeloma and an estimated 12,830 people will die of this disease.1 Although a rare disease, myeloma is more common in men than women and among individuals of African American descent, with a median age at diagnosis of 69. Despite the increased efficacy of new agents, nearly all patients will eventually relapse with their disease becoming drug resistant. There continues to be an unmet medical need for patients with relapsed and/or refractory MM (RRMM) that can provide a deep and durable response.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

2.2.1 Selinexor

Selective inhibitor of nuclear export (SINE) compounds, a new generation of exportin 1 (XPO1) inhibitors, were designed as drug-like small molecules that selectively inhibit XPO1 in order to increase efficacy and reduce toxicity secondary to non-specific binding and off-target effects. Mechanistic studies show that SINE compounds induce nuclear localization and activation of multiple tumor suppressor proteins (TSPs), along with reduction in oncoprotein levels (e.g., c-Myc and the anti-apoptotic protein BCL-XL) leading to rapid apoptosis of MM cells.

Selinexor is an orally bioavailable SINE compound that specifically blocks XPO1, with anti-MM activity demonstrated in preclinical studies. In a phase 1 clinical trial (NCT01607892) of selinexor in patients with advanced hematological malignancies, 25 patients with heavily pretreated MM (22) or Waldenstrom macroglobulinemia (3) were administered selinexor (3-60 mg/m^2) in 8 or 10 doses per 28-day cycle.[11] In the dose-expansion phase, 59 patients with MM received selinexor at 45 or 60 mg/m^2 with dexamethasone 20 mg, twice weekly in 28-day cycles, or selinexor (40 or 60 mg flat dose) without corticosteroids in 21-day cycles. The most common non-hematologic adverse events (AEs) were nausea (75%), fatigue (70%), anorexia (64%), vomiting (43%), weight loss (32%), and diarrhea (32%), which were primarily grade 1 or 2. The most common grade 3 or 4 AEs were hematologic, particularly thrombocytopenia (45%). Single-agent selinexor showed modest efficacy with an objective response rate (ORR) of 4% and a clinical benefit rate of 21%. In contrast, the addition of dexamethasone increased the ORR with all responses of greater than partial response occurring in the 45 mg/m^2 selinexor plus dexamethasone 20 mg twice weekly cohort (ORR = 50%). Furthermore, 46% of all patients showed a reduction in MM markers from baseline. These findings demonstrated the activity of selinexor in combination with dexamethasone in heavily pretreated MM.

In a phase 2 clinical trial (NCT02336815), 122 patients with triple-class refractory MM received selinexor (80mg) and dexamethasone (20mg) twice weekly.[9] A partial response or better was observed in 26% of patients, including two stringent complete responses; 39% of patients had a minimal response or better. The median duration of response was 4.4 months, median progression-free survival was 3.7 months, and median overall survival was 8.6 months. Fatigue, nausea, and decreased appetite were common and were typically grade 1 or 2 (grade 3 events

were noted in up to 25% of patients, and no grade 4 events were reported). Thrombocytopenia occurred in 73% of the patients (grade 3 in 25% and grade 4 in 33%). Thrombocytopenia led to bleeding events of grade 3 or higher in 6 patients. This trial showed that the combination of selinexor with dexamethasone resulted in objective treatment responses in patients with triple-class refractory multiple myeloma.

The phase 1/2 clinical trial of selinexor in combination with backbone treatments for relapsed/refractory multiple myeloma (STOMP; NCT02343042) is currently evaluating the efficacy and safety of multiple combinations. Preliminary results from the cohort of patients receiving selinexor, pomalidomide and dexamethasone were presented at the 61st American Society of Hematology Annual Meeting on December 7, 2019.[10] Oral selinexor was evaluated in a once-weekly or twice-weekly schedule with low-dose dexamethasone and escalating doses of pomalidomide 2, 3 or 4 mg PO (days 1-21). Fifty-one patients with relapsed/refractory multiple myeloma had been enrolled. Common hematologic treatment-related adverse events (TRAEs) included neutropenia, thrombocytopenia, anemia, and leukopenia; while non-hematologic TRAEs included nausea, fatigue, decreased appetite, weight decreased, diarrhea, and vomiting. Lower rates of ≥grade 3 thrombocytopenia (27% vs 44%) were observed in the weekly vs twice-weekly dosing. Among 46 evaluable patients for efficacy, the ORR was 50% (56% in patients who were pomalidomide-naïve), 15% achieved a VGPR, and the median PFS was 10.4 months (12.2 months in patients who were pomalidomide-naïve). Once-weekly selinexor can be safely combined with pomalidomide and low-dose dexamethasone in heavily pretreated patients with MM. The recommended phase 2 dose was defined as selinexor 60mg once-weekly, pomalidomide 4mg daily (days 1-21) and dexamethasone 40 mg once-weekly.

On July 3, 2019, the Food and Drug Administration granted accelerated approval to selinexor in combination with dexamethasone for adult patients with relapsed/refractory multiple MM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

2.2.2 Clarithromycin

The semisynthetic macrolide antibiotic, clarithromycin, is indicated for the treatment of mild to moderate infections caused by susceptible bacteria. In the treatment of patients with multiple myeloma, clarithromycin has resulted in deep responses when added to dexamethasone in combination with thalidomide, lenalidomide or pomalidomide.[3-8] It optimizes the pharmacologic effects of glucocorticoids by increasing the area under the curve and the maximum concentration levels of some steroids through inhibition of CYP3A4.[12] It has an immunomodulatory effect and may have direct antineoplastic properties by synergistically decreasing the secretion of tumor necrosis factor-α and interleukin-6 through the inhibition of ERK1/2 and AKT in combination with other immunomodulatory drugs like thalidomide and lenalidomide.[13] Other studies have suggested that clarithromycin inhibits autophagy, increasing the cytotoxic effect of immunomodulatory drugs on MM cells.[14]

The phase 2 clinical trial (NCT00151203) evaluated the safety and efficacy of combination therapy with clarithromycin, lenalidomide and dexamethasone for the treatment of newly diagnosed MM.[7] Of 72 patients enrolled, 90% achieved an objective response of which 39% were CR or better, and an actuarial 2-year event-free survival of 97%. The most common grade ≥3 hematologic AEs were neutropenia (19.4%), anemia (13.8%), and thrombocytopenia

(22.2%); common non-hematologic grade ≥3 AEs were myopathy (11.1%), rash (5.6%), diverticular abscess (5.6%), and thromboembolic events (12.5%).

A case–matched study compared the addition of clarithromycin to lenalidomide and dexamethasone vs lenalidomide and dexamethasone for the treatment of newly diagnosed myeloma.[4] It retrospectively analyzed the data obtained for the 72 patients enrolled in the above study and 72 pair mates selected among patients seen at the Mayo Clinic who received lenalidomide and dexamethasone. On an intention-to-treat analysis, CR rates (45.8% vs 13.9%, p<0.001) and ≥VGPR rates (73.6% vs 33.3%, p<0.001) were significantly higher with the addition of clarithromycin. Time-to-progression (median 48.3 vs 27.5 months, p=0.071), and progression-free survival (median 48.3 vs 27.5 months, p=0.044) also favored the addition of clarithromycin, however, overall survival was similar between both groups (3-year OS: 89.7% vs 73.0%, p=0.17).

A phase 3 clinical trial (NCT02575144) randomized 286 patients with newly diagnosed MM, transplant ineligible, to receive lenalidomide (daily for 21 days every 28 days) and weekly dexamethasone with or without twice-daily clarithromycin.[15] The preliminary results were presented at the 61st American Society of Hematology Annual Meeting on December 9, 2019. The addition of clarithromycin to lenalidomide and dexamethasone significantly increased the depth of response (≥CR 21% vs 11%; p = 0.037) but it was not associated with an improved PFS and OS due to a higher proportion of treatment-related deaths in the clarithromycin-containing arm, mostly infectious, and affecting primarily patients ≥75 years of age.

The addition of clarithromycin to pomalidomide and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma previously exposed to lenalidomide was evaluated in a phase 2 study (NCT01159574).[6] The median number of prior therapies was 5 (range 3-15). The overall response rate (ORR) was 60% with 23% achieving at least a very good partial response. The median PFS was 7.7 months and the median overall survival was 19.2 months. The most common grade ≥3 toxicities included neutropenia (58%), thrombocytopenia (31%), and anemia (28%).

2.2.3 Pomalidomide

Pomalidomide is an immunomodulatory drug approved for the treatment of patients with RRMM. In combination with dexamethasone, pomalidomide has been shown to be effective in patients with relapsed/refractory MM previously treated with bortezomib and/or lenalidomide, with ORR ranging from 31 to 47% (ORR pooled estimate 35%; 95% confidence interval: 30-42%).[16-20] Toxicity is mostly hematologic, with grade ≥3 neutropenia occurring in 40-48%, anemia in 22-33%, and thrombocytopenia in 19-22%; while non-hematologic grade ≥3 toxicity included pneumonia (13-22%) and fatigue (5-14%).[19,20]

More recently, multiple phase 2 and 3 clinical trials have demonstrated the efficacy of three-drug regimens including pomalidomide and dexamethasone in combination with clarithromycin (ORR 60%), carfilzomib (ORR 62%), ixazomib (ORR 48%), cyclophosphamide (ORR 51-65%), elotuzumab (ORR 53%), daratumumab (ORR 60%), or isatuximab (ORR 60%) (ORR pooled estimate 58%; 95% confidence interval: 54-62%).[6,21-27] These studies reported a median PFS of 7.7 to 11.5 months (median 9.9 months).

2.3 Rationale

Multiple myeloma (MM) is the second most common hematological malignancy.[1] Despite the increased efficacy of new agents, nearly all patients will eventually relapse and require further therapy. The prognosis of patients with MM who have relapsed/refractory disease is poor, with decreased response rates and duration of response to each subsequent line of treatment. Achieving a deep response is associated with improvement in quality of life and longer duration of freedom from disease symptoms and overall survival.[2] There continues to be an unmet medical need for effective treatment of patients with relapsed and/or refractory MM.

The use of clarithromycin, a semisynthetic macrolide antibiotic, in the treatment of patient with multiple myeloma has resulted in deep responses when added to dexamethasone in combination with thalidomide, lenalidomide or pomalidomide.[3-8] Recently, the combination of selinexor with dexamethasone, as well as with pomalidomide and dexamethasone, has shown to be a safe and effective treatment in patients with heavily pretreated MM.[9,10] The rationale for combining selinexor with clarithromycin, pomalidomide and dexamethasone in the current study is based on the clinical synergistic activity observed when clarithromycin is combined with pomalidomide and dexamethasone,[6] the clinical synergistic activity observed when selinexor is combined with pomalidomide and dexamethasone,[10] the clinical appeal of an all oral regimen, and the urgent need to induce deeper and more durable responses in patients with relapsed/refractory MM.

This study will explore the efficacy and safety of selinexor in combination with clarithromycin, pomalidomide and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma (RRMM) previously treated with at least one line of therapy.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All adverse events (AEs) and serious adverse events (SAEs) will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first.

2.4.1.1 Selinexor

The U.S. FDA granted approval for selinexor based on the STORM trial (KCP-330-012; NCT02336815), in which 122 patients with relapsed and refractory patients were treated with twice-weekly selinexor (80mg) in combination with dexamethasone (20mg). The most commonly reported hematological treatment emergent adverse events (TEAEs) were thrombocytopenia (74%), anemia (59%), leukopenia (28%), and neutropenia (34%). The most common non-hematological TEAEs were nausea (72%), fatigue (73%), decreased appetite (53%), diarrhea (44%) and vomiting (41%). Common (>10%) grade 3 or greater AEs included thrombocytopenia, fatigue, anemia, hyponatremia, neutropenia, leukopenia and lymphopenia. These results are generally consistent with the overall TEAE results reported for all selinexor studies in patients with hematological malignancies.

2.4.1.2 Clarithromycin

Based on pooled data across all indications, the most frequent adverse reactions for both adult and pediatric populations observed in clinical trials of clarithromycin are abdominal pain (5%), diarrhea (8%), nausea (11%), vomiting (6%) and dysgeusia (8%). Also reported were dyspepsia, liver function test abnormalities, anaphylactic reaction, candidiasis, headache, insomnia, and rash.

In a trial of clarithromycin use in immunocompromised adult patients, 8% who received clarithromycin 500 mg twice a day and 12% of the patients who received 1000 mg twice a day discontinued therapy due to drug related adverse reactions during the first 12 weeks of therapy. Adverse reactions leading to discontinuation in at least two patients included nausea, vomiting, abdominal pain, diarrhea, rash, and asthenia. In the first 12 weeks of starting on clarithromycin 500 mg twice a day, 5% of patients had an increase > 5 times the upper limit of normal in liver function tests. This includes only patients with baseline values within the normal range or borderline low.

In one clinical trial evaluating treatment with clarithromycin on outcomes in patients with coronary artery disease, an increase in risk of all-cause mortality was observed in patients randomized to clarithromycin. Clarithromycin for treatment of coronary artery disease is not an approved indication. Patients were treated with clarithromycin or placebo for 14 days and observed for primary outcome events (e.g., all-cause mortality or non-fatal cardiac events) for several years. A numerically higher number of primary outcome events in patients randomized to receive clarithromycin was observed with a hazard ratio of 1.06 (95% confidence interval 0.98 to 1.14). However, at follow-up 10 years post-treatment, there were 866 (40%) deaths in the clarithromycin group and 815 (37%) deaths in the placebo group that represented a hazard ratio for all-cause mortality of 1.10 (95% confidence interval 1.00 to 1.21). The difference in the number of deaths emerged after one year or more after the end of treatment. The cause of the difference in all-cause mortality has not been established. Other epidemiologic studies evaluating this risk have shown variable results.

2.4.1.3 Pomalidomide and Dexamethasone

The U.S. FDA granted accelerated approval for pomalidomide on the basis of the Phase 2 study (MM-002), comparing pomalidomide alone or in combination with dexamethasone for the treatment of relapsed and refractory MM. The most common hematologic Grade 3/4 AEs were neutropenia (41% vs. 48%), anemia (22% vs. 24%), and thrombocytopenia (19% vs. 22%). The most common nonhematologic AE was pneumonia (22% versus 15%) and fatigue (14% versus 11%) in the pomalidomide and dexamethasone arm compared to the pomalidomide alone arm, respectively. The frequency of febrile neutropenia was low (3% versus 5%), as was the incidence of DVT (2% versus 3%). There were no grade 3 or 4 events of peripheral neuropathy reported. The EMA granted approval for pomalidomide in Europe based on the phase 3 study (MM-003/NIMBUS trial) which evaluated the combination of pomalidomide with low-dose dexamethasone vs. high-dose dexamethasone in refractory or relapsed and refractory MM subjects. In the pomalidomide plus low-dose dexamethasone and high-dose dexamethasone arms, respectively, the most common grade 3–4 hematological adverse events were neutropenia (48% vs 16%), anemia (33% vs 37%), and thrombocytopenia (22% vs 26%). The most common grade 3–4 non-hematological adverse events were pneumonia (13% vs 8%), bone pain (7% vs 5%), and fatigue (5% vs 6%).

2.4.1.4 Selinexor in combination with pomalidomide and dexamethasone

The preliminary results of a phase 1b/2 clinical trial reported the most common AEs (≥20%) suspected to be related to once-weekly selinexor in combination with pomalidomide and dexamethasone to be neutropenia (67%), thrombocytopenia (52%), nausea (52%), fatigue (52%), anemia (45%), weight loss (39%), anorexia (36%), leukopenia (36%), vomiting (27%), diarrhea (24%), hyponatremia (21%) and dizziness (18%). Most of these effects can be managed effectively with dose modification and/or supportive care initiated prior to first dosing. There were three grade 5 adverse events: one intracranial hemorrhage in cycle 2; one febrile neutropenia in cycle 1 and one pneumonia in cycle 5.

2.4.1.5 Clarithromycin in combination with other immunomodulatory agents

Results from a case-matched study comparing the addition of clarithromycin to lenalidomide and dexamethasone to lenalidomide and dexamethasone for the treatment of newly diagnosed MM showed 76.4% vs 58.3% of patients at least one grade 3 or higher AE. The frequency of neutropenia was similar between the two groups while thrombocytopenia was significantly more frequent with the addition of clarithromycin (23.6% vs 8.3%, p = 0.01). One of the most common non-hematological toxicities reported with clarithromycin was steroid related myopathy (9.7% vs 0%, p = 0.01), while there was no difference in the rate of infections (9.7% vs 16.7%, p = 0.22) or dermatological toxicities (4.2% vs 12.5%, p = 0.13). The rate of thromboembolic events (VTE) was similar in the two groups (9.7% vs 12.5%, p = 0.6). There were two treatment-related deaths in the clarithromycin group, one due to pulmonary embolism and one due to myocardial infarction.

The preliminary results of a phase 3 clinical trial of lenalidomide and dexamethasone with or without clarithromycin showed a significantly higher incidence of treatment-related deaths in the clarithromycin-containing arm, mostly due to infections and affecting primarily patients 75 years of age or older.

2.4.1.6 Reproductive Risks

Patients should not become pregnant or father a child while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of childbearing potential must agree to use a highly effective method of contraception (see “Prevention of pregnancy”) and have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to receiving the first dose of study treatment. Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential, as per the requirements of the Risk Evaluation and Mitigation Strategy (REMS) program.

2.4.1.6.1 Selinexor

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies, most of which partially or fully resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development. It is unknown whether similar effect may occur in humans. As it is

unknown whether selinexor might have reproductive toxicity in humans, patients must agree to use effective contraception during the study and for 3 months after the end of treatment.

2.4.1.6.2 Clarithromycin

Based on findings from animal studies, clarithromycin is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus. Clarithromycin demonstrated adverse effects on pregnancy outcome and/or embryo fetal development, including fetal malformations, in pregnant animals administered oral clarithromycin. Administration of clarithromycin resulted in testicular atrophy in rats, dogs and monkeys. Limited data from a small number of published human studies with clarithromycin use during pregnancy are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, administration of oral clarithromycin to pregnant mice, rats, rabbits, and monkeys during the period of organogenesis produced malformations in rats (cardiovascular anomalies) and mice (cleft palate) at clinically relevant doses based on body surface area comparison. Fetal effects in mice, rats, and monkeys (e.g., reduced fetal survival, body weight, body weight gain) and implantation losses in rabbits were generally considered to be secondary to maternal toxicity. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

2.4.1.6.3 Pomalidomide

Pomalidomide is structurally and pharmacologically related to thalidomide, a known teratogen, and is contraindicated in pregnant women and women who are at risk of becoming pregnant. The pomalidomide product monographs/labeling contain the following boxed-text warning: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM (See full prescribing information for complete boxed warning EMBRYO-FETAL TOXICITY)· POMALYST (pomalidomide) is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe life-threatening birth defects. For females of reproductive potential: Exclude pregnancy before start of treatment. Prevent pregnancy during treatment by the use of 2 reliable methods of contraception. POMALYST is available only through a restricted program called POMALYST REMS®.

In order to prevent pregnant women from being exposed to pomalidomide, a Risk Evaluation and Mitigation Strategy (REMS) called POMALYST REMS, has been established by the manufacturer of pomalidomide. In order to participate in this study, investigators and patients must agree to comply with the requirements of the plans.

2.4.1.6.4 Dexamethasone

Animal studies have shown evidence of teratogenicity due to systemic corticosteroids. There are no controlled data in human pregnancy. Dexamethasone is only recommended for use during pregnancy when there are no alternatives and benefit outweighs risk.

2.4.2 Known Potential Benefits

2.4.2.1 Selinexor

Selective inhibitor of nuclear export (SINE) compounds, a new generation of exportin 1 (XPO1) inhibitors, were designed as drug-like small molecules that selectively inhibit XPO1 in order to increase efficacy and reduce toxicity secondary to non-specific binding and off-target effects. Mechanistic studies show that SINE compounds induce nuclear localization and activation of multiple tumor suppressor proteins (TSPs), along with reduction in oncoprotein levels (e.g., c-Myc and the anti-apoptotic protein BCL-XL) leading to rapid apoptosis of MM cells.

Selinexor is an orally bioavailable SINE compound that specifically blocks XPO1, with anti-MM activity demonstrated in preclinical studies. In a phase 1 clinical trial (NCT01607892) of selinexor in patients with advanced hematological malignancies, 25 patients with heavily pretreated MM (22) or Waldenstrom macroglobulinemia (3) were administered selinexor (3-60 mg/m^2) in 8 or 10 doses per 28-day cycle.[11] In the dose-expansion phase, 59 patients with MM received selinexor at 45 or 60 mg/m^2 with dexamethasone 20 mg, twice weekly in 28-day cycles, or selinexor (40 or 60 mg flat dose) without corticosteroids in 21-day cycles. The most common non-hematologic adverse events (AEs) were nausea (75%), fatigue (70%), anorexia (64%), vomiting (43%), weight loss (32%), and diarrhea (32%), which were primarily grade 1 or 2. The most common grade 3 or 4 AEs were hematologic, particularly thrombocytopenia (45%). Single-agent selinexor showed modest efficacy with an objective response rate (ORR) of 4% and a clinical benefit rate of 21%. In contrast, the addition of dexamethasone increased the ORR with all responses of greater than partial response occurring in the 45 mg/m^2 selinexor plus dexamethasone 20 mg twice weekly cohort (ORR = 50%). Furthermore, 46% of all patients showed a reduction in MM markers from baseline. These findings demonstrated the activity of selinexor in combination with dexamethasone in heavily pretreated MM.

In a phase 2 clinical trial (NCT02336815), 122 patients with triple-class refractory MM received selinexor (80mg) and dexamethasone (20mg) twice weekly.[9] A partial response or better was observed in 26% of patients, including two stringent complete responses; 39% of patients had a minimal response or better. The median duration of response was 4.4 months, median progression-free survival was 3.7 months, and median overall survival was 8.6 months. Fatigue, nausea, and decreased appetite were common and were typically grade 1 or 2 (grade 3 events were noted in up to 25% of patients, and no grade 4 events were reported). Thrombocytopenia occurred in 73% of the patients (grade 3 in 25% and grade 4 in 33%). Thrombocytopenia led to bleeding events of grade 3 or higher in 6 patients. This trial showed that the combination of selinexor with dexamethasone resulted in objective treatment responses in patients with triple-class refractory multiple myeloma.

The phase 1/2 clinical trial of selinexor in combination with backbone treatments for relapsed/refractory multiple myeloma (STOMP; NCT02343042) is currently evaluating the efficacy and safety of multiple combinations. Preliminary results from the cohort of patients receiving selinexor, pomalidomide and dexamethasone were presented at the 61st American Society of Hematology Annual Meeting on December 7, 2019.[10] Oral selinexor was evaluated in a once-weekly or twice-weekly schedule with low-dose dexamethasone and escalating doses of pomalidomide 2, 3 or 4 mg PO (days 1-21). Fifty-one patients with relapsed/refractory multiple myeloma had been enrolled. Common hematologic treatment-related adverse events (TRAEs) included neutropenia, thrombocytopenia, anemia, and leukopenia; while non-hematologic TRAEs included nausea, fatigue, decreased appetite, weight decreased, diarrhea, and vomiting. Lower rates of ≥grade 3 thrombocytopenia (27% vs 44%) were observed in the weekly vs twice-weekly dosing. Among 46 evaluable patients for efficacy, the ORR was 50% (56% in patients

who were pomalidomide-naïve), 15% achieved a VGPR, and the median PFS was 10.4 months (12.2 months in patients who were pomalidomide-naïve). Once-weekly selinexor can be safely combined with pomalidomide and low-dose dexamethasone in heavily pretreated patients with MM. The recommended phase 2 dose was defined as selinexor 60mg once-weekly, pomalidomide 4mg daily (days 1-21) and dexamethasone 40 mg once-weekly.

On July 3, 2019, the Food and Drug Administration granted accelerated approval to selinexor in combination with dexamethasone for adult patients with relapsed/refractory multiple MM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

2.4.2.2 Clarithromycin

The semisynthetic macrolide antibiotic, clarithromycin, is indicated for the treatment of mild to moderate infections caused by susceptible bacteria. In the treatment of patients with multiple myeloma, clarithromycin has resulted in deep responses when added to dexamethasone in combination with thalidomide, lenalidomide or pomalidomide.[3-8] It optimizes the pharmacologic effects of glucocorticoids by increasing the area under the curve and the maximum concentration levels of some steroids through inhibition of CYP3A4.[12] It has an immunomodulatory effect and may have direct antineoplastic properties by synergistically decreasing the secretion of tumor necrosis factor-α and interleukin-6 through the inhibition of ERK1/2 and AKT in combination with other immunomodulatory drugs like thalidomide and lenalidomide.[13] Other studies have suggested that clarithromycin inhibits autophagy, increasing the cytotoxic effect of immunomodulatory drugs on MM cells.[14]

The phase 2 clinical trial (NCT00151203) evaluated the safety and efficacy of combination therapy with clarithromycin, lenalidomide and dexamethasone for the treatment of newly diagnosed MM.[7] Of 72 patients enrolled, 90% achieved an objective response of which 39% were CR or better, and an actuarial 2-year event-free survival of 97%. The most common grade ≥3 hematologic AEs were neutropenia (19.4%), anemia (13.8%), and thrombocytopenia (22.2%); common non-hematologic grade ≥3 AEs were myopathy (11.1%), rash (5.6%), diverticular abscess (5.6%), and thromboembolic events (12.5%).

A case–matched study compared the addition of clarithromycin to lenalidomide and dexamethasone vs lenalidomide and dexamethasone for the treatment of newly diagnosed myeloma.[4] It retrospectively analyzed the data obtained for the 72 patients enrolled in the above study and 72 pair mates selected among patients seen at the Mayo Clinic who received lenalidomide and dexamethasone. On an intention-to-treat analysis, CR rates (45.8% vs 13.9%, $p<0.001$) and ≥VGPR rates (73.6% vs 33.3%, $p<0.001$) were significantly higher with the addition of clarithromycin. Time-to-progression (median 48.3 vs 27.5 months, $p=0.071$), and progression-free survival (median 48.3 vs 27.5 months, $p=0.044$) also favored the addition of clarithromycin, however, overall survival was similar between both groups (3-year OS: 89.7% vs 73.0%, $p=0.17$).

A phase 3 clinical trial (NCT02575144) randomized 286 patients with newly diagnosed MM, transplant ineligible, to receive lenalidomide (daily for 21 days every 28 days) and weekly dexamethasone with or without twice-daily clarithromycin.[15] The preliminary results were presented at the 61st American Society of Hematology Annual Meeting on December 9, 2019. The addition of clarithromycin to lenalidomide and dexamethasone significantly increased the depth of response (≥CR 21% vs 11%; $p = 0.037$) but it was not associated with an improved

PFS and OS due to a higher proportion of treatment-related deaths in the clarithromycin-containing arm, mostly infectious, and affecting primarily patients ≥75 years of age.

The addition of clarithromycin to pomalidomide and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma previously exposed to lenalidomide was evaluated in a phase 2 study (NCT01159574).[6] The median number of prior therapies was 5 (range 3-15). The overall response rate (ORR) was 60% with 23% achieving at least a very good partial response. The median PFS was 7.7 months and the median overall survival was 19.2 months. The most common grade ≥3 toxicities included neutropenia (58%), thrombocytopenia (31%), and anemia (28%).

2.4.2.3 Pomalidomide

Pomalidomide is an immunomodulatory drug approved for the treatment of patients with RRMM. In combination with dexamethasone, pomalidomide has been shown to be effective in patients with relapsed/refractory MM previously treated with bortezomib and/or lenalidomide, with ORR ranging from 31 to 47% (ORR pooled estimate 35%; 95% confidence interval: 30-42%).[16-20] Toxicity is mostly hematologic, with grade ≥3 neutropenia occurring in 40-48%, anemia in 22-33%, and thrombocytopenia in 19-22%; while non-hematologic grade ≥3 toxicity included pneumonia (13-22%) and fatigue (5-14%).[19,20]

More recently, multiple phase 2 and 3 clinical trials have demonstrated the efficacy of three-drug regimens including pomalidomide and dexamethasone in combination with clarithromycin (ORR 60%), carfilzomib (ORR 62%), ixazomib (ORR 48%), cyclophosphamide (ORR 51-65%), elotuzumab (ORR 53%), daratumumab (ORR 60%), or isatuximab (ORR 60%) (ORR pooled estimate 58%; 95% confidence interval: 54-62%).[6,21-27] These studies reported a median PFS of 7.7 to 11.5 months (median 9.9 months).

2.4.3 Assessment of Potential Risks and Benefits

Effective therapies for patients with relapsed/refractory MM remain a current and growing unmet medical need. Based on the previously described results of combination therapy with clarithromycin, pomalidomide and dexamethasone in patients with RRMM and the preliminary results of selinexor in combination with pomalidomide and dexamethasone, we propose the addition of selinexor to clarithromycin, pomalidomide and dexamethasone for the treatment of patients with RRMM. The risks associated with participation in this trial are commensurate with the expected risks of other potential therapies in the same setting and are reasonable given the potential benefit to patients. If the addition of selinexor to clarithromycin, pomalidomide and dexamethasone is as effective in patients with RRMM as anticipated, the achievement of deeper and more durable responses with an all-oral regimen could lead to improved survival and quality of life.

2.5 Correlative Studies Background

Not applicable.

3. Study Design

3.1 Overall Design

This is a phase 2, open-label, single-arm study to assess the efficacy and safety of selinexor in combination with clarithromycin, pomalidomide and dexamethasone (ClaSPd) in patients with RRMM previously treated with at least one line of therapy.

We hypothesize the addition of selinexor to clarithromycin, pomalidomide and dexamethasone will increase the overall response rate of patients with RRMM. Patients who sign informed consent and fulfill all eligibility criteria will be enrolled. A Simon's two-stage design will be used. In the first stage, 18 patients will be accrued. If there are 6 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 26. The null hypothesis that the true ORR is ≤ 35% will be tested against a one-sided alternative that the true ORR ≥ 60% (see Background section for further details regarding a pooled estimate of the ORR in studies of pomalidomide-containing two- and three-drug regimens). The null hypothesis will be rejected if 14 or more responses are observed in 26 patients.

Study treatment – selinexor, clarithromycin, pomalidomide and dexamethasone (ClaSPd):

Selinexor 60 mg PO on days 1, 8, and 15 of a 28-day cycle.
Clarithromycin 500 mg PO twice a day on days 1-28 of a 28-day cycle.
Pomalidomide 4 mg PO daily on days 1-21 of a 28-day cycle.
Dexamethasone 40 mg PO on days 1, 8, 15 and 22 of a 28-day cycle.

At the end of every cycle (which may coincide with day 1 of the next cycle), response and toxicity will be evaluated. Patients will receive the study treatment until disease progression, death, or toxicity that cannot be managed with medical care. Safety analyses will be performed on patients who received at least one dose of the study treatment.

Subjects will be screened and enrolled at Weill Cornell Medicine in New York, NY. There is no intention to include sites outside of the United States.

3.2 Scientific Rationale for Study Design

A two-stage design has been selected to in order to allow for the early termination of the trial when the treatment seems to be inactive, minimizing the number of subjects exposed to the therapy. This is an open-label, single-arm study without a control group, designed to explore the efficacy and safety of ClaSPd for the treatment of patients with RRMM previously treated with two to four prior lines of therapy. ClaSPd allows for the addition of the recently approved agent, selinexor, to the combination of clarithromycin, pomalidomide and dexamethasone, an effective regiment for the treatment of RRMM.

3.3 Justification for Dose

The selected dose of selinexor, pomalidomide and dexamethasone was derived from preliminary efficacy and safety data of the expansion phase of arm 1 of STORM (NCT02343042), as noted above. The dose of clarithromycin is in accordance to prior studies, including phase 3 randomized clinical trial (NCT02575144) evaluating lenalidomide and weekly dexamethasone with or without twice-daily clarithromycin, as well as the addition of clarithromycin to pomalidomide and dexamethasone (NCT01159574); further details of these studies have been noted above.

3.4 End of Study Definition

A participant is considered to have completed the study after completing all phases of the study including the last duration of response/survival follow-up assessment as stated in the Schedule of Activities (SoA). The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. Subject Selection

4.1 Study Population

Adult subjects (18 to 74 years of age) with a diagnosis of RRMM who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥18 and <75 years at the time of informed consent.
3. Histologically confirmed diagnosis of MM.
4. Symptomatic MM as per IMWG guidelines.
5. Measurable disease as defined by at least one of the following:
    a. Serum M-protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP) or, for IgA myeloma, by quantitative IgA, and/or
    b. Urinary M-protein excretion at least 200 mg/24 hours, and/or
    c. Serum FLC ≥ 100 mg/L, provided that FLC ratio is abnormal, and/or
    d. If serum protein electrophoresis is felt to be unreliable for routine M-protein measurement (e.g., for IgA MM), then quantitative Ig levels by nephelometry or turbidometry are acceptable.
6. Relapsed and refractory MM with:
    a. Documented evidence of PD after achieving at least SD for ≥ 1 cycle during a previous MM regimen (i.e., relapsed MM), and
    b. ≤ 25% response (i.e., patients never achieved ≥ MR) or PD during or within 60 days from the end of the most recent MM regimen (i.e., refractory MM).
7. Previously received two to four prior lines of therapy and be pomalidomide-naïve.

4.3 Exclusion Criteria

1. Documented active systemic light chain amyloidosis.
2. Active plasma cell leukemia.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status greater than 2.
4. Persistent non-hematological toxicity (except for peripheral neuropathy) from a prior treatment which has not resolved to at least Grade 2 or better by Cycle 1 Day 1 (C1D1).
5. Severe hepatic dysfunction with either:
    a. Total bilirubin > 1.5x ULN (> 3x ULN in subjects with Gilbert's syndrome [hereditary indirect hyperbilirubinemia]), and/or
    b. AST and/or ALT > 2.5x ULN
6. Severe renal dysfunction with an estimated creatinine clearance (CrCl) of < 15 mL/min calculated using the Cockcroft and Gault formula.
7. Impaired hematopoietic function with either:
    a. White blood cell count < 1,500/mm^3, and/or

   b. Absolute neutrophil count < 1000/mm^3, and/or
   c. Hemoglobin < 8.0 g/dL, and/or
   d. Platelet count < 100,000/mm^3 (for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells, platelets ≥ 75,000/mm^3 are acceptable).
8. Blood (or blood product) transfusions or blood growth factors within 7 days of C1D1.
   a. Use of hematopoietic growth factor support is acceptable, including erythropoietin (EPO), darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), and platelet stimulators (e.g., eltrombopag or romiplostim). However, patients must be platelet transfusion independent for > 1 week in order to be enrolled in the study.
9. Radiation, chemotherapy or immunotherapy, or any other anticancer therapy within 2 weeks prior to C1D1, or radio-immunotherapy within 6 weeks prior to C1D1. Patients on long-term glucocorticoids during Screening do not require a washout period. Prior radiation is permitted for treatment of fractures or to prevent fractures, as well as for pain management.
10. Patients with history of spinal cord compression with residual paraplegia.
11. Treatment with an investigational anti-cancer therapy within 3 weeks prior to C1D1.
12. Prior autologous stem cell transplantation < 1 month, or allogeneic stem cell transplantation < 3 months prior to C1D1.
13. Active graft versus host disease after allogeneic stem cell transplantation.
14. Life expectancy < 3 months.
15. Major surgery within 4 weeks prior to C1D1.
16. Active, unstable cardiovascular function with either:
   a. Symptomatic ischemia
   b. Uncontrolled clinically significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded)
   c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3
   d. Myocardial infarction (MI) within 6 months prior to C1D1
   e. Screening 12-lead ECG showing a baseline QT interval as corrected by Bazett's formula (QTc) > 470 msec
17. Uncontrolled active hypertension
18. Venous thromboembolism within 6 months prior to C1D1 or a known inherited thrombophilia
19. Inability to receive either prophylactic or therapeutic anticoagulation as determined appropriate by the Investigator
20. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to C1D1
21. Any active gastrointestinal dysfunction that prevents the patient from swallowing tablets or interferes with absorption of study treatment
22. Currently pregnant or breastfeeding. Lactating females must agree not to breast feed while receiving selinexor, pomalidomide and/or clarithromycin
23. A serious psychiatric or medical condition which, in the opinion of the Investigator, could interfere with treatment
24. Hypersensitivity or contraindication to selinexor, pomalidomide, dexamethasone and/or clarithromycin
25. Prior exposure to a SINE compound, including selinexor
26. Concomitant use of any strong CYP3A4 and/or CYP1A2 inhibitors (see Appendix 1) or other restricted drugs (see section 7.8.11)

27. Unable to obtain commercial clarithromycin, pomalidomide and dexamethasone through a regular and/or specialty pharmacy.
28. Unable or unwilling to register into the mandatory POMALYST REMS™ program and comply with its requirements.
29. Male and female patients unwilling or unable to use effective methods of contraception throughout the study and for three months following the last dose. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal.
    a. Female patients of childbearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at Screening.
    b. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential.

4.4 Lifestyle Considerations

Not applicable.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of impaired liver, renal or hematopoietic function may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Participants will be recruited by their primary oncologist at Weill Cornell Medicine and NewYork Presbyterian-Brooklyn Methodist Hospital. We estimate a study sample size of 26 participants without gender, race, ethnicity or age targets, and an anticipated accrual rate of 2 subjects per month.

Potential participants will be identified by their primary oncologist and approached by a co-investigator; the study coordinators will keep records of monthly screening and enrollment logs at each site. No other recruitment strategies are planned. Vulnerable participants are not eligible for this study. Participants will receive a $50 stipend for each completed study visit at Weill Cornell Medicine and NewYork Presbyterian-Brooklyn Methodist Hospital. The stipend will be provided via Clincard.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Study participants will be centrally registered with the Weill Cornell Medicine Joint Clinical Trials Office (JCTO). To register a new study subject, email the following documents to JCTOIIT@med.cornell.edu :

- Completed WCM subject registration form
- First and last page of the fully executed informed consent form, plus additional pages if checkboxes for correlative studies are required
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Source documentation to verify eligibility

Note that attachments larger than 4.5 MB are not accepted, so larger attachments should be split into more than one email. Central registration information is reviewed and entered into the REDCap database.

6. Study Procedures

6.1 Schedule of Assessments

Table 2. Schedule of Activities (SOA)

Activity/ Assessment	Screening	C 1			C 2		C ≥ 3	EoT Visit	FU Assessment	DOR and Survival FU
	D-21 to D-1	D1	D8 ± 1d	D15 ± 1d	D1 ± 2d	D15 ± 2d	D1 ± 2d	≤14d after LD	30d after LD ± 7d	every 3m after LD for 12m ± 14d
Informed consent	X									
Medication dispensation (1)		X			X		X			
Patient History										
Inclusion and exclusion criteria	X									
Demographics	X									
Medical history (2)	X									
Adverse events	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X			X		X	X		
Dose intensity (3)		X			X		X	X		

QOL assessment (4)	X	X			X		X	X	X	
Telephone contact (5)									X	X
Physical Examination										
Patient height	X									
Patient weight	X	X	X	X	X	X	X	X		
Vital signs (BP, pulse, temperature)	X	X	X	X	X	X	X	X		
Complete physical examination	X							X		
Symptom-directed physical examination		X	X	X	X	X	X			
12-lead ECG	X									
ECOG Performance Status	X				X		X	X		
Clinical Labs										
CBC with differential	X	X	X	X	X	X	X	X		
TSH	X									
Complete serum chemistry (6)	X	X	X	X	X	X	X	X		
Pregnancy test (7)	X	X			X		X	X		
Multiple Myeloma Disease Assessments										
SPEP and serum immunofixation (8)	X	X			X		X	X		X*
UPEP (24-hr urine) and urine immunofixation (8)	X	X*			X		X	X		X*
Quantitative Ig levels (8)	X	X			X		X	X		X*
Serum FLC (8)	X	X			X		X	X		X*
β2-microglobulin	X									
Skeletal survey (9)	X				X*		X*	X*		X*
Plasmacytoma assessment (10)	X	X*			X*		X*	X*		X*
Bone marrow biopsy and aspirate (11)	X				X*		X*	X*		

* indicates that additional schedule information is provided in the footnotes. Merged cells indicate that the procedure may be performed during either Screening or the C1D1 visit. Abbreviations: BP = blood pressure; BSA = body surface area; CBC = complete blood count; D = day; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = End of Treatment; FLC = free light chain; FU = follow-up; Ig = immunoglobulin; LD = last dose; M = month; MM = multiple myeloma; QOL = quality of life; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; Y = year.

Footnotes:

1. Only enough selinexor for 1 cycle will be provided to the patient at the beginning of each cycle.

2. Includes baseline symptoms as well as a detailed history of prior cancer therapies, especially MM therapies, including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness. Collect data on cigarette smoking status and, if current smoker, counsel regarding smoking cessation per institutional guidelines.
3. Dose intensity assessments involve the use of subject medication diaries, provided on C1D1 and assessed on day 1 of every cycle beginning at cycle 2.
4. QOL assessment as measured by the Functional Assessment of Cancer Therapy - MM (FACT-MM). See Appendix 6.
5. Telephone call (or visit) for:
    a. Follow-up assessment to evaluate adverse events.
    b. Durability of Response and Survival Follow-up: After treatment discontinuation, if possible and feasible for patients whose disease is not progressing, a telephone call will be made to the patient (or the patient's family) every 3 months for 18 months to inquire about the patient's survival, MM status, and information on any antineoplastic therapies utilized since discontinuation of study treatment, as well as available SPEP with serum immunofixation, UPEP with urine immunofixation, serum FLC, quantitative Ig levels, and plasmacytoma assessment when clinically appropriate.
6. Complete serum chemistry must include serum potassium and magnesium levels.
7. For women of childbearing potential, a serum hCG pregnancy test must be performed during Screening and at EoT Visit. After an initial negative serum hCG pregnancy test during Screening, urine pregnancy tests may be performed instead of serum testing. Women of childbearing potential require two negative pregnancy tests prior to receiving the first dose of study treatment (at Screening and at C1D1).
8. Response criteria include SPEP, serum immunofixation, quantitative Ig levels, and serum FLC assay on C1D1 and measurements must be taken either on Day -1 or pre-dose on C1D1. These are in addition to the disease assessments performed during Screening for enrollment. UPEP (24-hr urine) and urine immunofixation may be omitted on C1D1 if performed adequately during screening within ≤ 7 days.
9. Skeletal survey to be performed using X-rays, MRI, CT or PET/CT per institutional guidelines. Bone lesions seen at Screening should be re-assessed during the study using the same imaging modality that was used at Screening. Repeat scans should be done at a clinically appropriate frequency, as determined by the Investigator.
10. If plasmacytomas are detected at baseline by physical examination, they should be re-assessed during the physical exam on D1 of each cycle and at the EoT visit.
11. Bone marrow samples:
    a. At Screening, aspirate and biopsy for:
        i. Morphology, flow cytometry and FISH analysis to confirm diagnosis and classification
        ii. Clonotype identification for subsequent MRD analysis
    b. At suspicion of CR (negative serum and urine immunofixation), aspirate and biopsy for:
        i. Morphology, flow cytometry and FISH analysis to confirm CR and/or sCR
        ii. Aspirate for MRD analysis
    c. At suspicion of progressive disease, if clinically appropriate, aspirate and biopsy for:
        i. Morphology, flow cytometry and FISH analysis to confirm progressive disease

6.1.1 Screening Visit (*-21 to -1 days before start of treatment*)

- Informed consent
- Inclusion and exclusion criteria
- Demographics
- Medical history
- Adverse events
- Concomitant medications
- QOL assessment
- Height
- Weight
- Vital signs
- Complete physical exam
- 12-lead ECG (may be performed on C1D1)
- ECOG PS (may be performed on C1D1)
- CBC with differential
- TSH (may be performed on C1D1)
- Complete serum chemistry
- Pregnancy test
- SPEP and serum immunofixation
- UPEP (24-hr urine) and urine immunofixation
- Quantitative Ig levels
- Serum FLC
- LDH and β2-microglobulin
- Skeletal survey
- Plasmacytoma assessment
- Bone marrow biopsy and aspirate

6.1.2 Treatment Phase

6.1.2.1 Visit 1 (baseline; Cycle 1 Day 1)

- Medication dispensation
- Adverse events
- Concomitant medications
- Dose intensity
- QOL assessment
- Weight
- Vital signs
- Symptom-directed physical exam
- 12-lead ECG (may be performed on Screening visit)
- ECOG PS (may be performed on Screening visit)
- CBC with differential
- TSH (may be performed on Screening visit)
- Complete serum chemistry
- Pregnancy test

- SPEP and serum immunofixation
- UPEP (24-hr urine) and urine immunofixation
- Quantitative Ig levels
- Serum FLC
- Skeletal survey
- Plasmacytoma assessment

6.1.2.2 Visit 2 (Cycle 1 Day 8 ± 1 day)

- Adverse events
- Weight
- Vital signs
- Symptom-directed physical exam
- CBC with differential
- Complete serum chemistry

6.1.2.3 Visit 3 (Cycle 1 Day 15 ± 1 day)

- Adverse events
- Weight
- Vital signs
- Symptom-directed physical exam
- CBC with differential
- Complete serum chemistry

6.1.2.4 Visit 4 (Cycle 2 Day 1 ± 2 days)

- Medication dispensation
- Adverse events
- Concomitant medications
- Dose intensity
- QOL assessment
- Weight
- Vital signs
- Symptom-directed physical exam
- ECOG PS
- CBC with differential
- Complete serum chemistry
- Pregnancy test
- SPEP and serum immunofixation
- UPEP (24-hr urine) and urine immunofixation
- Quantitative Ig levels
- Serum FLC
- Skeletal survey*
- Plasmacytoma assessment*
- Bone marrow biopsy and aspirate*

6.1.2.5 Visit 5 (Cycle 2 Day 15 ± 2 days)

- Adverse events
- Weight
- Vital signs
- Symptom-directed physical exam
- CBC with differential
- Complete serum chemistry

6.1.2.6 Visit ≥ 6 (Cycle ≥ 3 Day 1 ± 2 days)

- Medication dispensation
- Adverse events
- Concomitant medications
- Dose intensity
- QOL assessment
- Weight
- Vital signs
- Symptom-directed physical exam
- ECOG PS
- CBC with differential
- Complete serum chemistry
- Pregnancy test
- SPEP and serum immunofixation
- UPEP (24-hr urine) and urine immunofixation
- Quantitative Ig levels
- Serum FLC
- Skeletal survey*
- Plasmacytoma assessment*
- Bone marrow biopsy and aspirate*

6.1.2.7 End of Treatment Visit (≤ 14 days after last dose)

- Adverse events
- Concomitant medications
- Dose intensity
- QOL assessment
- Weight
- Vital signs
- Complete physical exam
- ECOG PS
- CBC with differential
- Complete serum chemistry
- Pregnancy test
- SPEP and serum immunofixation
- UPEP (24-hr urine) and urine immunofixation
- Quantitative Ig levels

- Serum FLC
- Skeletal survey*
- Plasmacytoma assessment*
- Bone marrow biopsy and aspirate*

6.1.3 Follow-up Phase

6.1.3.1 Follow Up Assessment (30 days after last dose ± 7 days)

- Adverse events
- QOL assessment
- Telephone contact

6.1.3.2 Duration of Response and Survival (every 3 months ± 14 days after last dose for 12 months)

- Telephone contact
- SPEP and serum immunofixation
- UPEP (24-hr urine) and urine immunofixation
- Quantitative Ig levels
- Serum FLC
- Skeletal survey*
- Plasmacytoma assessment*
- Bone marrow biopsy and aspirate*

7. Study Intervention

7.1 Study Intervention/Device Description

The following drugs will be used in this study:

7.1.1 Selinexor

Provided as coated, immediate-release 20 mg tablets for oral administration in wallet-sized blister packs. Karyopharm Therapeutics Inc. will supply selinexor at no charge and ship it to each site. Selinexor will be dispensed from the investigational pharmacy at each site and participants will be provided with only enough tablets for one cycle on the first day of each cycle. For information regarding storage, handling, precautions and contraindications, please refer to the package insert.

7.1.2 Clarithromycin

Patients will receive a prescription for clarithromycin 250 or 500 mg tablets (generic) for oral administration. Study participants will obtain this drug at their local pharmacy. For information regarding storage, handling, precautions and contraindications, please refer to the package insert.

7.1.3 Pomalidomide

Patients will receive a 21-day supply of pomalidomide 1, 2, 3, or 4 mg capsules for oral administration, as appropriate, for each 28-day treatment cycle. The investigator will enter an electronic prescription for pomalidomide after the study participant enrolls in the POMALYST REMS program. A specialty pharmacy will ship pomalidomide to the study participant's home. For information regarding storage, handling, precautions and contraindications, please refer to the package insert.

7.1.4 Dexamethasone

Patients will receive a prescription for dexamethasone 4 mg tablets (generic) for oral administration. Study participants will obtain this drug at their local pharmacy. For information regarding storage, handling, precautions and contraindications, please refer to the package insert.

7.2 Availability

Selinexor is an FDA approved drug which will be supplied to investigators by Karyopharm Therapeutics Inc. Commercial co-therapies will be obtained by the study participant through retail and/or specialty pharmacies.

7.3 Acquisition and Accountability

Selinexor will be provided by Karyopharm Therapeutics Inc. Commercial co-therapies will be obtained by the study participant. All co-therapies should be reimbursed by insurance or designated healthcare systems. Study drug accountability records will be maintained at the site pharmacy and will be available for review. Drug accountability is to be performed on selinexor only. "All-selinexor" accountability must be reviewed by the study monitor prior to destruction or return shipment.

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of selinexor using the NCI Drug Accountability Record or another comparable drug accountability form. Available at the Cancer Therapy Evaluation Program website at http://ctep.cancer.gov/ protocol development for the "Policy and Guidelines for Accountability and Storage of Investigational Agents".

Selinexor will be ordered through DRIVE, Endpoint's supply management engine. Drug ordering instructions have been provided by Karyopharm Therapeutics, along with recommended initial and resupply stock orders. Orders submitted via DRIVE will be filled by Karyopharm Therapeutics within 5 business days of receipt.

At the end of the study, unused supplies of selinexor should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.4 Formulation, Appearance, Packaging, and Labeling

Selinexor is a Selective Inhibitor of Nuclear Export (SINE) compound. Selinexor specifically blocks nuclear export by binding to the nuclear export protein XPO1.

The chemical name is: (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-N'-(pyrazin-2-yl)acrylohydrazide

The molecular formula is: C17H11F6N7O.

The molecular weight is: 443.31.

Each Selinexor drug container will be labeled in accordance with current International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and specific regulatory requirements, e.g., FDA, Health Canada (HC), European Medicines Agency (EMA), etc. Containers for take-home use may require additional in-pharmacy labeling with take-home and patient-specific instructions (such as exact dose) depending on country-specific regulations or laws. All treatments will be labeled in accordance with current ICH, GCP, FDA, HC, and EMA regulations and guidelines. Labels will include the medication name, storage conditions, and batch number, and will comply with language and legal requirements of Canada, EU, and the US.

Selinexor will be supplied and administered as coated, immediate-release 20 mg oral tablets in wallet-sized blister packs.

Further information for Selinexor, as well as clarithromycin, pomalidomide and dexamethasone can be found on their respective package insert.

7.5 Product Storage and Stability

Selinexor tablets should be stored in a locked and secured area with access restricted to the site staff pharmacist or designee(s) at or below 30˚C (86˚F). Room temperature storage is recommended, refrigerated is acceptable. Tablets should not be stored frozen.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Selinexor tablets are coated for ease of use and handling. Tablets should not be broken or crushed due to increased risk of dermal exposure and/or toxicities.

All other study medications should be stored as described on their respective package insert.

7.6 Preparation

No special preparation required. Tablets of selinexor should not be crushed because of increased risk of dermatologic toxicity if powder comes in contact with skin.

7.7 Dosing and Administration

For doses of study medication that are to be taken on non-clinic days, the patient will be provided with selinexor by the investigational pharmacy, and clarithromycin, pomalidomide and dexamethasone by their local and/or specialty pharmacy.

The doses of study treatments for individual patients should remain constant throughout the study, except for allowed dose modifications.

Study medications will be dosed according to the schedule provided below. For doses of oral medications to be taken on non-clinic days, patients will either be provided with medication to take home or with a prescription to obtain the medication from their local and/or specialty pharmacy.

Selinexor should be given with at least 120 mL (4 ounces) of fluids (water, milk, etc.).

Dexamethasone should be administered at least one hour before selinexor. In general, where possible, each drug should be given at least 1-2 hours apart, however the sequence and times of administration are per the Investigator's discretion.

Clarithromycin, pomalidomide, and dexamethasone should be administered in a manner consistent with each product's approved labeling.

Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.

Missed doses of Selinexor should be managed as follows:

- If a dose was missed, the schedule of that week should be altered to accommodate one dose in that week with at least 36 hours between two consecutive doses.
- If a dose must be skipped (e.g., due to recommendation of treating physician), the next dose will be taken as per schedule. Doses should not be administered less than 36 hours apart and all missed and delayed doses should be documented.

If a patient missed a full one-week period of dosing for non-study drug-related events (e.g., a required medical procedure or an unanticipated personal emergency), the days missed will be replaced.

If a dose is vomited within 1 hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

All patients will receive selinexor, clarithromycin, pomalidomide and dexamethasone in 28-day cycles according to the following schedule:

Selinexor will be given orally at a dose of 60 mg on days 1, 8, and 15 of a 28-day cycle.
Clarithromycin will be given orally at a dose of 500 mg twice a day on days 1-28 of a 28-day cycle.
Pomalidomide will be given orally at a dose of 4 mg daily on days 1-21 of a 28-day cycle.

Dexamethasone will be given orally at a dose of 40 mg on days 1, 8, 15 and 22 of a 28-day cycle.

7.7.1 Dosing Delays/Dose Modifications

In order to optimize specific anti-tumor activity and tolerability, dose reductions and/or schedule modifications will be allowed. Patients should also be treated aggressively with supportive care to reduce toxicities. Doses must be adjusted for adverse events deemed related to study drug by the Investigator. Doses may be adjusted for adverse events related to study medications not listed below at the discretion of the Investigator.

Toxicity will be graded according to CTCAE v.5.0; the therapy modifications described below are to be applied according to severity grading. If more than one type of AE occurs concurrently, the most severe grade will determine the modification. Each dose modification or treatment delay must be documented, including the respective reason. Re-escalation of selinexor is allowed as outlined in Table 3. If drug-related toxicity requires a treatment delay of more than 28 days, the patient will be taken off study treatment. For all ≥ Grade 3 hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained.

Table 3 summarizes the study treatment dose levels; Table 4 describes supportive care and dose adjustment guidelines. General supportive care recommendations are provided below. Deviations from the guidelines are permitted after discussion between the PI and the treating physician.

In patients with renal impairment, start each drug at the following dose level:

1) Selinexor:
   (a) CrCl ≥15 mL/min: There are no dosage adjustments provided in the manufacturer's labeling.
   (b) CrCl <15 mL/min: Patients with severe renal impairment are excluded from this study.
2) Clarithromycin:
   (a) CrCl ≥30 mL/minute: No dosage adjustment necessary.
   (b) CrCl 15-29 mL/minute: Decrease clarithromycin dose by 50% by starting at dose level -1.
   (c) CrCl <15: Patients with severe renal impairment are excluded from this study.
3) Pomalidomide:
   (a) CrCl ≥15 to <60 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling. Compared to patients with normal renal function, pomalidomide pharmacokinetics were not significantly altered in patients with CrCl between 15 to 60 mL/minute.
   (b) CrCl <15 mL/min: Patients with severe renal impairment are excluded from this study.
4) Dexamethasone:

(a) There are no dosage adjustments provided in the manufacturer's labeling. The International Myeloma Working Group (IMWG) recommendations suggest that dexamethasone may be administered without dosage adjustment in multiple myeloma patients with renal impairment.

In patients with hepatic impairment, start each drug at the following dose level:

1) Selinexor:
   (a) Mild impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, there are no clinically significant effects on selinexor pharmacokinetics.
   (b) Moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
   (c) Patients with severe hepatic impairment are excluded from this study.
2) Clarithromycin:
   (a) No dosage adjustment necessary if renal function is normal; however, in patients with hepatic impairment and concomitant severe renal impairment, a dosage reduction or prolonged dosing intervals may be appropriate, and patients should be started at dose level -1.
3) Pomalidomide:
   (a) Mild or moderate impairment (Child-Pugh class A or B): Start at dose level -1 (3 mg once daily).
   (b) Severe impairment (Child-Pugh class C): Patients with severe hepatic impairment are excluded from this study.
4) Dexamethasone:
   (a) There are no dosage adjustments provided in the manufacturer's labeling.

Table 3. Study Drug Dose Modification Guidance

Dose Level	Selinexor	Clarithromycin	Pomalidomide	Dexamethasone
0	60 mg on days 1, 8 and 15	500 mg twice daily	4 mg daily on days 1-21	40 mg on days 1, 8, 15 and 22
-1	40 mg on days 1, 8 and 15	500 mg once daily	3 mg daily on days 1-21	20 mg on days 1, 8, 15 and 22
-2	20 mg on days 1, 8 and 15	250 mg once daily	2 mg daily on days 1-21	20 mg on days 1 and 15

Table 4. Supportive Care and Dose Adjustment Guidelines

Toxicity	Grade	Dose Modification
Selinexor		

Fatigue	Grade 1 or Grade 2 lasting ≤ 7 days	Maintain dose. Rule out other causes of fatigue, particularly dehydration and anemia. If found to be anemic, consider transfusing for Hb < 8 g/dL. Institute supportive care medications per institutional guidelines. Consistent with the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO), the use of methylphenidate should be considered. Additional options are provided in the NCCN CPGO. Patients with significant fatigue after several doses of selinexor may have an ongoing anti-tumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.
	Grade 2 lasting > 7 days or Grade 3	Interrupt selinexor dosing. Monitor until fatigue resolves to Grade 1 or baseline and restart selinexor at 1 dose level lower. Institute supportive care medications as described above for Grade 1 or 2. Patients with significant fatigue after several doses of selinexor may have an ongoing anti-tumor response. If fatigue is significant, consider assessment of tumor response as part of the patient's evaluation.
Anorexia or Weight Loss	Grade 1	Maintain dose. Rule out other causes of anorexia. Nutritional consultation can be helpful. Consider instituting supportive care medications per institutional guidelines. Consistent with the NCCN CPGO, megesterol acetate 200-400 mg twice daily should be considered. Other options are provided in the NCCN CPGO.
	Grade 2	Rule out other causes of anorexia and order a nutritional consultation. Institute supportive care medications as described for Grade 1 anorexia or weight loss above. For additional options, see NCCN CPGO. Interrupt dosing with selinexor until improves to Grade 1 or baseline and weight stabilizes, then restart selinexor at 1 dose level lower.
	Grade 3	Nutritional consultation and supportive care medications for anorexia per institutional guidelines should already be instituted. For additional options, see NCCN CPGO. Interrupt dosing with selinexor until improves to Grade 1 or baseline and the weight stabilizes. Restart selinexor at 1 dose level reduction.
Nausea and/or Vomiting	Grade 1 or 2	Maintain dose. Rule out other causes of nausea. Patients should be receiving 5HT3 antagonists unless contra-indicated. For those patients who cannot receive 5HT3 antagonists, consider olanzapine per NCCN CPGO. For additional options, see NCCN CPGO.

		If intolerable or persistent Grade 2, follow guidelines for Grade 3.
	Grade 3	Supportive care medications per institutional guidelines should already be instituted. For additional options, see NCCN CPGO. Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline. Restart selinexor at 1 dose level lower. If nausea stabilizes for at least 4 weeks at Grade ≤ 1, may re-escalate to the original dose after consulting Medical Monitor.
Hyponatremia	Grade 1	Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mmol/L). Treat hyponatremia per institutional guidelines including dietary review. Consider addition of salt tablets to patient's diet.
	Grade 2	Correct for hyperglycemia as outlined under Grade 1. Treat hyponatremia per institutional guidelines. If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that intravenous saline and/or salt tablets (1-3 times daily) are provided. If Grade 2 is persistent or worsens or does not respond to treatment, dose interruptions may be considered after consulting with the Medical Monitor.
	Grade 3 or 4	Treat per institutional guidelines. Delay selinexor until sodium resolved to Grade ≤ 1 (≥ 130 mmol/L) then reduce selinexor dose by 1 level. If serum sodium stabilizes to Grade ≤ 1 for at least 4 weeks, may re-escalate to previous dose of selinexor.
Diarrhea	Grade 1 or 2	Initiate treatment for any Grade 1 diarrhea. Treat per institutional guidelines with antidiarrheals and maintain dosing. For persistent Grade 2 only that does not respond to anti-diarrheals within 3 days, interrupt selinexor dosing until resolved to Grade 1, then restart at the current dose level.
	Grade 3 or 4	Delay selinexor until resolved to Grade 1, then reduce selinexor dose by 1 dose level. If diarrhea stabilizes for at least 4 weeks at Grade ≤ 1, may re-escalate to previous dose of selinexor after consulting with the Medical Monitor.
Thrombocytopenia	Grade 1	Maintain dose.
	Grade 2 or 3 without bleeding	Consider platelet growth factors, e.g., romiplostim, which may take up to four weeks for an effect. Reduce selinexor at 1 dose level lower. Patients with stable platelet counts for ≥ 4 weeks following dose reduction may have their dose of selinexor increased by one dose level.

	Grade 4 without bleeding	Strongly consider platelet growth factors and transfuse per clinical practice/institutional guidelines. Delay dosing until recovery to ≤ Grade 2 or baseline and resume selinexor at 1 dose level lower.
	Grade 2 or 3 with bleeding	Delay dosing until the bleeding has stopped and the patient is clinically stable. Reduce selinexor at 1 dose level lower.
Neutropenia	Grade 3 or 4 Neutropenia without fever	Institute colony stimulating factors, and delay dosing with selinexor until ANC returns to Grade ≤ 2. Reduce selinexor by 1 dose level. After stabilization for at least 4 weeks, a re-escalation may be considered after discussing with the Medical Monitor.
	Grade 3 or 4 Neutropenia with fever	Institute colony stimulating factors, and delay dosing with selinexor until the patient's ANC returns to Grade ≤ 2 or baseline, fever has resolved, and patient's condition is stable. Reduce selinexor by 1 dose level.
Anemia	Grade 3	Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for Hb < 8 g/dL. Reduce selinexor by 1 dose level.
	Grade 4	Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for Hb < 8 g/dL. Delay dosing of selinexor until Hb is 8 g/dL or higher. Reduce selinexor by 1 dose level.
Ocular Toxicity	Grade 2, excluding cataract	Perform ophthalmologic evaluation. Interrupt selinexor and provide supportive care. Monitor until ocular symptoms resolve to Grade 1 or baseline. Restart selinexor at 1 dose level lower.
	Grade 3 or 4, excluding cataract	Permanently discontinue selinexor. Perform ophthalmologic evaluation.
Other Selinexor-related AEs	Grade 1 or 2	Maintain dose. Initiate standard supportive care per institutional guidelines.
	Grade 3	Delay dosing with selinexor until recovery to Grade ≤ 2 or baseline and resume selinexor at 1 dose level lower. Re-escalation can be considered after ≥ 4 weeks at the lower dose with reduction of the AE to Grade 1 or baseline.
	Grade 4	Delay dosing until resolved to Grade ≤ 2 or baseline, then resume at 1 dose level lower. If further dose reduction/interruption is desired, consultation with the Medical Monitor is required.
Clarithromycin		
Nausea and/or Vomiting	Grade 1 or 2	Maintain dose. Rule out other causes of nausea. Patients should be receiving 5HT3 antagonists unless contra-indicated. For those patients who cannot receive 5HT3 antagonists, consider olanzapine per NCCN CPGO. For additional options, see NCCN CPGO.

		If intolerable or persistent Grade 2, follow guidelines for Grade 3.
	Grade ≥ 3	Supportive care medications per institutional guidelines should already be instituted. For additional options see NCCN CPGO. If AE is thought to be due to clarithromycin, interrupt clarithromycin dosing until resolved to Grade ≤ 2 or baseline. For first occurrence of Grade 3, if adequate supportive care resulted in an improvement to Grade 1 or baseline within 3 days, restart clarithromycin at current dose. Otherwise (i.e., the recovery took longer than 3 days), restart clarithromycin at 1 dose level lower. If nausea stabilizes for at least 4 weeks at Grade ≤ 1, may re-escalate to the original dose after consulting Medical Monitor.
Other Clarithromycin-related Non-hematologic AEs	Grade ≥ 3	Hold (interrupt) clarithromycin and follow weekly. If toxicity has resolved to Grade ≤ 1, restart clarithromycin at next lower dose level.
Dexamethasone		
Dyspepsia, Gastritis, Gastric or Duodenal Ulcer	Grade ≥ 3	Hold (interrupt) dexamethasone and follow weekly. If toxicity has resolved to Grade ≤ 1, restart dexamethasone at next lower dose level.
Edema	Grade ≥ 3	Reduce the dose of dexamethasone by 1 dose level. Use diuretics as needed.
Agitation, Confusion, and/or other Psychiatric Disorder	Grade ≥ 2	Hold (interrupt) dexamethasone and follow weekly. If toxicity has resolved to Grade ≤ 1, restart dexamethasone at next lower dose level.
Generalized Muscle Weakness	Grade ≥ 3	Reduce the dose of dexamethasone by 1 dose level, if symptoms persist, continue to reduce the dose of dexamethasone by 1 dose level as needed until toxicity has resolved to Grade ≤ 2.
Hyperglycemia	Grade ≥ 3	Reduce the dose of dexamethasone by 1 dose level. Start insulin or other hypoglycemic therapy as needed.
Acute Pancreatitis	Grade ≥ 3	Discontinue dexamethasone. Remove patient from study.
Other Dexamethasone-related Non-hematologic AEs	Grade ≥ 3	Hold (interrupt) dexamethasone and follow weekly. If toxicity has resolved to Grade ≤ 1, restart dexamethasone at next lower dose level.
Pomalidomide		
	Onset day 1-14 of cycle	**Onset ≥ day 15 of cycle**

Neutropenia	Grade 3 without fever	Maintain dose.	Maintain dose.
	Grade 3 with fever or Grade 4	Hold (interrupt) pomalidomide and follow CBC weekly. If neutropenia has resolved to Grade ≤ 2 prior to day 21, restart pomalidomide at next lower dose level and continue the cycle through day 21. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the pomalidomide dose maintained.	Omit pomalidomide for the remainder of cycle. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the pomalidomide dose maintained for the next cycle at the Investigators discretion.
Thrombocytopenia	Grade 1 or 2	Maintain dose.	Maintain dose.
	Grade 3 or 4	Hold (interrupt) pomalidomide and follow CBC weekly. If thrombocytopenia has resolved to Grade ≤ 2 prior to day 21, restart pomalidomide at next lower dose level and continue the cycle through day 21.	Omit pomalidomide for the remainder of cycle. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.
Non-blistering rash	Grade 3	Hold (interrupt) pomalidomide and follow weekly. If toxicity has resolved to Grade ≤ 1 prior to day 21, restart pomalidomide at next lower dose level and continue the cycle through day 21.	Omit pomalidomide for the remainder of cycle. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.
	Grade 4	Discontinue pomalidomide. Remove patient from study.	Discontinue pomalidomide. Remove patient from study.
Desquamating (blistering) rash	Any grade	Discontinue pomalidomide. Remove patient from study.	Discontinue pomalidomide. Remove patient from study.
Neuropathy	Grade 3	Hold (interrupt) pomalidomide and follow weekly. If toxicity has resolved to Grade ≤ 1 prior to day 21, restart pomalidomide at next lower	Omit pomalidomide for the remainder of cycle. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.

		dose level and continue the cycle through day 21.	
	Grade 4	Discontinue pomalidomide. Remove patient from study.	Discontinue pomalidomide. Remove patient from study.
Thromboembolic event	Grade 3 or 4	Hold (interrupt) pomalidomide and start therapeutic dose anticoagulation. Restart pomalidomide at the Investigator's discretion mainatining dose level.	Omit pomalidomide for the remainder of cycle and start therapeutic dose anticoagulation.
Hyperthyroidism	Grade 3 or 4	Omit pomalidomide for the remainder of the cycle, evaluate etiology and initiate appropriate therapy. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.	Omit pomalidomide for the remainder of the cycle, evaluate etiology and initiate appropriate therapy. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.
Hypothyroidism	Grade 3 or 4	Omit pomalidomide for the remainder of the cycle, evaluate etiology and initiate appropriate therapy. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.	Omit pomalidomide for the remainder of the cycle, evaluate etiology and initiate appropriate therapy. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.
Other Pomalidomide-related non-hematologic AEs	Grade 1 or 2	Maintain dose. Initiate standard supportive care per institutional guidelines.	Maintain dose. Initiate standard supportive care per institutional guidelines.
	Grade 3 or 4	Hold (interrupt) pomalidomide and follow weekly. If toxicity has resolved to Grade ≤ 2 prior to day 21, restart pomalidomide at next lower dose level and continue the cycle through day 21.	Omit pomalidomide for the remainder of the cycle. See instructions for initiation of a new cycle and reduce the dose of pomalidomide by 1 dose level.

All dose modifications should be based on the worst preceding toxicity.

Note: For combinations of Grade 1 or 2 AEs (e.g., nausea, fatigue, anorexia) that significantly impair the patient’s quality of life, 1-2 doses of selinexor may be skipped and aggressive supportive care implemented. Selinexor may then be restarted at the original dose.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Fatigue, Palliative Care, and Antiemesis. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Isolated values of ≥ Grade 3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

The possibility of overlapping toxicities with selinexor, pomalidomide, and dexamethasone should be considered.

7.7.1.1 Dose Modifications for Overlapping Toxicities

Thrombocytopenia and neutropenia are potential overlapping toxicities for selinexor with pomalidomide. If a patient experiences drug-induced thrombocytopenia or neutropenia while receiving the combination under investigation in this study, the Investigator should attempt to determine which drug may be responsible and treat appropriately, including dose modifications, as necessary. If the cause cannot be attributed to a single drug, suggested management strategies for possibly drug-induced thrombocytopenia and neutropenia Grade 3/4 events are provided below.

7.7.1.2 Thrombocytopenia

1. Grade ≥ 2: Hold/adjust selinexor dose as described in Table 4, under Thrombocytopenia.
2. Grade ≥ 3: Hold/adjust pomalidomide dose as described in Table 4, under Thrombocytopenia.

7.7.1.3 Neutropenia

1. Grade 3 without fever: Reduce selinexor by 1 dose level and consider supportive care as described in Table 4, under Neutropenia.
2. Grade 4 without fever: Hold selinexor until ANC returns to Grade ≤ 2. Reduce selinexor by 1 dose level. See additional supportive care in Table 4, under Neutropenia.
3. Grade ≥ 3 with fever: Hold selinexor until ANC returns to Grade ≤ 2, fever resolves, and patient is clinically stable. Reduce selinexor by 1 dose level. See additional supportive care in Table 4, under Neutropenia.
4. Grade ≥ 3: If holding selinexor does not resolve the neutropenia, consider holding/adjusting pomalidomide dose as described in Table 4, under Neutropenia.

The manufacturer of pomalidomide has provided dose adjustment guidelines for managing Grade ≥ 3 thrombocytopenia and neutropenia that occur during treatment in the package insert. These guidelines, together with the recommended dose adjustments provided in Table 4, should be consulted by the Investigator to manage thrombocytopenia and neutropenia associated with study treatments, as needed.

7.7.2 Conditions Not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be held in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions. Treat hypokalemia and hypomagnesemia per institutional guidelines and repeat a 12-lead ECG to monitor the QTc as clinically indicated.

7.7.3 Selinexor Dose Reduction for Decreased Glomerular Filtration Rate

Selinexor is not significantly eliminated by the kidney; therefore, no dose alteration of selinexor is required with renal dysfunction.

7.8 General Concomitant Therapy and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

7.8.1 Required Anti-emetics: 5-HT3 Antagonists and Olanzapine

In order to minimize nausea, anorexia and fatigue, unless contraindicated, all patients should receive serotonin receptor subtype (5-HT3) antagonists (ondansetron 8 mg or equivalent), starting Q8 hours before each dosing and continue 2-3 times daily for a few days (2-4 days) after dosing for the first 2 cycles, after which it may be tapered of discontinued as tolerated. Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonists.

In addition, patients should receive olanzapine 2.5 mg PO daily starting on the evening prior to Day 1 and continuing for at least the first 2 months of the study. The dose of olanzapine can be increased as deemed necessary. The olanzapine dose may be dose reduced or stopped after 2 months of combination therapy period if nausea is well controlled. Please note that olanzapine can induce fatigue and should be discontinued in the case for fatigue grade >2.

Alternatives to olanzapine include:

- Megesterol Acetate - patients may receive megesterol acetate 80-400 mg daily, starting 1-3 days before the first dosing day of selinexor. In addition, megesterol acetate 80-400 mg daily may be added for any patients as part of general supportive care for anorexia.
- Mirtazapine 7.5-15 mg daily (QHS), starting 0-3 days in the evening before the first dosing day of selinexor. Please note that mirtazapine can induce fatigue and should be discontinued in the case for fatigue grade >2.

Avoid the use of strong CYP3A4 and/or CYP1A2 inhibitors (Appendix 1).

7.8.2 Supportive Care

Supportive care guidelines for managing adverse events (AEs) are provided in Table 4.

Patients may receive other supportive care, including hydration prophylaxis, antibiotics, as appropriate.

Supportive care including additional anti-nausea/anti-emetic therapy, acid suppression (proton-pump inhibitors [PPI] and/or H2-blockers) and other treatments may be administered as follows:

- Appetite stimulants: megestrol acetate at a dose of 400-800 mg daily. Mirtazapine 15mg PO qPM can also be given
- Centrally acting agents: per *National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines®*.

7.8.3 Infection Prophylaxis

Patients will receive sulfamethoxazole/trimethoprim (800 mg/160 mg) PO three times weekly (i.e., Monday, Wednesday and Friday), or equivalent in case of allergy or intolerance. Patients considered by the Investigator to be at high risk for a bacterial infection should receive levofloxacin prophylaxis.

7.8.4 Glucocorticoid Side Effects

The management of common glucocorticoid side effects is well documented. Aggressive use of PPIs, anti-hypertensives, glucose-lowering drugs and other agents is strongly encouraged in order to maintain the use of dexamethasone in combination with selinexor, clarithromycin and pomalidomide in this study.

Patients with documented osteopenia or osteoporosis should continue to take dexamethasone with selinexor as indicated in the study. Standard precautions such as use of antiresorptive therapy should be instituted unless contraindicated.

7.8.5 Non-study Related Concomitant Medication and Treatment

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s), unless listed below under Restrictions or Prohibited Medications, as noted below. All concomitant medication(s) must be reported in the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

7.8.6 Prevention of pregnancy

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of childbearing potential must agree to use two methods of contraception (one highly effective and one effective) and have a negative serum pregnancy test at Screening and a negative urine test prior to receiving the first dose of study treatment, and male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential.

Highly effective methods include:

- Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
- Intrauterine device or intrauterine system
- Vasectomy or tubal ligation

Effective methods include:

- Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge). Notes: No barrier method by itself achieves a highly effective standard of contraception. The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception. When used consistently and correctly, “double barrier” methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Male and female condoms should not be used together as they can tear or become damaged.

Alternatively, the following fulfill the contraception requirements:

- A sexual partner who is surgically sterilized or post-menopausal.
- Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose of study treatment. Please refer to the “Reproductive Risks” section above for additional safety information.

7.8.7 Thrombosis Prophylaxis

Study participants should receive adequate prophylaxis for venous thromboembolism (VTE) depending on the thrombotic risk as assessed by the Investigator. Low VTE risk patients should receive aspirin 81 mg PO daily while receiving pomalidomide. Patients with multiple VTE risk factors (eg, previous VTE, known inherited thrombophilia, central venous catheter or pacemaker, severe cardiac disease, uncontrolled diabetes mellitus, prolonged immobilization, use of erythropoietin, obesity, chronic kidney disease [eGFR <30 mL/min], elevated D-dimer levels) should receive prophylactic or therapeutic dose low molecular weight heparin, warfarin or a non-vitamin K oral anticoagulant, rather than low-dose aspirin, while receiving pomalidomide.

7.8.8 Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted but study drug should be held for ≥ 1 day before the start of palliative radiation therapy and ≥ 1 day following each dose of palliative radiation therapy. Treatment with selinexor shall not be discontinued solely due to palliative radiation.

7.8.9 Hematopoietic support

Thrombocytopenia should be treated conservatively. In the absence of bleeding, platelet transfusions should only be given for a platelet count below 10,000/mm^3. If the patient develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count ≥ 50,000/mm^3. Platelet growth factors may be used according to Table 4.

Treat anemia per institutional guidelines including blood transfusions and/or erythropoietin stimulating agents with concurrent anticoagulation as described above. Consider transfusing for hemoglobin < 8 g/dL.

Granulocyte colony stimulating factors may be used for the management of neutropenia according to Table 4.

7.8.10 Prevention of skeletal related events

Patients should receive osteoclast inhibitor therapy as deemed appropriate by the Investigator. Routine dental care is recommended.

7.8.11 Restrictions

There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with selinexor, except on days of selinexor dosing, when acetaminophen use must not exceed a total daily dose of 1 g.

Patients should not take any strong CYP3A4 and/or CYP1A2 inhibitors; please see Appendix 1 for a list of representative products. Patients should not take glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-containing products during their participation in this study as these products may enhance the metabolism of selinexor. However, they are permitted if the patient has elevated liver function tests; please see Appendix 2 for a list of representative products.

Patients should not take drugs that are contraindicated with clarithromycin: colchicine, cisapride, pimozide, ergot alkaloids (e.g., ergotamine, dihydroergotamine), lomitapide, HMG-CoA reductase inhibitors extensively metabolized by CYP3A4 (e.g., lovastatin, simvastatin), saquinavir, midazolam (oral), ticagrelor, astemizole, domperidone, terfenadine, or ranolazine.

Prescribing Information for pomalidomide and dexamethasone should serve as a reference for potential restrictions and/or prohibitions.

There are no dietary restrictions in this study. Patients on selinexor should maintain adequate caloric and fluid intake.

7.8.12 Prohibited Medications

Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during

the study must be confirmed by the Medical Monitor. The package insert should serve as a reference for potential restrictions and/or prohibitions. Avoid the use of strong CYP3A4 and/or CYP1A2 inhibitors (Appendix 1).

7.8.13 Day one dosing guidelines

On day one of study treatment, the patient will take:

- Selinexor 60 mg by mouth
- Clarithromycin 500 mg by mouth twice a day
- Pomalidomide 4 mg by mouth
- Dexamethasone 40 mg by mouth

Unless dose reduction is warranted due to renal and/or hepatic impairment, see section 7.7.1.

The patient will also be directed to take the following prophylactic medications:

- Aspirin 81 mg by mouth daily
- Omeprazole 20 mg by mouth (or equivalent) daily
- Ondansetron 8 mg by mouth (or equivalent) starting 8 hours before Selinexor dosing and continue 2-3 times daily for 2-4 days after dosing for at least the first 2 cycles.
- Olanzapine 2.5 mg by mouth every evening, starting on the evening before day 1 and continuing for at least the first 2 cycles.
- Trimethoprim-sulfamethoxazole 1 DS tablet by mouth three times per week (Monday, Wednesday, Friday).

Documentation of two negative pregnancy tests (serum hCG at Screening visit, and a urine pregnancy test on C1D1) is required prior to first dose in all female patients of childbearing potential.

7.8.14 Instructions for initiation of a subsequent cycle

A new course of treatment may begin on the scheduled day 1 of a new cycle if:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3
- Platelets count ≥ 75,000/mm^3
- Any drug-related somnolence, rash, peripheral neuropathy, sinus bradycardia/other cardiac arrhythmia, allergic reaction/hypersensitivity, dyspepsia, gastritis, gastric or duodenal ulcer or confusion or mood alterations that may have occurred has resolved to ≤ grade 1 severity.
- Any other drug-related non-hematologic adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

If the toxicity does not resolve within four weeks, the patient will be taken off the study. If the dosing of selinexor, clarithromycin, pomalidomide or dexamethasone was halted during the previous cycle and was restarted with a one-level dose reduction without

requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the new cycle.

If the dosing of selinexor, clarithromycin, pomalidomide or dexamethasone was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled day 1, then the new cycle will be started with dose modifications as described in Tables 3 and 4.

If the start of a new cycle is delayed more than 4 weeks, the patient will be taken off study.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

Patients may discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial. All patients will be followed until disease progression, withdrawal of consent, death or loss to follow up.

7.10 Duration of Follow Up

Subjects will be followed for 12 months after end of treatment (EoT) visit or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

End of study will occur after the last patient to be enrolled has completed the one year follow up period, died, withdrawn consent, or been lost to follow up, whichever comes first.

7.10.1 Safety Follow Up

Study procedures will be performed 30 days (+ 7 days) after the last dose of study medication. Patients will be contacted by telephone or visit to obtain the following information:

- Follow-up on any AEs that had not resolved by the EoT visit
- Information on any antineoplastic therapies utilized since discontinuation of ClaSPd treatment

7.10.2 Duration of Response and Survival Follow Up

Every three months (± 14 days) for 12 months after the EoT visit, if feasible and clinically appropriate, the following assessments should be obtained for patients who have not progressed to assess durability of response:

- SPEP and serum protein immunofixation
- UPEP (24-hour urine) and urine protein immunofixation
- Serum FLC
- Quantitative Ig levels
- Bone marrow aspirate, as clinically indicated, to assess progression
- Re-assessment of plasmacytomas by physical examination (if detected by physical examination at Screening)
- Skeletal survey (imaging) for bone lesions, including tumor measurements as clinically indicated to document response, at frequency determined by the Investigator

If these procedures cannot be obtained, at a minimum, a telephone call will be made to the patient (or the patient's family) every 3 months to inquire about the patient's MM status, general health, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

7.11 Measures to Minimize Bias: Randomization and Blinding

Not applicable.

7.12 Study Intervention/Follow-up Compliance

Not Applicable.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the those outlined in the EoT visit as well as the Follow Up Phase.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. Patients who elect to discontinue study treatment should be encouraged to continue in

the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial. All patients will be followed until disease progression, withdrawal of consent, death or loss to follow up.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant lost to follow-up after three attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for two or more visits for the beginning of a cycle and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not Applicable.

9.1 Laboratory Correlative Studies

Not Applicable.

9.2 Special Studies

Not Applicable.

10. Measurement of Effect

10.1 Response Criteria

Overall response rate (ORR): the sum of partial response (PR), very good partial response (VGPR), complete response (CR) and stringent complete response (sCR), based on the IMWG response criteria (Appendix 4). Response will be assessed on day 1 of every cycle starting on cycle 2.

10.2 Duration of Response

Duration of response: The duration of response is measured from the time measurement criteria for PR, VGPR, CR or sCR (whichever is first recorded) is first met until the date of progressive disease (PD) or death, whichever comes first.

10.3 Progression-Free Survival

Progression-Free Survival: defined as the length of time measured from start of study treatment to PD or death, whichever comes first.

10.4 Other Response Parameters

- Clinical benefit rate (CBR), defined as overall response rate (ORR) plus minimal response (MR), as defined by the IMWG criteria (Appendix 4)
- Disease control rate (DCR), defined as CBR plus stable disease (SD) for a minimum of 12 weeks
- Overall survival (OS), defined as the length of time measured from start of study treatment to death
- Minimal residual disease (MRD), as defined by the IMWG criteria (Appendix 4)
- Relative dose intensity, defined as the ratio of delivered to the planned dose intensity expressed as a percentage
- Quality of life (QOL) score, as measured by the Functional Assessment of Cancer Therapy - MM (FACT-MM) (Appendix 5)

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval

before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

A Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true ORR is ≤ 35% will be tested against a one-sided alternative that the true ORR ≥ 60% (see Background section for further details regarding a pooled estimate of the ORR in studies of pomalidomide-containing two- and three-drug regimens).

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as 95% confidence intervals (CI), unless otherwise stated. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 95% CI, as well as percentage of censored observations.

The analysis will be performed on an intent-to-treat population, consisting of all patients who receive at least one dose of the study treatment. This population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause, including those related to study drug or disease. This population will be used for the analyses of both efficacy and safety.

Demographic characteristics will include gender, race, ethnicity (Hispanic/non-Hispanic origin), and age at time of consent. For gender, race, and ethnicity, the summary statistics will be the number and percentage of patients within each category. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each group and the total sample. Baseline characteristics include ECOG Performance Status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight. Baseline data will be tabulated for the same categories as used for demographics, using summary statistics. Medical history and physical examination results at baseline will be tabulated by cohort.

12.2 Sample Size/Accrual Rate

In the first stage, 18 patients will be accrued. If there are 6 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 26. The null hypothesis will be rejected if 14 or more responses are observed in 26 patients. This design yields a one-sided type I error rate of 0.05 and power of 0.8 when the true ORR is 60%.

12.3 Stratification Factors

Not applicable.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

The analysis of Overall Response Rate (ORR) will be performed by calculating the point estimate of the percentage of patients who have a response of sCR, CR, VGPR or PR, as assessed by IMWG criteria. A 95% CI for the ORR will be calculated using exact methods and presented for descriptive purposes.

12.4.2 Analysis of Secondary Endpoints

Safety analyses will be performed using data available from all patients who receive ≥ 1 dose of the study treatment. Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term. Analyses of AEs will be performed for those events that are considered to be treatment emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 30 days following last dose or any event considered drug-related by the Investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

AEs will be summarized by patient incidence rates. In all tabulations, a patient may contribute only once to the count for a given AE preferred term. The number and percentage of patients with TEAEs will be summarized, as well as the number and percentage of patients with TEAEs assessed by the Investigator as at least possibly related to treatment. The number and percentage of patients with any Grade ≥ 3 TEAE will be tabulated in the same manner. In the event that a patient experiences repeated episodes of the same TEAE, the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations. Serious AEs (SAEs) will also be tabulated. No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment emergent and post-treatment) will be listed in patient data listings. Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

The actual value and change from baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, and for all study patients combined. In the event of repeat values, the last non-missing value per study day/time will be used. Severity of select clinical lab measures will be determined using CTCAE criteria (i.e., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades ≥ 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.

Physical examination results at screening will be summarized; all other abnormal physical examination data were to be recorded on the AE eCRF. All examination findings will be presented in a data listing.

The use of concomitant medications will be included in by-patient data listings.

12.4.3 Analysis of Exploratory Endpoints

Duration of Response (DOR) will be analyzed by Kaplan-Meier descriptive statistics for patients who have a response of sCR, CR, VGPR or PR, as assessed by IMWG criteria. DOR will be calculated as the number of days from the date of the first evidence of response until progression or death. Patients who have not progressed at the time of analysis will be censored at the last available assessment date at which no evidence of disease was observed. Estimates will include the 25th, 50th (median), and 75th percentiles and associated 95% CIs, as well as the number and percentage of censored patients.

The clinical benefit rate (CBR) will be performed by calculating the point estimate of the percentage of patients who have a response of sCR, CR, VGPR, PR or MR, as assessed by IMWG criteria. Analysis will be performed by calculation of the point estimate of CBR, as well as a two-sided 95% CI, using exact methods.

The disease control rate (DCR) will be performed by calculating the point estimate of the percentage of patients who have a response of sCR, CR, VGPR, PR, MR or SD, as assessed by IMWG criteria. Analysis will be performed by calculation of the point estimate of DCR, as well as a two-sided 95% CI, using exact methods.

Progression-free Survival (PFS) will be calculated from the date of start of study therapy to the date of progression based on IMWG criteria, or date of death due to any cause should progression not have occurred. Patients who drop out prior to study end will be censored at the last available assessment date at which no evidence of disease was observed. The analysis of PFS will be based on the Kaplan-Meier method for estimation of summary statistics, and include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.

Overall Survival (OS) will be calculated from the date of start of study therapy to the date of death due to any cause. This analysis will be performed in the same manner as the analysis of PFS.

Patients will be provided medication diaries at the beginning of each cycle. Delivered dose intensity will be assessed on day 1 of each cycle starting on cycle 2; defined as the total amount of study drug taken in one cycle.

The standard dose intensity is defined as the cumulative planned dose for cycle 1.

The relative dose intensity (RDI) is calculated by dividing the average delivered dose intensity over the standard dose intensity, expressed as a percentage.

Quality of life (QOL) will be assessed by completing the Functional Assessment of Cancer Therapy - MM (FACT-MM) (Appendix 5) questionnaire as outlined in Table 2. The FACT-MM questionnaire consists of the four core FACT HRQoL subscales measuring physical, functional, social, and emotional well-being (FACT-G; 27 items) and an additional subscale (MM subscale) measuring MM-specific concerns (14 items). Items are rated using a 0- to 4-point scale based on the past 7 days, with higher scores indicating better HRQoL and fewer MM-related symptoms. The actual value and change from baseline of each subscale and total score will be summarized for all study patients

combined. By-patient listings of each subscale and total score will be presented in data listings.

12.5 Interim Analysis

As stated above, the study design is a two-stage design. In the first stage, 18 patients will be accrued. If there are 6 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 8 additional patients will be accrued for a total of 26.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with ClaSPD.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least one treatment dose.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Life-threatening adverse event or life-threatening suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose,

results in death; is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- *Suspected adverse reaction*: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.
- *Unexpected adverse event or unexpected suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not but are not specifically mentioned as occurring with the particular drug under investigation.

13.1.1 Expected Adverse Events

Please refer to the package insert included in the Appendix for each of the components of the study treatment (ClaSPd).

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

The severity of the AE will be graded by the Investigator according to the CTCAE Grading Scale, version 5.0. If NCI CTCAE grading does not exist for an AE, the severity

will be characterized as “mild,” “moderate,” “severe,” or “life-threatening (corresponding to Grades 1 to 4) according to the following definitions:

- Grade 1 (Mild) events are usually transient and do not interfere with the patient’s daily activities.
- Grade 2 (Moderate) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Grade 3 (Severe) events interrupt the patient’s usual daily activities.
- Grade 4 events are Life-threatening.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as a “serious” AE.

Causality of the AE:

- Not related: The lack of a strong temporal relationship of the event to the study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation.
- Related: The temporal relationship of the event to the study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

13.1.3 Recording of Adverse Events

All AEs that begin or worsen after the patient has provided informed consent will be recorded on the AE eCRF, regardless of whether dosing with study drug has commenced. AE monitoring should be continued for at least 30 days following the last dose of study treatment (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study treatment by the Investigator). AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the patient non-leading questions to determine if AEs occur during the study. AEs may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

Laboratory abnormalities that constitute an AE in their own right (i.e., are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the Adverse Events eCRF.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline (at screening) or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (severe per NCI CTCAE version 5.0) does not automatically indicate an SAE unless it meets the definition of serious, as defined above, and/or as per Investigator's discretion. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRFs.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

The investigator or co-investigator will inform each participant about AEs and SAEs, and study-related results on an individual level. In addition, incidental findings associated with study procedures will be disclosed at the earliest opportunity to the participant.

13.1.6 Events of Special Interest

All secondary primary malignancies will be captured and reported as an AE.

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered. SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries.

In the event that an overdose is associated with an SAE, the SAE report form must be submitted to the IRB and Karyopharm Pharmacovigilance within 24 hours of awareness.

13.1.7 Reporting of Pregnancy

Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE. To ensure patient safety, a pregnancy occurring while the patient is on study treatment must be reported to Karyopharm Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence as well as to the Pomalidomide REMS

program.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancies must be reported to Karyopharm, regardless of whether the patient received selinexor or other study drugs, regardless of whether the patient withdraws from the study or the study is completed, for 3 months after the patient receives his/her last dose of study treatment. Patients should be instructed to inform the Investigator regarding any
pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

A pregnancy in a female partner of a male patient must be reported to Karyopharm and the Pomalyst REMS program within 24 hours of learning of its occurrence.

13.2 Definition of SAE

Any untoward medical occurrence that, at any dose, results in death; is life threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Please note that SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment, must be reported (in addition to SAEs that occur after the first dose of study treatment).

Hospitalizations for elective surgery or other medical procedures that are not due to an AE are not considered SAEs. A hospitalization meeting the regulatory definition for ‘serious’ is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility greater than 24 hours or results in a prolongation of a current hospitalization. An emergency room visit is not considered a hospitalization unless it results in an official admission to the hospital.

Progression of the malignancy (including fatal outcomes) should not be reported as an SAE during the study or within the safety reporting period. Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy, the finding should be reported as an AE or

SAE, as appropriate.

Progression of the malignancy (including fatal outcomes) if documented per IMWG criteria for progression of MM (see Appendix 4), should not be reported as an SAE during the study or within the safety reporting period (see below).

The Investigator will record and document all SAEs occurring from the signing of the ICF until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the SAE Report Form in addition to being recorded in the eCRF. The original SAE report form must be retained in the Investigator's site file.

All applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the SAE Report Form. Key data elements required for expedited reporting will follow ICH E2A standards (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA

The Investigator must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematologic Malignancies

5901-B Ammendale Road
Beltsville, MD 20705-1266

13.2.3 Reporting of SAE to Karyopharm Therapeutics, Inc.

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance Department within 24 hours of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department, including:

- Protocol number
- Site and/or Investigator's number
- Patient's number
- Brief description of the event
- Resolution date and time, if the event resolved
- Any medication administered to treat the event
- Investigator's assessment of the SAE's relationship to investigational product
- Outcome of the event on the date of report

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com

Fax: +1-617-334-7617 (USA)

+49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

13.2.4 Reporting of SAE to WCM by Sub-sites

Within 24 of the Investigator's knowledge of the event, participating sites must report SAE to WCM by sending the following forms via email to **jctoiit@med.cornell.edu:**

WCM SAE Cover Sheet

- Karyopharm SAE form
- Form FDA 3500A for Mandatory Reporting (MedWatch) https**://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/**UCM048334.pdf

The SAE should be reported to the participating site's institutional regulatory board (IRB), as per institutional guidelines. Proof of submission and IRB acknowledgment should be sent via email to **jctoiit@med.cornell.edu** when received.

WCM (Sponsor-investigator) is responsible for reporting the SAE to the Karyopharm Therapeutics, the FDA, and any other applicable regulatory agencies.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized, and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study, as outlined in the Follow Up Phase above.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study treatment (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be

documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator or research nurse will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

Weill Cornell Medicine Data and Safety Monitoring Committee (WCM DSMC) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the WCM DSMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The WCM DSMC may request additional meetings or safety reports as deemed necessary upon discussion with Karyopharm Therapeutics and its representatives. The PI, Dr. Jorge Monge, will be the safety contact for all WCM DSMC related analysis outcomes and can be contacted at:

Weill Cornell Medicine Myeloma Center
425 E 61st St, 8th Floor
New York, NY 10065
Phone: +1-646-962-6500
Fax: +1-212-746-8961
Email: jum9127@med.cornell.edu

The WCM DSMC may stop the study following review of results from each interim analysis. The first interim analysis will take place 3 months after the study begins subject accrual or after 6 patients have been enrolled, whichever occurs first, and will examine the safety and tolerability of minimum one cycle of study treatment prior to enrolling additional subjects. A subsequent interim analysis will take place 6 months after the study begins subject accrual or after 12 patients have been enrolled, whichever occurs first, and every six months thereafter, and will examine both safety and efficacy. The WCM DSMC will also review the study at the end of the first stage of accrual (18 patients) including toxicity data, protocol adherence, and protocol deviations. Efficacy and safety data summaries will be provided to the WCM DSMC after each interim analysis.

Early discontinuation of the study may result from the following study-terminating events:

1. Any abrupt or unexpected patient death that appears to be related to study medication.
2. Early death (defined by death within 30 days of beginning therapy) of more than 50% of subjects at any interim analysis.

3. Early need for hospitalization (defined by hospitalization within 30 days of beginning therapy) of more than 50% of subjects at any interim analysis.
4. Unacceptable toxicity (defined by a Grade 4 or higher drug-related adverse event) in more than 50% of subjects at any interim analysis.
5. The interim stopping rule for the study is defined by statistical futility of the ClaSPD regimen, as outlined in the two-stage study design.

The WCM DSMC will submit their comments/review to the IRB at the time of continuing review and to participating sites upon receipt of review comments.

Written documentation will be provided to investigators and regulatory agencies if the protocol is stopped or paused for toxicity concerns.

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17. Appendices

Appendix 1. Cytochrome P450 Drug Interactions

Inducers

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A457
beta-naphthoflavone	artemisinin	rifampin	carbamazepine	carbamazepine	dexamethasone	ethanol	barbiturates
broccoli	carbamazepine		enzalutamide	efavirenz	rifampin	isoniazid	brigatinib
brussel sprouts	efavirenz		nevirapine	enzalutamide			carbamazepine
carbamazepine	nevirapine		phenobarbital	norethindrone			efavirenz
char-grilled meat	phenobarbital		rifampin	not pentobarbital			enzalutamide
insulin	phenytoin		secobarbital	prednisone			glucocorticoids
methylcholanthrene	rifampin		st. john's wort	rifampicin			modafinil
modafinil				ritonavir			nevirapine
nafcillin				st. john's wort			oxcarbazepine
omeprazole							phenobarbital2
rifampin							phenytoin2
rucaparib							pioglitazone
teriflunomide							rifabutin
tobacco							rifampin1
							st. john's wort
							troglitazone1

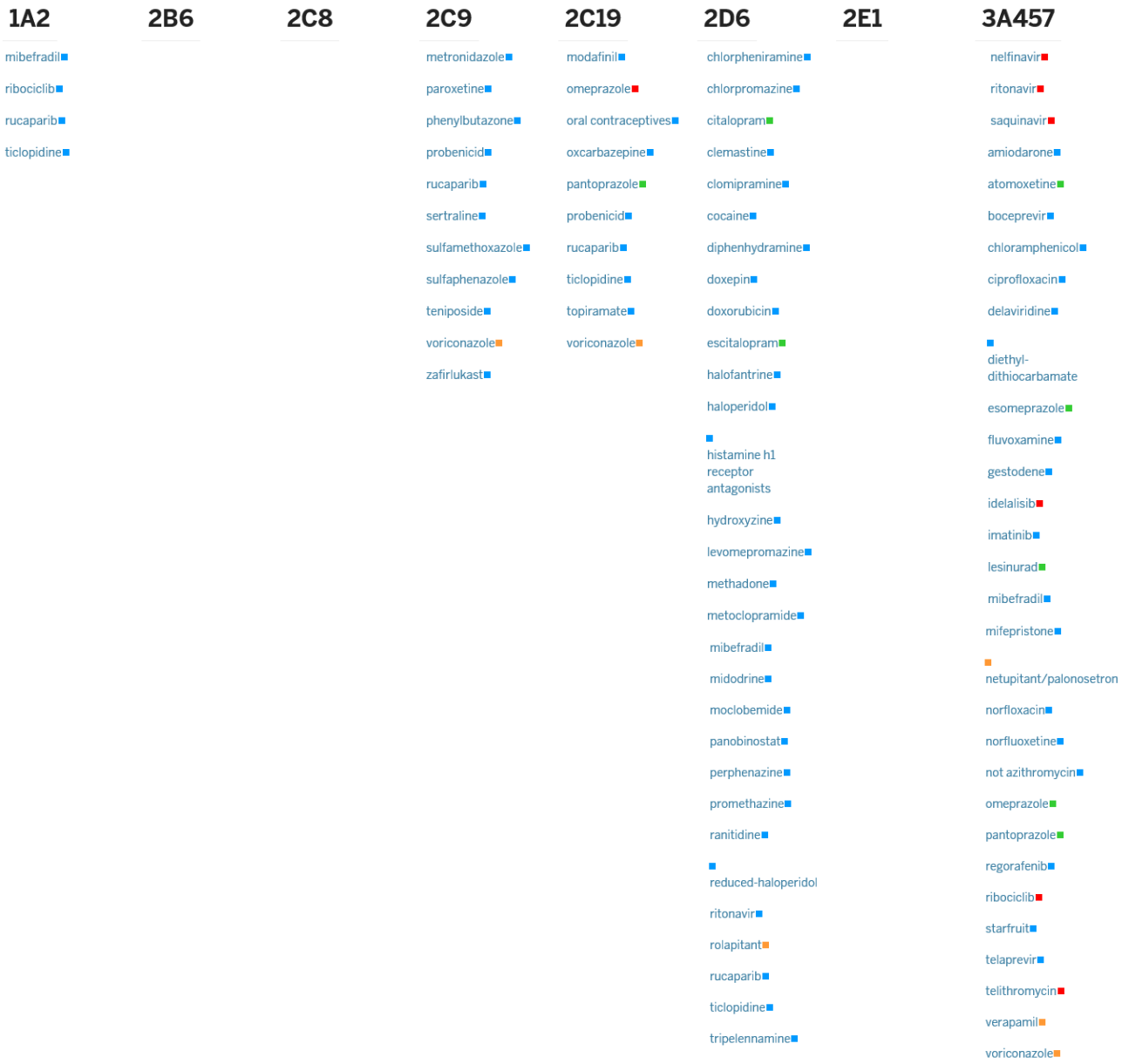
Inhibitors

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's respor to that particular medication, e.g. making it ineffective.

- A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.
- **TBD** Inhibitor strength level is under review.

FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments.*

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A457
amiodarone	clopidogrel	gemfibrozil	amiodarone	chloramphenicol	amiodarone		aprepitant
cimetidine	crisaborole	glitazones	capecitabine	cimetidine	bupropion	diethyl-dithiocarbamate2	cimetidine
ciprofloxacin	rucaparib	montelukast	clopidogrel	citalopram	cimetidine	disulfiram	clarithromycin
citalopram	thiotepa	quercetin	crisaborole	esomeprazole	cinacalcet	ribociclib	diltiazem
crisaborole	ticlopidine	teriflunomide	efavirenz	felbamate	duloxetine		erythromycin
efavirenz	voriconazole	trimethoprim	fenofibrate	fluoxetine	fluoxetine		fluconazole
fluoroquinolones			fluconazole	fluvoxamine	paroxetine		grapefruit juice
fluvoxamine			fluvastatin	indomethacin	quinidine1		indinavir
furafylline			fluvoxamine	isoniazid	sertraline		itraconazole1
interferon			isoniazid	ketoconazole	terbinafine		ketoconazole
methoxsalen			lovastatin	lansoprazole	celecoxib		nefazodone


1A2
mibefradil
ribociclib
rucaparib
ticlopidine
2B6
2C8
2C9
metronidazole
paroxetine
phenylbutazone
probenicid
rucaparib
sertraline
sulfamethoxazole
sulfaphenazole
teniposide
voriconazole
zafirlukast
2C19
modafinil
omeprazole
oral contraceptives
oxcarbazepine
pantoprazole
probenicid
rucaparib
ticlopidine
topiramate
voriconazole
2D6
chlorpheniramine
chlorpromazine
citalopram
clemastine
clomipramine
cocaine
diphenhydramine
doxepin
doxorubicin
escitalopram
halofantrine
haloperidol
histamine h1 receptor antagonists
hydroxyzine
levomepromazine
methadone
metoclopramide
mibefradil
midodrine
moclobemide
panobinostat
perphenazine
promethazine
ranitidine
reduced-haloperidol
ritonavir
rolapitant
rucaparib
ticlopidine
tripelennamine
2E1
3A457
nelfinavir
ritonavir
saquinavir
amiodarone
atomoxetine
boceprevir
chloramphenicol
ciprofloxacin
delaviridine
diethyl-dithiocarbamate
esomeprazole
fluvoxamine
gestodene
idelalisib
imatinib
lesinurad
mibefradil
mifepristone
netupitant/palonosetron
norfloxacin
norfluoxetine
not azithromycin
omeprazole
pantoprazole
regorafenib
ribociclib
starfruit
telaprevir
telithromycin
verapamil
voriconazole

Substrates

1A2

acetaminophen
amitriptyline
caffeine
clomipramine
clozapine
cyclobenzaprine
doxepin
duloxetine
estradiol
fluvoxamine
haloperidol
imipramine n-deme
mexiletine
nabumetone
napqi
naproxen
olanzapine
ondansetron
phenacetin
pirfenidone
propranolol
riluzole
ropivacaine
rucaparib
tacrine
theophylline
tizanidine
triamterene
verapamil
warfarin
zileuton
zolmitriptan

2B6

artemisinin
bupropion
cyclophosphamide
efavirenz
ifosphamide
ketamine
meperidine
methadone
nevirapine
propafol
selegiline
sorafenib
tramadol
velpatasvir

2C8

amodiaquine
cerivastatin
paclitaxel
repaglinide
selexipag
sorafenib
torsemide

2C9

amitriptyline
capecitabine
celecoxib
clopidogrel
diclofenac
doxepin
fluoxetine
fluvastatin
glibenclamide
glimepiride
glipizide
glyburide
ibuprofen
irbesartan
lesinurad
lornoxicam
losartan
meloxicam
nateglinide
phenytoin-4-oh2
piroxicam
rosiglitazone
s-naproxen-nor
s-warfarin1
suprofen
tamoxifen
tolbutamide
tolbutamide1
torsemide
valproic acid
venlafaxine
voriconazole
zakirlukast

2C19

amitriptyline
atomoxetine
brivaracetam
carisoprodol
chloramphenicol
citalopram
clomipramine
clopidogrel
cyclophosphamide
diazepam-nor
doxepin
escitalopram
esomeprazole
flibanserin
hexobarbital
imipramine n-deme
indomethacin
labetalol
lansoprazole
moclobemide
nelfinavir
nilutamide
omeprazole
pantoprazole
phenobarbitone
phenytoin(o)
primidone
progesterone
proguanil
propranolol
r-mephobarbital
r-warfarin
s-mephenytoin
suvorexant
teniposide
venlafaxine

2D6

alprenolol
amitriptyline
amphetamine
aripiprazole
atomoxetine
brexpiprazole
bufuralol1
cariprazine
carvedilol
chlorpheniramine
chlorpromazine
citalopram
clomipramine
clonidine
codeine
codeine (?o-desme)
debrisoquine
desipramine
deutetrabenazine
dexfenfluramine
dextromethorphan1
donepezil
doxepin
duloxetine
eliglustat
encainide
escitalopram
flecainide
fluoxetine
fluvoxamine
haloperidol
ibrutinib
imipramine
lidocaine
methoxyamphetamine
metoclopramide

2E1

acetaminophen?
napqi
aniline
benzene
chlorzoxazone1
enflurane
ethanol
halothane
isoflurane
methoxyflurane
n,n-
dimethylformamide
sevoflurane
theophylline?8-oh

3A457

abemaciclib
acalabrutinib
alectinib
alfentanil
alprazolam
amitriptyline
amlodipine
aprepitant
aripiprazole
astemizole
atorvastatin
boceprevir
brexpiprazole
brigatinib
buspirone
cafergot
caffeine -tmu
carbamazepine
cariprazine
cerivastatin
chlorpheniramine
cilostazol
cisapride
citalopram
clarithromycin
clopidogrel
cobimetinib
cocaine
codeine
codeine-n-
demethylation
copanlisib
cyclosporine
daclatasvir
dapsone
deflazacort
dexamethasone

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A457
				voriconazole	mexiletine		dextromethorphan2
					minaprine		diazepam?3oh
					nebivolol		diltiazem
					netupitant/palonosetron		docetaxel
					nortriptyline		domperidone
					ondansetron		doxepin
					oxycodone		efavirenz
					paroxetine		elbasvir/grazoprevir
					perhexiline		eliglustat
					perphenazine		eplerenone
					phenacetin		erythromycin2 (not 3a5)
					phenformin		escitalopram
					pimavanserin		esomeprazole
					promethazine		estradiol
					propafenone		felodipine
					propranolol		fentanyl
					risperidone		finasteride
					risperidone?9-oh		flibanserin
					rucaparib		gleevec
					s-metoprolol		haloperidol
					sparteine		hydrocortisone
					tamoxifen		ibrutinib
					tetrabenzine		idelalisib
					thioridazine		indinavir
					timolol		irinotecan
					tramadol		isavuconazonium sulfate
					valbenazine		ivabradine
					venlafaxine		laam
					zuclopenthixol		lansoprazole
							lenvatinib
							lercanidipine
							lidocaine
							lovastatin
							methadone
							midazolam1
							naldemedine
							naloxegol
							nateglinide
							nelfinavir
							neratinib
							netupitant/palonose
							nevirapine

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A457
							nifedipine2
							nisoldipine
							nitrendipine
							not azithromycin
							not pravastatin
							not rosuvastatin
							olaparib
							omeprazole
							ondansetron
							osimertinib
							palbociclib
							panobinostat
							pantoprazole
							pimavanserin
							pimozide
							progesterone
							propranolol
							quetiapine
							quinidine?3-oh (not 3a5)
							quinine
							regorafenib
							ribociclib
							risperidone
							ritonavir
							rolapitant
							romidepsin
							salmeterol
							saquinavir
							selexipag
							sildenafil
							simvastatin
							sirolimus
							sonidegib
							sorafenib
							sunitinib
							suvorexant
							tacrolimus
							tacrolimus(fk506)
							tamoxifen
							taxol
							telaprevir
							telithromycin
							terfenadine
							testosterone1

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A457
							torisel
							tramadol
							trazodone
							valbenazine
							velpatasvir
							vemurafenib
							venetoclax
							venlafaxine
							verapamil
							vincristine
							voriconazole
							zaleplon
							ziprasidone
							zolpidem

Source: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "https://drug-interactions.medicine.iu.edu" Accessed 01/20/2020.

Appendix 2. Glutathione (GSH)-, S-adenosylmethionine (SAM)-, or N-acetylcysteine (NAC)-Containing Products

Glutathione (GSH)		S-adenosylmethionine (SAM)		N-acetylcysteine (NAC)	
Product Name	**Ingredient**	**Product Name**	**Ingredient**	**Product Name**	**Ingredient**
Glutathione	glutathione	Acetadote for acetaminophen overdose	acetylcysteine	SAM-e Complete	S-adenosyl-methionine
L-Glutathione	L-glutathione	Cerefolin NAC: medical food for age-related memory loss	L-methylfolate, vitamin B12, N-acetyl cysteine	SAMe	S-adenosyl-L-methionine
Glutathione reduced	glutathione	NAC	N-acetyl cysteine	Double Strength SAMe 400	S-adenosyl-methionine
Reduced glutathione with alpha lipoic acid	Setria L-glutathione	N-A-C Sustain	N-acetyl L-cysteine		
Glutathione, Cysteine & C	Glutathione, L-cysteine, vitamin C	Best NAC Detox Regulators	N-acetyl cysteine		

(Mega-) Liposomal Glutathione	glutathione				
Lyposperic GSH	glutathione				
Ivory Caps Skin Enhancement Formula	glutathione				

Appendix 3. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Appendix 4. International Myeloma Working Group (IMWG) Response Criteria

Category	**Response Criteria**
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated method with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher

Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid hemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anemia, lytic bone lesions. FCM=flow cytometry. SUVmax=maximum standardized uptake value. MFC=multiparameter flow cytometry. 18F-FDG PET=18F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However,

radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

† Sustained MRD negativity when reported should also annotate the method used (e.g., sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ Bone marrow MFC should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta), now ClonoSEQ (Adaptive).

¶ Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2·5 within osteolytic CT areas >1 cm in size, or SUVmax=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

‖ When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

†† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§ Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

lll In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Source: Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.

Appendix 5. Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM)

Appended as a PDF file at the end of this document. Also available at:
https://tinyurl.com/yb5rexhe

Appendix 6. FDA Label (package insert) for Selinexor, Clarithromycin Pomalidomide and Dexamethasone

Appended as 4 PDF files at the end of this document. Also available at:
https://tinyurl.com/y7wl3gqf
https://tinyurl.com/ybynjh4d
https://tinyurl.com/y7bjfde9
https://tinyurl.com/y83wmadx