NCT03440411

Protocol Title:

A MULTICENTER, OPEN LABEL, RANDOMIZED PHASE III STUDY OF POMALIDOMIDE-DEXAMETHASONE (Pom-dex) versus POMALIDOMIDE-CYCLOPHOSPHAMIDE-DEXAMETHASONE (Pom-cyclo-dex) IN MULTIPLE MYELOMA (MM) PATIENTS WHO EXPERIENCE BIOCHEMICAL (EARLY TREATMENT) OR CLINICAL RELAPSE (LATE TREATMENT) DURING LENALIDOMIDE MAINTENANCE TREATMENT

PROTOCOL NUMBER:	PO-3887 (PO-CL-MM-PI-003887)
DATE FINAL:	08 October 2015
AMENDMENT:	**11 April 2016**
EudraCT Number:	2015-001142-28

Investigator and Study Center:

Principal investigator: Antonio Palumbo

This is an investigator-initiated study. The principal investigator is Antonio Palumbo and the Sponsor is Fondazione Neoplasie Sangue Onlus, the first is conducting the study, the latter is acting as the Sponsor.

CONFIDENTIAL

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Principal Investigator **dd mmm yyyy**

Printed Name of Principal Investigator

Institution Name:

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

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Signature of Site Principal Investigator **dd mmm yyyy**

Printed Name of Site Principal Investigator

Institution Name:_____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

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Signature of Sponsor Representative	Date
Printed Name of Representative	

By my signature, I agree to supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and local regulations governing the conduct of clinical studies.

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SUMMARY

1. PROTOCOL SYNOPSIS

A MULTICENTER, OPEN LABEL, RANDOMIZED PHASE III STUDY OF POMALIDOMIDE-DEXAMETHASONE (Pom-dex) versus POMALIDOMIDE-CYCLOPHOSPHAMIDE-DEXAMETHASONE (Pom-cyclo-dex) IN MULTIPLE MYELOMA (MM) PATIENTS WHO EXPERIENCE BIOCHEMICAL (EARLY TREATMENT) OR CLINICAL RELAPSE (LATE TREATMENT) DURING LENALIDOMIDE MAINTENANCE TREATMENT.	
PROTOCOL NUMBER:	PO-3887 (PO-CL-MM-PI-003887)
DATE PROTOCOL FINAL:	08 October 2015
AMENDMENT:	11 April 2016
STUDY DRUG:	Pomalidomide
INDICATION:	Multiple Myeloma
STUDY PHASE:	III

STUDY DESIGN:	**Rationale** The combination lenalidomide plus low-dose dexamethasone (Rd) is an active treatment for Multiple Myeloma (MM) patients, both at diagnosis and at relapse (1-4). Three trials with lenalidomide maintenance treatment after autologous stem cell transplant (ASCT) and one study after conventional induction therapy showed a significant risk reduction for progression-free survival (PFS); an increase in overall survival (OS) in one of the transplant trials was also reported (5-8). Pomalidomide, is an immunomodulatory molecule (IMID), derivative of thalidomide, developed to improve the efficacy and reduce the toxicity of the parent molecule. Pomalidomide and dexamethasone (pom-dex) proved to be an effective and safe treatment in MM patients refractory to lenalidomide and refractory/intolerant to bortezomib (9-10). The addition of chemotherapy to novel drugs has been evaluated both at diagnosis and at relapse (11-13). The combination of pomalidomide-cyclophosphamide-prednisone proved to be safe and effective in relapsed/refractory MM patients (14). The combination pomalidomide-cyclophosphamide-dexamethasone (pom-cyclo-dex) was tested in a phase II study in patients with relapsed and refractory MM, demonstrating a good tolerability using pomalidomide at the dose of 4 mg. Pom-cyclo-dex resulted in a superior response rate and PFS compared to pom-dex. The increased hematologic toxicities, as a result of the addition of oral cyclophosphamide, were manageable. With an overall response rate of 65% the combination demonstrated a promising efficacy (15) The first aim of our trial, is to compare the combination of pom-cyclo-dex vs pom-dex. Relapsed myeloma is defined as previously treated myeloma that progresses and requires the initiation of salvage therapy (16). According to IMWG recommendation, biochemical relapse is defined as an increase of ≥ 25% of tumor burden from the lowest value, without any CRAB feature (CRAB is defined as the

	onset of clinical symptoms: hypercalcemia, renal failure, anemia and bone lesions) and detected in 2 consecutive determinations (16- 18). The increase of 25% from the lowest response value must be in any of the following: - serum M-component (absolute increase must be ≥0.5 g/100 ml) - and/or urine M-component (absolute increase must be ≥200 mg per 24 hours); - and/or only in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain (FLC) levels must be >10 mg/dL, Clinical relapse requires one or more direct indicators of progressive disease and end organ dysfunction (CRAB features) (16-19). Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder: • hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL) • renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 µmol/L (>2 mg/dL) • anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L • bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT Any one or more of the following biomarkers of malignancy: • clonal bone marrow plasma cell percentage ≥60% • involved:uninvolved serum free light chain ratio ≥100 • >1 focal lesions on MRI studies (each focal lesion must be 5 mm or more in size) Treatment at relapse should start in case of clinical relapse or a significant paraprotein increase (doubling of M-component in 2 months)(17). In case of biochemical relapse the standard is observation only, as in case of asymptomatic MM at diagnosis. However, a recently published trial, showed improved PFS and OS for newly diagnosed asymptomatic patients treated with lenalidomide and dexamethasone in comparison with observation only. Our hypothesis is that similarly, in the relapse setting, patients may benefit from an early intervention, meaning a treatment at biochemical relapse and not only in case of clinical relapse or rapid increase of M-component. The second aim of our trial is to compare early treatment (i.e. treatment at biochemical relapse generally managed with follow-up only)

	vs late treatment (i.e treatment at clinical relapse or in case of significant paraprotein relapse, as per standard clinical practice).
OBJECTIVES:	**Primary Objectives:** o Compare the efficacy of pom-dex versus pom-cyclo-dex in terms of OS o Evaluate the best treatment strategy (EARLY TREATMENT at biochemical relapse versus LATE TREATMENT at onset of CRAB symptoms/significant paraprotein increase) in terms of OS **Secondary Objectives:** o Compare the best therapy, pom-dex vs pom-cyclo-dex in terms of PFS o Compare the best strategy, EARLY TREATMENT versus LATE TREATMENT, in terms of PFS2 o Evaluate quality of life (QoL) and health related costs in the two therapies, pom-dex versus pom-cyclo-dex, and in the two strategies, EARLY TREATMENT versus LATE TREATMENT. o Explore the presence of clinically meaningful interactions between therapies and strategies o Determine whether tumor response, PFS, PFS2 and OS might significantly change in particular subgroups of patients defined by prognostic factors (such as International Staging System, chromosomal abnormalities) and by performance status o Evaluate the safety and tolerability of the strategy and of the combination pom-dex and pom-cyclo-dex
ENDPOINTS	**Primary:** *The primary endpoint for both comparisons is Overall Survival (OS),* defined as the time from the date of random disclosure to the date of death from any cause. **Secondary:** - *Time to clinical progression,* defined as the time from random assignment to the early or late strategy to the date of onset of CRAB symptoms or death. - *PFS*, defined as the time from random disclosure to the date of disease progression or death (16). - *PFS2*, defined as time from random disclosure to the date of disease progression while on the subsequent line of treatment or death from any cause (18). - *Objective overall response rate* - *Quality of life*, measured with EORTC-QLQ-C30 and QLQ-MY24 at baseline, every 2 months during the first year, and then every 6 months. - *Health related costs* - *Incidence of hematologic and non-hematologic adverse events (AEs)*

STUDY POPULATION:	Multiple myeloma patients at the first biochemical relapse, defined as an increase of 25% of the monoclonal component from the lowest value response in absence of CRAB symptoms (17), who are receiving lenalidomide maintenance as part of the first line of treatment. When patients experience biochemical relapse, they will stop lenalidomide maintenance, as established in the related protocol. Afterwards, patients can be considered for the enrollment in the present study if all inclusion and exclusion criteria are met.
INCLUSION CRITERIA:	• Patients >18 years and < 80 years • Patient is, in the investigator(s) opinion, willing and able to comply with the protocol requirements. • Patient has given voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care. • Male patient agrees to use an acceptable method for contraception (i.e., condom or abstinence) for the duration of the study. • Females of childbearing potential agree to use two acceptable methods for contraception [implant, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot, tubal sterilization, sexual intercourse with a vasectomised male partner only (vasectomy must be confirmed by two negative semen analyses), ovulation inhibitory progesterone-only pills (i.e. desogestrel)] or absolute and continuous sexual abstinence for the duration of the study. • Patient has measurable disease, defined as follows: any quantifiable serum monoclonal protein value (generally, but not necessarily, ≥ 0.5 g/dL of M-protein) and, where applicable, urine light-chain excretion of >200 mg/24 hours; only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must be >10 mg/dL.- Less than 10% of oligo- or non-secretory MM patients with free light chains will be admitted to this study in order to maximize interpretation of benefit results. • Patient receiving lenalidomide maintenance therapy as part of first line treatment (concomitant use of prednisone is accepted) and has experienced a biochemical relapse, with evidence of progressive disease defined as an increase of 25% from lowest response value in any one or more of the following: serum M-component (absolute increase must be ≥0.5 g/100 ml) and/or urine M-component (absolute increase must be ≥200 mg per 24 hours); only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must be >10 mg/dL (17). • Patient who received as first line treatment a bortezomib-based therapy, including lenalidomide maintenance during the same line of therapy, can be included in the trial. • Patient has a life-expectancy > 3 months

	• Patient has not a currently active malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, and has not invasive malignancies within the past 5 years • No history of allergic reactions attributed to study agents • Patient has the following laboratory values within 28 days before baseline day 1 of the cycle 1: a) absolute neutrophil count (ANC) > 1 x 10^9/L b) platelet count > 75 x 10^9/L c) haemoglobin > 8 g/dl. d) aspartate transaminase (AST): < 2 x the upper limit of normal (ULN). e) Alanine transaminase (ALT): < 2 x the ULN
EXCLUSION CRITERIA:	• Pregnant or lactating females. • Patient with Creatinine Clearance (CrCl) < 45 mL/minute • Patient with peripheral neuropathy ≥ Grade 2 • Subject with any one of the following: • Congestive heart failure (NY Heart Association Class III or IV) • Myocardial infarction within 12 months prior to starting study treatment • Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris • Any significant medical disease or conditions (e.g. pulmonary disease, infection) that, in the investigator's opinion, may interfere with protocol adherence or subject's ability to give informed consent or could place the subject at unacceptable risk. • Clinical active infectious hepatitis type A, B, C or HIV. • Acute active infection requiring antibiotics or infiltrative pulmonary disease. • Contraindication to any of the required drugs or supportive treatments. • Known allergy to any of the study medications, their analogues, or excipients in the various formulations.
STUDY TREATMENT:	**Patients at biochemical relapse during lenalidomide maintenance, will stop lenalidomide treatment and then will be randomized to:** **Arm A**: pom-dex Pomalidomide: 4 mg/day on days 1-21 Dexamethasone: 40 mg on days 1, 8, 15, 22 For 28-day cycles until progression or intolerance **or** **Arm B**: pom-cyclo-dex Pomalidomide: 4 mg/day on days 1-21 Cyclophosphamide: 50 mg every other day Dexamethasone: 40 mg on days 1, 8, 15, 22 For 28-day cycles until progression or intolerance

	AND **ARM I**: EARLY TREATMENT: patients will receive treatment at biochemical relapse with pomalidomide-dexamethasone (Arm A) or pomalidomide-cyclophosphamide-dexamethasone (Arm B) according to randomization. The randomization between Arm A and B will be disclosed at biochemical relapse. **or** **ARM II:** LATE TREATMENT: patients will be randomized at biochemical relapse and they will start treatment with pomalidomide-dexamethasone (Arm A) or pomalidomide-cyclophosphamide-dexamethasone (Arm B) at the onset of CRAB symptoms/significant paraprotein increase. The randomization between Arm A and B will be disclosed at the onset of CRAB symptoms/significant paraprotein increase.
TREATMENT REGIMEN AND DOSING RATIONALE:	Since pomalidomide has shown efficacy in patients previously treated with lenalidomide, and in patients refractory to lenalidomide, our hypothesis is that the treatment with pom-dex or pom-cyclo-dex, in patients experiencing a relapse during a lenalidomide maintenance ongoing therapy, can overcome lenalidomide-drug resistance and result in a significant response rate, that could translate into a significant improvement in outcome of MM patients. The addition of an alkylating agent to novel drugs has demonstrated an additive positive effect. Patients may benefit from an early intervention of treatment at biochemical relapse and not only in case of clinical relapse, as demonstrated in asymptomatic myeloma patients treated with lenalidomide and dexamethasone.
SAFETY SECTION – DOSE MODIFICATION PLAN:	The safety is assessed through: • Physical examination • Thrombosis assessment • Neurotoxicity assessment • Cardiac and pulmonary tests • Karnofsky assessment • Laboratory evaluation Reductions dose are required in case of grade 4 thrombocytopenia, grade 4 neutropenia lasting for more than 4 days and extra-haematological toxicity grade 3-4 not resolved within 2 weeks, according to the following dose modification plans: **ARM A and B:** Starting dose Pomalidomide 4 mg daily for 21 days every 28 days Dose Level -1 Pomalidomide 3 mg daily for 21 days every 28 days Dose Level -2 Pomalidomide 2 mg daily for 21 days every 28 days Dose Level -3 Pomalidomide 1 mg daily for 21 days every 28 days More details are reported in the section 8.12.1

STOPPING RULES:

Historical data on similar patients show, on average, a toxicity rate of haematological adverse events ≥ grade 4 or non-hematological adverse events ≥ grade 3 of 40% (9, 10, 14, 15).

Toxicity will be evaluated for the entire duration of the study according to the NCI CTCAE, version 4.03. Arm specific stopping rules for toxicity during the first 3 cycles of therapy are pre-specified to assure safety of treatments.

A toxicity rate of <=45% is considered acceptable, otherwise the treatment will be stopped for excessive toxicity.

Any of the following toxicities occurring during the first 3 cycles will be considered for safety monitoring and stopping rules:

1. Hematological toxicities ≥ grade 4
2. Non-hematological toxicities ≥ grade 3

The stopping boundaries are calculated using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998).

For each arm, the following table describes the toxicity stopping boundary for cohorts of 10 patients (boundaries calculated with a posterior probability >= 0.95 that the experimental treatment toxicity is more than 45%).

# Patients (in complete cohorts of 10)	# Toxicities (inclusive) The trial will be stopped if there are at least this many toxicity
10	8
20	14
30	19
40	25
50	30
60	36
70	41
80	46
90	52
100	57
110	62
120	68
130	Always stop with this many patients

STATISTICAL METHODS: This is a 2x2 factorial randomized study.

The sample size of the study has been calculated in order to demonstrate both the primary objectives, assuming no major interaction between the 2 factors.

The sample size calculation is performed on the basis of the following assumptions:

- Median OS in the late treatment group: 14 months
- Median OS in the early treatment group (experimental): 21 months (HR 0.67)
- Two sided α= 0.05
- β= 0.20
- Accrual time: 36 months
- Follow-up: 24 months
- Rate of lost at follow up: 5%
- Allocation ratio: 1:1:1:1 (2x2 design)

	The total sample size needed for the study is 256 patients (rounded to 260) and the final analyses will be performed when at least 191 deaths will be recorded. This sample size is based on the early vs late strategy because it is the maximum sample size required; it should be also sufficient to assess a similar OS advantage of pom-cyclo-dex vs pom-dex with the same statistical assumptions
REFERENCES:	References: 1. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11: 29-37. 2. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007 Nov 22;357(21):2133-42. 3. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma. N Engl J Med 2007; 357:2123-2132. 4. Benboubker L, Dimopoulos MA, Dispenzieri A,et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014 Sep 4;371(10):906-175. Attal M, Lauwers-Cances V, Marit G et al, Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma, N Engl J Med 2012; 366:1782-91. 6. Palumbo A, Hajek R, Delforge M, et al, Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma, N Engl J Med 2012;366:1759-69. 7. McCarthy PL, Owzar K, ,Craig C, et al, Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma, N Engl J Med 2012; 366:1770-81. 8. Palumbo A, Cavallo F, Gay F, et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. N Engl J Med 2014;371:895-905. 9. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-66. 10. Richardson PG, Siegel DS, Vij R, Hofmeister CC,, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014 Mar 20;123(12):1826-32. doi: 10.1182/blood-2013-11-538835. Epub 2014 Jan 13. Erratum in: Blood. 2014 May 15;123(20):3208-9. 11. Mateos MV, Richardson PG, Schlag R,et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol. 2010

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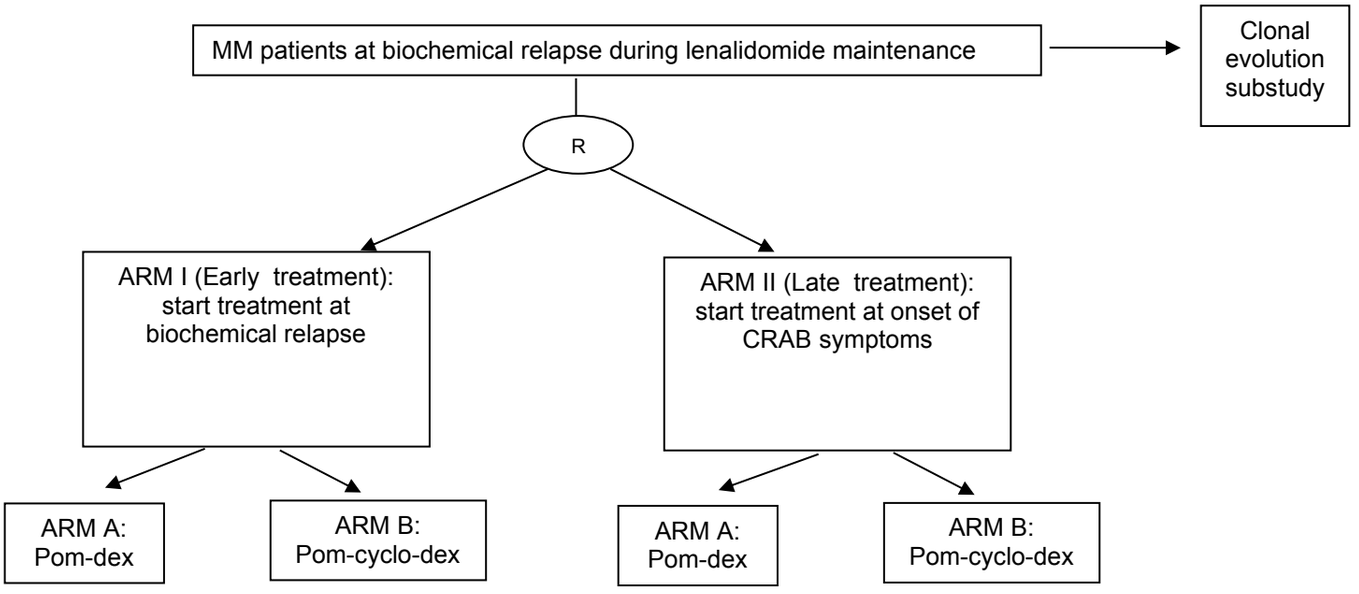
2. SCHEMA OF THE STUDY



3. STUDY TESTS AND OBSERVATIONS

Procedure for all patients enrolled in the study	Screening[a] ≤ 28 days from Baseline	ARM I[s]	ARM II		Follow-up		
		Every 28 days	All Cycles Day 1	Cycles 1-6 Day 14	End of treatment[b]	PFS[c]	OS[d]
Informed consent	X						
Inclusion/exclusion criteria	X						
Clinical history	X						
Medical history	X						
Physical examination[e]	X	X	X	X	X		
ECOG Performance Status[e]	X	X	X		X		
Vital signs[f]	X	X	X	X	X		
Pregnancy test[g]	X	X	X		X		
Neurological assessment[h]	X	X	X	X	X		
A postero-anterior and lateral chest X-ray[i]	X						
12-lead EKG[i]	X						
Hematology[l]	X	X	X	X	X		
Clinical chemistry[l]	X	X	X	X	X		
Urynalisis	X				X		
QoI assessment[m]	X	X[m]	X[m]		X		
Thyroid function	X	X[r]	X[r]				
Skeletal Survey[n]	X						
Radiography Disease Assesment[o]	X						
β2-microglobulin, C-reactive protein and LDH	X				X		
M-protein measurements (SPEP)	X	X	X		X	X	
M-protein measurements (UPEP [24-hr Urine Collection])	X	X	X		X	X	
Serum FLC[p]	X	X	X		X	X	
Quantification of Ig	X	X	X		X	X	
Bone Marrow assessment [q]	X				X		
Research samples (Clonality evolution analysis)[t]	X				X		
Adverse event		Recorded from the first dose of study drug through 30 days after last dose of study drug					
Serious adverse event		Recorded from the time informed consent is signed through 30 days after the last dose of study drug					
Concomitant Medications/Procedures		Recorded from the first dose of study drug through 30 days after last dose of study drug					

Follow-up survival information							X

a Evaluations during the Screening period are to be conducted within 28 days before the first dose of study drug. Computed tomography (CT) scans, magnetic resonance imaging (MRI), and skeletal surveys may be performed within 8 weeks of the first dose of study drug.

b Patients who do not continue treatment must complete the End of Treatment (EOT) visit, which should occur after the last dose of study drug and prior to the start of subsequent antineoplastic therapy.

c Conducted at the site every 4-6 weeks (± 2 weeks) from EOT until occurrence of progressive disease (PD) or the start of subsequent antineoplastic therapy. If a patient comes off treatment due to PD they should continue to be followed for OS follow-up.

d Conducted every 16 weeks (± 2 weeks) after PD or the start of subsequent antineoplastic therapy. Data may be collected by methods that include, but are not limited to, telephone, e-mail, mail, and social security indices.

e A full physical exam will occur at screening, every cycle, and at EOT; it should be repeated if clinically needed during treatment.

f Vital signs include: blood pressure, heart rate, oxygen saturation, temperature, respiratory rate, height and weight. Only on screening visit measurement of weight and height will be done.

g A serum or urine pregnancy test will be performed for women of childbearing potential during screening and day 1 of each cycle. The serum or urine pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the first drugs dose are administered. If the subject is pregnant, she cannot take study drugs. The subject must have a pregnancy test done by the doctor every week during the first 4 weeks of treatment. She will then have a pregnancy test every 4 weeks if her menstrual cycles are regular or every 2 weeks if her cycles are irregular. The subject may also need to have a pregnancy test if she misses her period or has unusual menstrual bleeding. A serum or urine pregnancy test will be repeated at the EOT visit (see appendix IX).

h Neurologic physical exam includes PN Grade using CTCAE v 4.03, assessment muscle weakness, peripheral sensory neuropathy, and neuralgia. The neurologic physical exam should occur each visit day (see appendix XII and XV). The FACT/GOG survey of neurotoxicity (Appendix XII) will be administered to patients at the screening and at day 1 of each cycle

i It should be repeated during the treatment if screening results are abnormal or if clinically indicated.

l Hematology and clinical chemistry should occur on day 1 and 14 for cycles 1-6 and on day 1 for the following cycles or at any time if clinically indicated. Hematology included: Red blood cell (RBC) count, hemoglobin, hematocrit, MCV, MCH, MCHC, white blood cell (WBC) count and differential, absolute neutrophil count (ANC), and platelet count; Clinical chemistry included: sodium, potassium, creatinine, calcium, glucose, total bilirubin, AST, ALT, ALP, GGT, uric acid and magnesium. At disease assessment albumin and total protein will be included in hematology exams. m Questionnaires will be evaluated at day 1 every 2 cycles for the first year of treatment and then every 6 months.

n During the screening period and at any time the physician believes there are symptoms or signs that suggest increased or new bone lesions. Plain films of symptomatic sites for signs or symptoms of new bone lesions may be obtained instead of a full skeletal survey.

o For those with documented extramedullary disease, radiographic assessments should be made every 3 cycles during the first 6 cycles, then every 6 cycles, at treatment discontinuation, and when clinically indicated to confirm a response ≥ PR. The same imaging modality used at screening (CT,MRI,PET/CT) should be used for all follow-up assessments.

p They will be performed at screening, to monitor response in patients with disease measurable on FLCs only, and to confirm sCR for patients with baseline serum FLC levels > 10 mg/dl.

q Post Screening: when a CR is suspected based on lab values, a bone marrow aspirate is required to confirm a CR/sCR and when PD occurs

r Thyroid function must be performed at screening visit and at then approximately every three months during therapy.

s During observation period, until clinical relapse. Then, during treatment, patients in arm I will follow the same evaluations of arm II.

t For patients in ARM I (early treatment) BM and PB should be collected at biochemical relapse and no response or progression during pomalidomide treatment. For patients in ARM II (late treatment) BM and PB should be collected at onset of CRAB symptoms and no response or progression during pomalidomide treatment.

LIST OF TABLES

4. BACKGROUND AND STUDY RATIONALE

4.1 Scientific Background

Multiple myeloma (MM) is a neoplastic disease of older adults, with a higher incidence in elderly patients: 26% are aged 65-74 years, and 37% are older than 75 years (1). The annual prevalence of MM is approximately 31 cases per 100,000 people in patients aged 65-74 years, and it increases to 46 cases per 100,000 people in patients aged ≥75 years. The prevalence of myeloma is likely to increase due to the extended survival and the growing life expectancy of the general population (2).

Recently, the introduction of novel agents such as thalidomide, lenalidomide, pomalidomide and bortezomib, has changed the treatment paradigm of MM and extended survival (3).

The prognosis of patients who are refractory to novel agents is especially poor. A retrospective study has recently demonstrated that patients with relapsed MM, who were refractory to bortezomib and were relapsed following, refractory to or ineligible to receive treatment with an IMiD, had a median overall survival (OS) and event free survival (EFS) of 9 and 5 months, respectively (4).

4.2 Immunomodulatory drugs (IMIDs)

Immunomodulatory drugs (IMIDs) have immunomodulatory, anti-angiogenic and direct apoptotic properties. Thalidomide is the first generation IMID approved for the treatment of multiple myeloma on May 2006. Six randomized clinical trials demonstrated the superiority of the combination MP-thalidomide versus MP (5). Besides thalidomide's teratogenicity, the most common side effects of thalidomide are peripheral neuropathy (PN), fatigue and constipation. It is also associated with an increased risk of deep vein thrombosis (DVT), especially when combined with dexamethasone (6). The encouraging activity of thalidomide in multiple myeloma has prompted the search for more potent and less toxic thalidomide derivatives: lenalidomide (CC-5013) and pomalidomide (CC-4047).

4.2.1 Lenalidomide

Lenalidomide, 3-(4-amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione, is a synthetic glutamic acid derivative obtained from thalidomide by the removal of an oxy group from the phthalyl ring and by the addition of an amino group. It is rapidly absorbed after oral administration and co-administration with food reduces the maximal plasma concentration (C_{max}) (7).

Some studies demonstrated that cereblon (CRBN), a human protein, is the primary teratogenic target of thalidomide; lenalidomide directly binds CRBN, but with higher affinity compared with thalidomide. CRBN is an essential requirement for IMID antimyeloma activity, in fact direct antimyeloma activity of lenalidomide could be associated with CRBN-mediated down-regulation of IRF-4 (8). Moreover CRBN expression resulted three times higher in responding patients treated with lenalidomide and dexamethasone, compared to non-responders, suggesting CRBN expression as a potential biomarker to predict IMID response (9).

The activity profile of Lenalidomide is similar to that of thalidomide but, *in vitro*, is 50 to 2000 times more potent in inhibiting cytokines production by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC) (10-11).

4.2.2 Lenalidomide-Dexamethasone (RD)

Two phase I studies started in April 2000 identified the maximum tolerated dose (MTD) of lenalidomide as 25 mg/day for 21 days/month; cytopenias were the dose-limiting toxicity in both studies. No significant somnolence, constipation and neuropathy were observed with continued lenalidomide therapy. However, reversible cytopenias were observed during the second cycle of treatment (10, 12).

A phase III , placebo-controlled trial investigated the efficacy of lenalidomide plus dexamethasone in the treatment of relapsed or refractory MM. Lenalidomide plus dexamethasone increased time to progression, rate and median duration of response and

overall survival as compared with placebo in all stratified subgroups. The most frequently reported adverse events were neutropenia, muscle cramps, constipation, nausea, tremor and dizziness (13).

Another phase III study, conducted in North America, compared lenalidomide dexamethasone with placebo in patients who received at least a prior line of therapy. The study demonstrated that lenalidomide plus dexamethasone increased the median duration of response, overall response rate, median time to progression and median overall survival. The most frequently reported non-hematological adverse events were fatigue, insomnia, diarrhea, constipation, muscle cramps and infection (14).

A recent phase III study evaluated lenalidomide treatment in newly diagnosed myeloma patients ineligible for ASCT. The median progression-free survival was 25.5 months with continuous lenalidomide–dexamethasone, 20.7 months with 18 cycles of lenalidomide–dexamethasone, and 21.2 months with melphalan-prednisone-thalidomide (MPT). Continuous lenalidomide–dexamethasone was associated with a significant improvement in progression-free survival, as compared with MPT. Continuous lenalidomide–dexamethasone also reduced the risk of progression or death, as compared with 18 cycles of lenalidomide–dexamethasone (15).

Lenalidomide in combination with dexamethasone (Len/Dex) is approved in the USA and the EU for the treatment of patients with MM who have received at least one prior antimyeloma therapy, based primarily on the results of two multicenter, randomized, placebo-controlled trials (13-14).

4.2.3 Lenalidomide maintenance

Three trials with lenalidomide maintenance treatment after autologous stem cell transplant (ASCT) demonstrated a significant increase of PFS or event-free survival compared with placebo maintenance (16-18). One trial evaluated lenalidomide maintenance in ASCT ineligible patients. Results showed that lenalidomide treatment significantly increased PFS after transplant and also in ASCT ineligible patients (19).

4.2.4 Pomalidomide

Pomalidomide, (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione, is a small glutamic acid developed as amino-phthaloyl-substituted analogue of thalidomide, developed in order to reduce the toxic effects and enhancing the anti-tumor activity of Thalidomide (20). It is a racemic mixture of the S/R-enantiomers which interconvert in plasma through enzymatic and non-enzymatic pathways.

Pomalidomide, like lenalidomide, has a direct toxic effect on myeloma cells (21), it induces apoptosis via the caspase 8/death receptor pathway (21), reduces adhesion molecule expression and pro-survival cytokine signaling (22) and may augment antimyeloma natural killer cell activity (23). A recent in vitro study (24) has demonstrated that CC-4047 blocks osteoclast differentiation during early phase of osteoclastogenesis. Therefore, CC-4047 might be a new drug to evaluate in patients with MM, because of its dual mechanism of action targeting both tumors and osteoclastic activity.

In 2013 pomalidomide was approved by EMA, in MM patients who have received at least two prior therapies, including both lenalidomide and bortezomib, and whose disease progressed after the last treatment.

4.2.5 Pomalidomide-Dexamethasone

A total of 38 patients were enrolled in a phase I/II study, and 4 pomalidomide dose-level cohorts were evaluated. The MTD of oral pomalidomide was determined as 4 mg/day when administered as single agent. The most common grade 3 and 4 treatment-emergent AEs included neutropenia, anemia, thrombocytopenia and fatigue. The results of this phase I study showed that pomalidomide was associated with encouraging response rates and manageable safety, in patients with RRMM previously treated

with lenalidomide and bortezomib (25). The phase II portion of this study showed that the efficacy of pomalidomide was enhanced by the addition of dexamethasone and significantly increased the median PFS. The limited cross-resistance between pomalidomide and lenalidomide supports the effectiveness of sequential use of immunomodulatory drugs, as well as combinations (26).

A phase II randomized open label study of the combination of pomalidomide and dexamethasone given either 21 days out of 28 or continuous in advanced MM included 92 patients with a median of 5 lines of prior treatment. All patients had received prior treatment with bortezomib and lenalidomide. Patients who responded to treatment benefited with improved TTP, PFS and OS. The results showed that the combination of pomalidomide and low dose dexamethasone was highly active and well tolerated in the treatment of relapsed and refractory MM. (27)

In the first phase III study of pomalidomide (MM-003) were enrolled 455 patients with advanced refractory or relapsed/refractory MM already treated with bortezomib and lenalidomide. Pomalidomide plus low-dose dexamethasone resulted in significantly longer PFS and OS and, an increased response rate compared with high-dose dexamethasone in patients with advanced MM. The main grade 3-4 adverse event was neutropenia (28).

The most common hematologic grade 3-4 adverse events associated with pomalidomide treatment were neutropenia (28-48%), anemia (16%-33%), thrombocytopenia (12%-22%). Non-hematological grade 3-4 adverse events were all less frequent than 15% (26-28).

This data demonstrated that pomalidomide can be safely administered and has significant efficacy in MM, even in the context of patients previously exposed and/or refractory to bortezomib and lenalidomide.

4.2.6 Pomalidomide-Cyclophosphamide-Dexamethasone

A phase I/II study was conducted in MM patients relapsed and/or refractory to lenalidomide to identify the most appropriate dose of pomalidomide in combination with cyclophosphamide-prednisone (PCP) and to determine its safety, tolerability and efficacy. Pomalidomide 2.5 mg/day was defined as the MTD. At the MTD, the most frequent grade 3 to 4 adverse events were neutropenia (42%), thrombocytopenia (11%), anemia (9%), neurologic (7%), dermatologic reactions (7%), and infections (5%) (29). In another study, pomalidomide-dexamethasone in combination with oral weekly cyclophosphamide resulted in a superior response rate and PFS compared to pomalidomide-dexamethasone alone in patients with relapsed and refractory MM. In this phase II study the pomalidomide dose was 4 mg on day 1-21, cyclophosphamide was given at 400 mg on day 1, 8, 15 and dexamethasone 40 mg on days 1-4 and 15-19. An increased hematologic toxicity was observed; hematologic grade 3 to 4 adverse events were more frequent in the cyclophosphamide arm, although this was not statistically significant (33). In several studies currently ongoing the dose of pomalidomide used is 4 mg daily (25-27, 39-41), alone or in combination with other agents.

4.3 Study Rationale

The combination lenalidomide plus low-dose dexamethasone (Rd) is an active treatment for Multiple Myeloma (MM) patients, both at diagnosis and at relapse (7, 13-15). Three trials with lenalidomide maintenance treatment after autologous stem cell transplant (ASCT) and one study after conventional induction therapy showed a significant risk reduction for progression-free survival (PFS); an increase in overall survival (OS) in one of the transplant trials was also reported (16-19).

Pomalidomide, is an immunomodulatory molecule (IMID), derivative of thalidomide, developed to improve the efficacy and reduce the toxicity of the parent molecule. Pomalidomide and dexamethasone (pom-dex) proved to be an effective and safe treatment in MM patients refractory to lenalidomide and refractory/intolerant to bortezomib (26, 28).

The addition of chemotherapy to novel drugs has been evaluated both at diagnosis and at relapse (30-32). The combination of pomalidomide-cyclophosphamide-prednisone was proved to be safe and effective in relapsed/refractory MM patients (29).

The combination pomalidomide-cyclophosphamide-dexamethasone (pom-cyclo-dex) was tested in a phase II study in patients with relapsed and refractory MM, demonstrating a good tolerability using pomalidomide at the dose of 4 mg. Pom-cyclo-dex resulted in a superior response rate and PFS compared to pom-dex. The increased hematologic toxicities, as a result of the addition of oral cyclophosphamide, were manageable (33).

Relapsed myeloma is defined as previously treated myeloma that progresses and requires the initiation of salvage therapy (34).

According to IMWG recommendation, biochemical relapse is defined as an increase of ≥ 25% of tumor burden from lowest value, without any CRAB feature (CRAB is defined as the onset of clinical symptoms: hypercalcemia, renal failure, anemia and bone lesions) and detected in 2 consecutive determinations (34- 36). The increase of 25% from lowest response value in any one or more of the following:

- Serum M-component (absolute increase must be ≥0.5 g/100 ml)
- and/or Urine M-component (absolute increase must be ≥200 mg per 24 hours),
- and/or only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved (FLC) levels must be >10 mg/dL

Clinical relapse requires one or more of direct indicators of progressive disease and/or end organ dysfunction (CRAB features) (34-36). Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder:

• hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)

• renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 µmol/L (>2 mg/dL)

• anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L

• bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

Any one or more of the following biomarkers of malignancy:

• clonal bone marrow plasma cell percentage ≥60%

• involved:uninvolved serum free light chain ratio ≥100

• >1 focal lesions on MRI studies (each focal lesion must be 5 mm or more in size)

Treatment at relapse should start in case of clinical relapse or a significant paraprotein increase (35). In case of biochemical relapse, the standard is observation only, as in case of asymptomatic MM at diagnosis. However, a recently published trial,

showed improved PFS and OS for newly diagnosed asymptomatic patients treated with lenalidomide and dexamethasone in comparison with observation only. Our hypothesis is that similarly, in the relapse setting, patients may benefit from an early intervention, meaning a treatment at biochemical relapse and not only in case of clinical relapse of rapid increase of M-component.

The second aim of our trial is to compare early treatment (i.e. treatment at biochemical relapse generally managed with follow-up only) vs late treatment (i.e treatment at clinical relapse or in case of significant paraprotein relapse, as per standard clinical practice).

5. OBJECTIVES

5.1 Primary objectives

- Compare the efficacy of combinations pom-dex versus pom-cyclo-dex in terms of OS.
- Evaluate the best treatment strategy (EARLY TREATMENT at biochemical relapse versus LATE TREATMENT at onset of CRAB symptoms/significant paraprotein increase) in terms of OS.

5.2 Secondary objectives

- Compare the best therapy, pom-dex vs pom-cyclo-dex in terms of PFS.
- Compare the best strategy, EARLY TREATMENT versus LATE TREATMENT, in terms of PFS2.
- Evaluate quality of life (QoL) and health related costs in the two therapies, pom-dex versus pom-cyclo-dex, and in the two strategies, EARLY TREATMENT versus LATE TREATMENT.
- Explore the presence of clinically meaningful interactions between therapies and strategies.
- Determine whether tumor response, PFS, PFS2 and OS might significantly change in particular subgroups of patients defined by prognostic factors (such as International Staging System, chromosomal abnormalities) and by performance status.
- Evaluate the safety and tolerability of the strategy and of the combination pom-dex and pom-cyclo-dex

5.3 ENDPOINTS

5.3.1 Starting point of the time-to-event endpoints

According to the study design, all patients are randomized when a biochemical relapse is documented. However while the assignment to a strategy (Early or Late) is disclosed at enrollment, the disclosure of the assigned therapy (pom-dex or pom-cyclo-dex) is kept concealed until the clinical relapse is documented in the Late treatment group. Thus, the starting point for the calculation of time-to-event endpoints to compare therapies will be different according to the early or late arm assignment.

5.3.2 Primary endpoint

The primary endpoint for both comparisons is Overall Survival (OS), defined as the time from the date of random disclosure to the date of death from any cause.

5.3.3 Secondary endpoints

- *Time to clinical progression,* defined as the time from random assignment to the early or late strategy to the date of onset of CRAB symptoms or death.
- *PFS,* defined as the time from random disclosure to the date of disease progression or death (34).
- *PFS2*, defined as the time from random disclosure to the date of disease progression while on the subsequent line of treatment or death from any cause (36).
- Objective overall response rate,
- *Quality of life*, measured with EORTC-QLQ-C30 and QLQ-MY24 at baseline, every 2 months during the first year, and then every 6 months.
- *Health related costs*
- Incidence of hematologic and non-hematologic adverse events (AEs)

6. EXPERIMENTAL PLAN

6.1 Study design

When patients experience biochemical relapse during lenalidomide maintenance, they will stop lenalidomide, as established in the related experimental protocol. Afterwards, patients can be considered for the enrollment in the present study if all inclusion and exclusion criteria are met.

This is a multicenter, randomized, open label phase III study designed to assess the safety and the efficacy of two different pomalidomide combinations as salvage treatment in multiple myeloma (MM) patients.

Patients will be evaluated at scheduled visits in up to 3 study periods: pre-treatment, treatment and long-term follow-up (LTFU).

The pre-treatment period includes screening visits, performed at study entry. After providing written informed consent to participate in the study, patients will be evaluated for study eligibility. The screening period includes the availability of inclusion criteria described above.

The treatment period includes administration of pomalidomide and dexamethasone in arm A and pomalidomide combined with cyclophosphamide and dexamethasone in arm B. The response will be assessed after each cycle. Patients will be randomized to receive treatment at biochemical relapse (ARM I) or at clinical relapse (ARM II).

The LTFU periods will start after development of confirmed progression disease (PD), all patients are to be followed for survival during the LTFU period every 3 months via telephone or office visit.

6.2 Numbers of centres

Approximately 35 sites will participate to the protocol.

6.3 Numbers of subjects

260 patients will be enrolled from different sites.

6.4 Estimated study duration

Treatments will be administered until the subsequent clinical relapse. The estimation of treatment duration is about 12-18 months. Patients will be followed for at least 5 years from randomization or until death.

6.5 Treatment schema

Patients at biochemical relapse during lenalidomide maintenance, will stop lenalidomide treatment and then will be randomized to:

ARM A: Pom-dex

Pomalidomide: at the dose of 4 mg/daily as oral administration (PO) on days 1-21.

Dexamethasone: at the dose of 40 mg as oral administration (PO) on days 1, 8, 15, 22.

Each cycle will be repeated every 28 days until progression or intolerance.

ARM B: Pom-cyclo-dex

Pomalidomide: at the dose of 4 mg/daily as oral administration (PO) on days 1-21.

Cyclophosphamide: 50 mg every other day as oral administration (PO) on days 1-28.

Dexamethasone: at the dose of 40 mg as oral administration (PO) on days 1, 8, 15, 22.

Each cycle will be repeated every 28 days until progression or intolerance.

AND

ARM I: EARLY TREATMENT

Patients will receive treatment at biochemical relapse with pomalidomide-dexamethasone (Arm A) or pomalidomide-cyclophosphamide-dexamethasone (Arm B), according to randomization. The randomization between Arm A and B will be disclosed at biochemical relapse.

ARM II: LATE TREATMENT

Patients will be randomized at biochemical relapse; at clinical relapse the randomization between Arm A and B will be disclosed and patients will receive pomalidomide-dexamethasone (Arm A) or pomalidomide-cyclophosphamide-dexamethasone (Arm B).

7. SUBJECT SELECTION

7.1 Inclusion criteria

- Patients >18 years and <80 years.
- Patient is, in the investigator(s) opinion, willing and able to comply with the protocol requirements.
- Patient has given voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care.

- Male patient agrees to use an acceptable method for contraception (i.e. condom or abstinence) for the duration of the study.
- Female of childbearing potential agrees to use two acceptable methods for contraception [implant, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot, tubal sterilization, sexual intercourse with a vasectomised male partner only (vasectomy must be confirmed by two negative semen analyses), ovulation inhibitory progesterone-only pills (i.e. desogestrel)] or absolute and continuous sexual abstinence.
- Patient has measurable disease, defined as follows: any quantifiable serum monoclonal protein value (generally, but not necessarily, ≥ 0.5 g/dL of M-protein) and, where applicable, urine light-chain excretion of >200 mg/24 hours; only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must be > 10 mg/dL. Less than 10% of oligo- or non-secretory MM patients with free light chains will be admitted to this study in order to maximize interpretation of benefit results.
- Patient receiving lenalidomide maintenance therapy as part of first line treatment (concomitant use of prednisone is accepted) and has experienced a biochemical relapse, with evidence of progressive disease defined as an increase of 25% from lowest response value in any one or more of the following: serum M-component (absolute increase must be ≥0.5 g/100 ml) and/or urine M-component (absolute increase must be ≥200 mg per 24 hours) only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must be >10 mg/dL (35).
- Patient who received as first line treatment a bortezomib-based therapy, including lenalidomide maintenance during the same line of therapy, can be included in the trial.
- Patient has a life-expectancy > 3 months
- Patient has not a currently active malignancy, other than non melanoma skin cancer and carcinoma in situ of the cervix, and has not invasive malignancies within the past 5 years.
- No history of allergic reactions attributed to study agents
- Patient has the following laboratory values within 28 days before baseline day 1 of the cycle 1:

  a) absolute neutrophil count (ANC) > 1 x 10^9/L
  b) platelet count > 75 x 10^9/L
  c) haemoglobin > 8 g/dl.
  d) aspartate transaminase (AST): < 2 x the upper limit of normal (ULN).
  e) alanine transaminase (ALT): < 2 x the ULN.

7.2 Exclusion criteria

- Pregnant or lactating females.
- Patient with Creatinine Clearance (CrCl) < 45 mL/minute
- Patient with peripheral neuropathy ≥ Grade 2
- Subject with any one of the following:
  - Congestive heart failure (NY Heart Association Class III or IV)
  - Myocardial infarction within 12 months prior to starting study treatment
  - Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris

- Any significant medical disease or conditions (e.g. pulmonary disease, infection) that, in the investigator's opinion, may interfere with protocol adherence or subject's ability to give informed consent or could place the subject at unacceptable risk.
- Clinical active infectious hepatitis type A, B, C or HIV
- Acute active infection requiring antibiotics or infiltrative pulmonary disease
- Contraindication to any of the required drugs or supportive treatments.
- Known allergy to any of the study medications, their analogues, or excipients in the various formulations.

8. STUDY DRUG MATERIAL AND MANAGEMENT

8.1 Supplier(s)

Commercial available supplies of dexamethasone and cyclophosphamide will be used.
Celgene Corporation will supply pomalidomide.

8.2 Dosage form

- Dexamethasone 0.2% drops, 20 mg vials for oral administration will be used
- Cyclophosphamide 50 mg tablets for oral administration will be used
- Pomalidomide will be supplied as 4 mg, 3 mg, 2 mg or 1 mg capsules for oral administration.

8.3 Packaging

- Dexamethasone 20 mg drop is available as vials.
- Cyclophosphamide 50 mg tablet is available as blister containing 50 tablets.
- Pomalidomide will be shipped in blister with tear-off labels. Blister will contain a sufficient number of capsules to last for 21 days of dosing. Drug will be supplied in 1, 2, 3 or 4 mg capsules.

8.4 Special Handling Instructions

Women of childbearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

8.5 Labelling

Dexamethasone and cyclophosphamide will be packaged and labelled by the manufacturer(s) according to their standard practices. Drug labels will contain at least the following information:

- Product amount.
- Directions for storage.
- Expiratory date.
- Manufacturer name and address.

Pomalidomide will be supplied by Celgene Corp., in blister labelled with detail Sponsor's name and address, the protocol number, EudraCT number, product name, dosage form, and strength, medication identification/kit number, dosing instructions, storage conditions, the quantity of study drug contained, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as needed and/or applicable.

8.6 Receipt of study drug

The Investigator is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

8.7 Storage

Dexamethasone and Cyclophosphamide may be stored at controlled room temp (15-36°C), in a dry place.

Pomalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat, cold and moisture.

At the study site, all investigational study drugs will be stored in a double locked, safe area to prevent unauthorized access.

8.8 Unused study drug supplies

Patients will be instructed to return empty blister or unused capsules. Unused or returned study drug will be destroyed locally in compliance with local pharmacy destruction procedures and drug disposition must be appropriately documented in the study file. Furthermore, the documentation reporting the drug destruction has to be sent to local Medical Affairs Dept. in Celgene srl. The local pharmacy is responsible for the drug destruction, and Celgene srl is not involved in any related activity. If any study drug is lost or damaged, its disposition should be documented in source documents.

8.9 Record of administration

Accurate records will be kept of all study drug administration (including dispensing and dosing) and will be made in source documents.

8.10 Dose-modification guidelines

Patients will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE (see Appendix I). Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction of one agent and not the other is appropriate if toxicity is related primarily to one of the agents. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

8.11 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment

If a patient fails to meet the criteria below for beginning the next cycle of treatment, initiation of the next cycle should be delayed for one week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for treatment have been met.

To initiate a new cycle of treatment following a dose interruption:

- the neutrophil count must be ≥ 1000/μL with or without G-CSF
- the platelet count must be ≥ 50,000/μL,
- and non-hematologic AEs must have recovered to grade ≤ 1.

If recovery from toxicities is prolonged beyond 14 days, then the dose of pomalidomide will be decreased by one dose level when dosing is restarted.

The maximum delay before treatment should be discontinued will be 4 weeks.

8.12 Criteria for Dose Modification

Toxicities should be attributed to a specific study drug, if possible, so that dose modifications can be made rationally. If multiple toxicities are noted, the dose adjustments and/or delays should be made once per cycle according to the most severe toxicity guidelines.

8.12.1 Pomalidomide Dose Adjustments

A decision regarding which study drug requires dose reduction will be dependent upon the toxicity, its onset, and time course. Alternative dose modifications may be recommended to maximize exposure to study treatment while protecting patient safety, given that there may be overlapping toxicities (eg, thrombocytopenia).

Table 11.1 Pomalidomide Dose Adjustments For Hematologic Toxicity

NCI CTC-AE Grade	Pomalidomide dose modification/recommended action
Neutropenia Grade 4 neutropenia (ANC < 500/μL) or Febrile neutropenia (ANC <1,000/μL with a single temperature of > 38.3°C or a sustained temperature of ≥ 38.3°C for more than one hour) lasting for more than 4 days	Hold the dose until ANC >1000/μL and resolution of the suspected infection. If the subject was not receiving GCSF therapy, GCSF therapy may be started at the discretion of the treating physician. On day 1 of the next cycle, the dose of pomalidomide may be maintained if neutropenia was the only pomalidomide-related toxicity requiring a dose modification and GCSF treatments are continued. Otherwise decrease by one dose level at start of next cycle.
Thrombocytopenia Grade 4 (platelets <25,000/μL)	Hold the dose. Dosing may resume at one dose level lower once the platelet count has recovered to ≥50,000/μL

Table 11.2 Pomalidomide Dose Adjustments For non-Hematologic Toxicity

NCI CTC-AE Grade	Pomalidomide dose modification
Rash	
Grade 2	Add antihistaminic therapy
Grade 3	Hold therapy, add antihistaminic and steroid therapy and decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1)
Grade 4	Discontinue study drug and subject from study
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ grade 1 before restarting dose)
Hypo/Hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Venous thromboembolism (VTE) ≥ Grade 3	Hold dose. Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.

Other ≥ Grade 3 pomalidomide-not related adverse events	Hold dose. Decrease by one dose level when dosing restarted at next cycle (adverse event must resolve to ≤ Grade 2 before restarting dosing)

Table 11.3 – Pomalidomide dose reduction step in Arm A and B	
Dose level 0	Pomalidomide 4 mg/day for 21 days every 28 days
Dose Level-1	Pomalidomide 3 mg/day for 21 days every 28 days
Dose level-2	Pomalidomide 2 mg/day for 21 days every 28 days
Dose level-3	Pomalidomide 1 mg/day for 21 days every 28 days

8.12.2 Dexamethasone dose adjustment

To minimize patient discomfort, dietary salt restriction, antiacids, histamine type 2 (H_2)- blockers, potassium supplements and other comparable medications (i.e. proton pump inhibitors) may be used as needed.

Precautions should be taken when patients are withdrawing from high dose corticosteroid therapy. Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids. Table 11.4 provides dose adjustments guidelines for the management of common dexamethasone-related toxicities. For toxicities that occur but are not specifically listed in the table, the general guideline is that dexamethasone should be held until the toxicity resolves to Grade ≤ 1 and the dose decreased 50% for Grade 3 or greater non-haematological toxicity. The patient should be given all support therapy necessary in these instances.

Table 11.4 Dexamethasone Dose Adjustments For related toxicities

NCI CTC-AE Grade	**Dexamethasone dose modification**
Dyspepsia, gastric or duodenal ulcer, or gastritis Grade 1-2 (requiring Medical Management)	Treat with H_2 blockers, sucralfate, omeprazole, or other comparable medications (i.e. proton pump inhibitors). If symptoms persist despite treatment, permanently decrease the dexamethasone dose by two dose levels.
Dyspepsia, gastric or duodenal ulcer, or gastritis ≥Grade 3 (requiring hospitalisation or surgery)	Interrupt dexamethasone until symptoms are adequately controlled. Thereafter, resume dexamethasone at a dose reduced by two dose levels with concomitant H_2 blockers, sucralfate, omeprazole, or other comparable medications (i.e. proton pump inhibitors). If symptoms persist despite above measures, permanently discontinue dexamethasone.
Acute pancreatitis ≥Grade 3	Permanently discontinue dexamethasone.
Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	Administer diuretics, as needed, and decrease dexamethasone dose by one dose level. If edema persists despite above measures, decrease dexamethasone dose by two dose levels. If symptoms persist despite a decrease by two dose levels, then permanently discontinue dexamethasone.

Confusion or mood alteration ≥Grade 2 (interfering with function +/- interfering with ADLs)	Interrupt dexamethasone until symptoms resolve. If symptoms resolve, restart dexamethasone at a dose reduced by two dose levels. If symptoms persist above measures, then permanently discontinue dexamethasone.
Muscle weakness ≥Grade 2 (symptomatic and interfering with function +/- interfering with ADLs)	Decrease dexamethasone dose by one dose level. If symptoms persist despite above measures, decrease dexamethasone dose by two dose level. If symptoms persist despite decrease by two dose levels, then permanently discontinue dexamethasone.
Hyperglycemia ≥Grade 3	Administer insulin or oral hypoglycemics as needed. If hyperglycemia is not controlled despite treatment, decrease the dexamethasone dose by one dose level until satisfactory glucose levels are achieved.

Table 11.5 – Dexamethasone dose reduction step	
Dose level 0	Dexamethasone 40 mg daily (on days 1, 8, 15, 22)
Dose Level-1	Dexamethasone 20 mg daily (on days 1, 8, 15, 22)
Dose level-2	Dexamethasone 10 mg daily (on days 1, 8, 15, 22)
Dose level-3	Dexamethasone 10 mg daily (on days 1, 15)

8.12.3 Cyclophosphamide Dose Adjustment

Table 11.6 –Cyclophosphamide Dose Adjustments For related toxicities

NCI CTC-AE Grade	**Cyclophosphamide dose modification**
Grade 4 neutropenia (ANC<500 µl) or febrile neutropenia (fever ≥ 38.5°C and ANC < 1000 µl)	Hold therapy. If subject was not receiving GCSF therapy, initiate GCSF therapy. On day 1 of next cycle, continue GCSF as needed and maintain dose of cyclophosphamide if neutropenia was the only toxicity. Otherwise, decrease by one dose level at start of next cycle
Grade 4 thrombocytopenia (PLTs < 25.000 µl)	Hold therapy. Decrease by one dose level when dosing restarted at next cycle
Grade 4 anemia (Hb < 6.5 g/dL in the absence of bleeding and despite therapy with an erythropoietin agent)	Hold therapy. Decrease by one dose level when dosing restarted at next cycle if anemia study-drug related

For Grade 3-4 non-hematological “drug-related” toxicities specifically related to cyclophosphamide, the drug should be held for up to 4 weeks until the toxicity resolves to Grade <2 and decrease by one dose level

Table 11.7 –Cyclophosphamide dose reduction step	
Dose level 0	Cyclophosphamide 50 mg every other day for 28 days (day 1-28)
Dose Level-1	Cyclophosphamide 50 mg every other day for 21 days (day 1-21)
Dose level-2	Cyclophosphamide 50 mg every other day for 15 days (day 1-15)

8.13 Excluded Concomitant Medications and Procedures

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM, other than study drugs. Subsequent anti-myeloma treatment should not be initiated prior to PD or study treatment discontinuation.
- The need of radiation therapy is considered to be a treatment failure. However an exception is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics, because pathological bone fractures do not by themselves fulfil a criterion for disease progression.
- Chronic use of steroids (other than dexamethasone) or any other immunosuppressive therapies is prohibited in this study.
- Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary (see Appendix XV).

8.14 Required concomitant medications and procedures

During pomalidomide therapy all patients will receive anti-thrombotic prophylaxis, aspirin or low-molecular weight heparin, according to their risk, as outlined in Appendix XI.

8.15 Permitted concomitant medications and procedures

- All subjects will be allowed to receive bisphosphonate therapy (intravenous pamidronate or zolendronic acid) according to the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines; it is indicated for multiple myeloma patients with lytic bone disease and it is recommended that bisphosphonates be continued until the benefit of the patient is believed to be less than the inconvenience of receiving an intravenous monthly infusion or until the patient develop significant side effects to the drug.
- Patients will receive G-CSF for febrile neutropenia and in case of grade 3 neutropenia (ANC less than < 1000 µl).
- Antiviral prophylaxis should be used in case history of Herpes Zoster Virus (HZV) infection. Appropriate antibacterial, antifungal, or antiviral therapy should be used if infections occur. Oral antibiotic prophylaxis is suggested if neutropenia or recurrent infections occur.
- Anti-emetics will be given during chemotherapy and the following days if needed.
- Subjects may receive supportive care with erythropoietin or darbepoetin, in accordance with institutional guidelines.
- The use of platelet transfusions should be considered in the following circumstances:
  a) as preparation for an invasive surgical procedure, in order to maintain a platelet count ≥50 $x10^9$/L;
  b) if the patient has an active infection and/or high fever, in order to maintain a platelet count ≥20 x 10^9/L;
  c) if the patient has a platelet count ≥10 x 10^9/L
- The use of any red cell product should be considered in the following circumstances:
  a) If the patient has a haemoglobin < 8 g/dL in order to reduce the risk of inadequate oxygenation.
  b) If the patient is asymptomatic and has a haemoglobin between 7 and 8 g/dL, the investigator may consider transfusion on a per-patient basis in order to maintain a haemoglobin > 8 g/dL
  c) If the patient is actively bleeding or has symptomatic cardiac or pulmonary disease or other extenuating circumstances where oxygenation is impaired, the investigator may elect to transfuse on a per-patient basis. In these instances, the trigger haemoglobin value may be >8 g/dL.
- Other therapies considered necessary for the subject's wellbeing may be administered at the discretion of the Investigator. These therapies may include:
  a) antacids, histamine type 2 (H_2)- blockers, and other comparable medications (i.e. proton pump inhibitors);
  b) analgesics;
  c) antihistaminic;

d) laxatives.

- Allopurinol (in subjects at risk for tumour lysis syndrome due to high tumor burden) is optional and will be prescribed at the Investigator's discretion.
- Supportive measures consistent with optimal patient care may be given throughout the study.

9. STUDY DISCONTINUATION

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

Treatment with study drug is discontinued when any of the following occurs:

- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator.
- Major violation of the study protocol.
- Withdrawal of consent.
- Lost to follow up.
- Death.
- Suspected pregnancy.
- Confirmed Progression of disease.

10. ASSESSMENT

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. For those subjects who fail screening the reason(s) for exclusion must be recorded in the subject's source documents. Screening assessments occur 28 days from Baseline (Baseline: first day of study drug administration, Cycle 1, Day 1) with an exception for skeletal survey that can be performed within 2 months before baseline.

Women of childbearing potential must have two negative pregnancy tests. The first should be performed at screening and the second from 1 to 3 days before each cycle of pomalidomide therapy. If the subject is pregnant, she cannot take pomalidomide. The subject must have a pregnancy test done by the doctor every week during the first 4 weeks of treatment. She will then have a pregnancy test every 4 weeks if her menstrual cycles are regular or every 2 weeks if her cycles are irregular. The subject may also need to have a pregnancy test if she misses her period or has unusual menstrual bleeding. A serum or urine pregnancy test will be repeated at the EOT visit (Appendix IX). -

10.1 Efficacy assessment

Baseline assessments must occur within 28 days of study drug administration. Efficacy assessments are scheduled to occur every 28 days for Myeloma protein measurements in serum and urine. Other efficacy assessments are scheduled to occur as indicate in the report below and as per Section 3, Study tests and observations.

All partial and complete responses must be confirmed with another efficacy assessment at any time following the first test provided it is before any new/non-protocol therapy.

10.1.1 Myeloma Monoclonal Protein and serum free-light chain.

The date of start of study drug is designated as Study Day 1 (coincides with Cycle 1, Day 1). Therefore, serum M-protein levels (quantified from the serum protein electrophoresis [SPEP] test), urine M-protein levels (quantified from the urine protein

electrophoresis [UPEP] test performed on 24-hour urine collection), and serum immunoglobulin levels are obtained at screening, at Study Day 1, and then every 28 days (4 weeks) during the study period. Serum and urine immunofixation (IFE) tests are performed at screening to identify the immunoglobulin subtype of multiple myeloma and thereafter are triggered to be performed whenever M-protein is undetectable in both serum and urine by protein electrophoresis studies to confirm complete response (CR). Serum Free-light chain (FLC) assay will be performed at screening and to confirm sCR for patients with baseline serum FLC levels > 10 mg/dl.

10.1.2 Bone marrow examination

Bone marrow aspiration and/or biopsy for morphology are to be performed for all patients during the screening, when clinically indicated during treatment, and to confirm CR/sCR or PD. A bone marrow sample for cytogenetic testing must be obtained at the screening visit and will be sent to a centralized laboratory. A sample for immunophenotype will be obtained at screening, to confirm CR/sCR and when PD occurs.

10.1.3 Skeletal survey and other radiographs

During the screening period and if at any time the physician believes that are symptoms or signs that suggest increased or new bone lesions. Plain films of symptomatic sites for signs or symptoms of new bone lesions may be obtained instead of a full skeletal survey. It is important in the screening period to document sites of myelomatous disease, especially in extramedullary areas. This documentation may require clinical examination, CT-scanning, MRI or PET/CT evaluations. For those with documented extramedullary disease, radiographic assessments should be made every 3 cycles during the first 6 cycles, and then every 6 cycles, at treatment discontinuation, and when clinically indicated to confirm a response ≥ PR. The same imaging modality used at screening (CT,MRI,PET/CT) should be used for all follow-up assessments.

10.1.4 β2-microglobulin, C-reactive protein and LDH

Blood sample for β2-microglobulin, C-reactive protein and LDH are to be collected at the screening visit and at PD.

10.1.5 ECOG performance status

ECOG performance status scores are to be determined during the screening period and every 28 days, during treatment (Appendix IV).

10.1.6 Assessment of disease response

The investigator will perform tests that will allow evaluation of response to therapy according to the International Response Criteria for Multiple Myeloma presented in Appendix V.

Assessment of disease response using non-invasive procedures will be performed every 28 days during treatment. Non-invasive assessments include clinical examination and blood/urine tests. Skeletal surveys are done at screening for all patients. Other radiographs to document changes in extramedullary disease may also be necessary.

Assessment of disease response using invasive procedures will be performed at screening, and when clinically indicated. Invasive assessments include bone marrow aspirates/biopsies.

10.2 Safety assessment

All patients will attend study visits to assess safety of treatment during the study as outlined below and in Section 3, Study tests and observations.

During treatment, patients will attend study visits every 14 days during the first 6 cycles and then every 28 days in order to assess the haematologic and extra-haematologic toxicity of the treatment, until evidence of progressive disease or unless clinically indicated.

The Discontinuation from Study Drug Visit will be scheduled as soon as possible after a subject has been discontinued from the study treatment, regardless of the reason.
After development of confirmed PD all patients are to be followed for survival during the LTFU period every 3 months via telephone or office visit. An unscheduled visit can occur at any time during the study.

10.2.1 Medical History

A complete medical history will be obtained to include descriptions of all prior and ongoing diseases and disorders. All medications, treatments and therapies used in the prior 4 weeks as well as those currently being taken will be documented.

10.2.2 Physical Examination

A complete physical examination and collection of vital signs (blood pressure, heart rate, temperature, oxygen saturation and respiratory rate) will be conducted during the screening period, every visit and at the end of treatment to evaluate any changes from screening. On screening visit measurement of weight and height will be done.
Symptom-directed physical examinations and collection of vital signs will be performed for all patients throughout the treatment period.

10.2.3 Thrombosis assessment

Patients will be informed of the possible occurrence of thrombotic events. Symptom-directed physical examinations will be performed for all patients throughout the treatment period. Compression ultrasonography (CUS) and measurements of plasma D-dimer (DD) will be done when VTE will be suspected. Lung scan, spiral CT-scan and/or pulmonary angiography and/or TE echocardiography will be performed if pulmonary embolism is suspected.

10.2.4 Neurotoxicity assessment

The FACT/GOG survey of neurotoxicity (Appendix XII) will be administered to patients at the screening and at day 1 of each cycle. The neurotoxicity assessment includes also a questionnaire that must be filled in by the physician at each visit day (Appendix XIV). After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

10.2.5 Cardiac and pulmonary tests

A 12-lead electrocardiogram will be obtained during the screening period and should be repeated during the treatment period if screening results are abnormal and/or if clinically indicated for the management of new or worsening symptoms or signs.
A postero-anterior and lateral chest X-ray will be performed during the screening period and should be repeated during the treatment period if screening results are abnormal and/or if clinically indicated for the management of new or worsening symptoms or signs.

10.2.6 Clinical Laboratory Evaluations

The following clinical laboratory evaluations will be performed:

- ***Serum Chemistry:*** Sodium, potassium, creatinine, calcium, glucose, total bilirubin, AST, ALT, ALP, GGT, uric acid and magnesium, must be performed:
    a) at screening visit
    b) when clinically indicated.
    c) every 14 days during cycle 1-6.
    d) every 28 days after the 6th cycle

e) albumin and total protein will be evaluated at assessment of disease response

- ***Thyroid function*** must be performed at screening visit and at then approximately every three months during therapy
- ***Hematology***: Red blood cell (RBC) count, hemoglobin, hematocrit, MCV, MCH, MCHC, white blood cell (WBC) count and differential, absolute neutrophil count (ANC), and platelet count must be performed:
    a) at screening visit
    b) when clinically indicated
    c) every 14 days during cycle 1-6
    d) every 28 days after the 6th cycle

10.2.7 Quality of Life Evaluation

Health-related QoL instruments have been recognized as important measures of subject satisfaction with therapy for MM. Quality-of-life assessments will be measured using the EORTC QLQ-C30 and the EORTC QLQ-MY24.

The EORTC QLQ-C30 is a validated QoL instrument that has been translated into languages spoken at sites where this study will be conducted. The QLQ-C30 (Appendix VII) and QLQ-MY24 (Appendix VIII) will be administered at Baseline, and at day 1 every 2 cycles for the first year and then every 6 months.

11. ADVERSE EVENTS

11.1 Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

If special reporting conditions are applicable (e.g., disease progression is not to be reported as an adverse event), it should be clearly explained here and also cross-referenced to the section defining efficacy endpoints in the protocol.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 30 days after last dose of study drug, or until the start of subsequently antineoplastic therapy, or until the last study visit, whichever period is longer. AEs and serious adverse events (SAEs) will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to the Drug Safety Unit of Celgene Italy within 24 hours of the Investigator's knowledge of the event by facsimile, using the SAE Report Form.

Serious unexpected suspected adverse reaction (SUSAR) are all SAEs that are judged to be unexpected and related to study drug(s), as specified in ICH E2B guidelines: Clinical Safety Data Management Data Elements for Transmission of Individual Case

Safety Reports. Any SUSARs from sites participating in the trial which are considered to be reportable, have to be reported to Sponsor in the same timeline of SAE report.

Any death occurring within 30 days from the last study drug received by the patient regardless of the subject having discontinued from the study must be reported to the promoters as a SAE

The Sponsor will supply Celgene with a copy of all SAEs which involve exposure to a Celgene product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (IB).

11.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1 Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect in the offspring of an exposed subject;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in (see Section 11.5). This includes any second primary malignancy, regardless of causal relationship to the study drug, occurring at any time for the duration of the study, from the time of signing the ICD up to 3 years (follow-up period for the study). Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate: for each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study drug action taken regarding study drug and outcome.

11.2.2 Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); Appendix I

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3 Causality

The Investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

11.2.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5 Action Taken

The Investigator will report the action taken with study drug as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of study drug as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6 Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

11.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of study drug dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfil a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

11.4 Pregnancy

11.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug or within 28 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Sponsor pharmacovigilance contact. The exposure of any pregnant female (e.g., caregiver or pharmacist) to pomalidomide is also an immediately reportable event.

The Sponsor will inform Celgene immediately, using the Pregnancy Reporting Form provided by Celgene or an approved equivalent form, of any information related to pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state)

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counselling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Sponsor pharmacovigilance contact immediately about the outcome of the pregnancy (either normal or abnormal outcome). The Sponsor will inform Celgene immediately.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study drug should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

If a pregnancy related event is reported in a female partner of a male subject, the investigator should ask if the female partner is willing to share information with Celgene Drug Safety and allow the pregnancy related event to be followed up to completion.

The Sponsor will inform Celgene immediately, using the Pregnancy Reporting Form provided by Celgene or an approved equivalent form, of any information related to pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in partner of Patients while the Patients are still treated with the Investigational Product or within 28 days of the Patients' last dose of Investigational Product.

11.5 Expedited Reporting of Adverse Events

11.5.1 Reporting to Regulatory Authorities and the Ethics Committee

The Sponsor will inform relevant Regulatory Authorities and Ethics Committees;

- Of all relevant information about serious unexpected adverse events suspected to be related to the study drug that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently submitted within additional eight days.

- Any SUSARs will be notified into EVWEB database within 7 calendar days for fatal or life-threatening reports and within 15 calendar days for all the other cases. Sponsor will inform with CIOMS form, all Principal investigators of the sites, Regulatory Agencies and Companies representative, Ethic Committee of the coordinating site .

- Of all other serious unexpected events suspected to be related to the study drug as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

11.5.2 Immediate reporting by Investigator to Sponsor and Sponsor to Celgene

The investigator will inform the Sponsor of all SAEs within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

The Sponsor will supply Celgene with a copy of all SAEs which involve exposure to a Celgene product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (IB).

The Sponsor will provide Celgene with a copy of the annual periodic safety report e.g. Annual Safety Report (ASR) at the time of submission to the Regulatory Authority and Ethics Committee.

11.6 Contact details for Sponsor

Pharmacovigilance

Fondazione Neoplasie Sangue Onlus (FO.NE.SA Onlus)

Sede legale: Via Saluzzo 1/A – 10125 Torino

Sede operativa: Via Genova 3 – 10126 Torino

Italy

Phone no.: +39/0116336107

Fax no.: +39/0116334187

Email for Responsible for Pharmacovigilance : pharmacovigilance@torinotrial.it

Drug Safety Unit – Celgene Italy

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Mobile: +39 340 8369630

e-mail: drugsafety-italy@celgene.com

12. STATISTICAL ASPECTS

12.1 Sample Size determination

This is a 2x2 factorial randomized study.

The sample size of the study has been calculated in order to demonstrate both the primary objectives, assuming no major interaction between the 2 factors.

The sample size calculation has been performed on the basis of the following assumptions:

- Median OS in the late treatment group: 14 months
- Median OS in the early treatment (experimental) group: 21 months (HR 0.67)
- Two sided α= 0.05
- β= 0.20
- Accrual time: 36 months
- Follow-up: 24 months
- Rate of expected losses during follow up: 5%
- Allocation ratio: 1:1:1:1 (2x2 design)

The total sample size needed for the study is 256 patients (rounded to 260) and the final analyses will be performed when at least 191 deaths will be recorded.

This sample size is based on the early vs late strategy because it is the maximum sample size required; it should be also sufficient to assess a similar OS advantage of pom-cyclo-dex vs pom-dex with the same statistical assumptions.

12.2 Analysis Populations

The following analysis populations are defined:

- *Treatment strategy population*. The Strategy Population includes all patients who are randomised to the Early or Late strategy arm.
- *Therapy population*. The Therapy Population includes:
    - all patients of Early strategy who are simultaneously randomised to the pom-dex or pom-cyclo-dex arm
    - all patients of Late strategy who are still available at the time of disclosure of random allocation to the pom-dex or pom-cyclo-dex arm

12.3 Prognostic factors and planned subgroup analyses

Subgroup analyses on the primary efficacy endpoint (OS) will be performed to explore potential heterogeneity of treatment strategy and therapy effects by patient's characteristics. Subgroup analyses will be carried out irrespective of whether there is an overall significant effect on the primary outcome.

The following subgroup analyses will be performed:

- Early/Late Strategy (for pom-cyclo-dex vs pom-dex comparison only)
- pom-cyclo-dex/pom-dex therapy (for Early vs Late Strategy comparison only)
- Age groups
- Gender
- International Staging System,

- Chromosomal abnormalities
- ECOG Performance status
- If, during the course of the study, other relevant subgroups are identified in the literature, then these subgroups will also be examined.

12.4 Efficacy Analyses

For all statistical tests performed, the calculated p-values will be two-tailed and an alpha level of 0.05 will be used to assess statistical significance. For each point estimates, its 95 percent confidence interval (95%CI) will be reported.

12.5 Evaluation of Time-to-events endpoints according to planned comparisons

According to the factorial design of this study, the primary endpoint (Overall Survival) will be evaluated for both the planned comparisons (Early vs Late Strategy, pom-cyclo-dex vs pom-dex).
Secondary time-to-events endpoints will be evaluated and compared according to the table below:

Comparisons:	OS	TTCP	PFS	PFS2
Early vs Late Strategy	Yes	Yes	No	Yes
pom-cyclo-dex vs pom-dex	Yes	No	Yes	No

Abbreviations: OS=Overall Survival, TTCP=Time to clinical Progression, PFS=Progression free Survival, PFS2= PFS on next line therapy.

12.5.1 Overall Survival (Primary Endpoint)

Overall survival will be determined from the date of random disclosure (treatment strategy comparison or therapy comparison) to the date of death from any cause. Patients alive at the time of the final analysis will be censored at the date of the last contact.
For each randomization arm, estimates of the overall survival function will be made by the Kaplan-Meier product-limit method. Difference between arms will be evaluated with the Hazard Ratio (HR) and its 95%CI, using the Cox proportional-hazards model adjusted for the randomization stratification factors (ISS, age and chromosomal abnormalities). Pre-specified subgroup analyses on primary endpoint (OS) will be performed to explore potential heterogeneity of treatment strategy and therapy effect by patient's characteristics (see 12.3 Prognostic factors and planned subgroup analyses).
For each subgroup, a Cox proportional-hazards model will be used and interaction will be tested by inserting an interaction term between the randomization group and the subgroup covariate of interest. The effect (HR) and its 95%CI will be presented along with the p-value of the interaction test.

12.5.2 Time to clinical Progression

Time to clinical Progression will be determined from the date of random disclosure (for the early vs late strategy comparison only) to the date of the onset of CRAB symptoms or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date.

For each randomization arm, the PFS function will be estimated by the Kaplan-Meier product-limit method. Difference between arms will be evaluated with the Hazard Ratio (HR) and its 95%CI, using the Cox proportional-hazards model adjusted for the randomization stratification factors.

12.5.3 Progression-Free Survival

Progression-free survival will be determined from the date of random disclosure (for the therapy comparison only) to the date of documented disease progression or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date.

For each randomization arm, the PFS function will be estimated by the Kaplan-Meier product-limit method. Difference between arms will be evaluated with the Hazard Ratio (HR) and its 95%CI, using the Cox proportional-hazards model adjusted for the randomization stratification factors.

12.5.4 PFS on next line therapy (PFS2)

PFS2 will be determined from the date of random disclosure (treatment strategy comparison only) to the date of documented disease progression on the subsequent line treatment or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date.

For each randomization arm, the PFS2 function will be estimated by the Kaplan-Meier product-limit method. Difference between arms will be evaluated with the Hazard Ratio (HR) and its 95%CI, using the Cox proportional-hazards model adjusted for the randomization stratification factors.

12.5.5 Quality of life analysis

Repeated QoL measurements will be collected at baseline, every 2 months during the first year of treatment and then every six months. Generalized linear mixed models will be applied to compare the randomization arms. The pattern of missing data (which individuals, at which assessments) and the reasons will be investigated to reconstruct the missing data mechanism to some extent and sensitivity analyses for the methods of imputation and estimation will be performed.

12.5.6 Cost-effectiveness analysis

A within trial cost-effectiveness analysis, with total healthcare costs and QALYs gained per patient calculated during the trial follow up, will be performed.

Mean healthcare costs during the study period will be estimated for every patient in each randomization arm. Incremental cost-effectiveness ratio (ICER) will be calculated by dividing the difference in mean total costs between the randomization arms by the difference in the mean effects. The ICER will be calculated for the primary clinical efficacy measure of the trial (OS) and for QALYs.

12.5.7 Stopping rules

Historical data on similar patients show, on average, a toxicity rate of haematological adverse events ≥ grade 4 or non-hematological adverse events ≥ grade 3 of 40% (9, 10, 14, 15).

Toxicity will be evaluated for the entire duration of the study according to the NCI CTCAE, version 4.03. Arm specific stopping rules for toxicity during the first 3 cycles of therapy are pre-specified to assure safety of treatments.

A toxicity rate of ≤45% is considered acceptable, otherwise the treatment will be stopped for excessive toxicity.

Any of the following toxicities occurring during the first 3 cycles will be considered for safety monitoring and stopping rules:

1. Hematologocal toxicities ≥ grade 4
2. Non-hematological toxicities ≥ grade 3

The stopping bundarie are calculated using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998) (43, 44, 45).

For each arm, the following table describes the toxicity stopping boundary for cohorts of 10 patients (boundaries calculated with a posterior probability >= 0.95 that the experimental treatment toxicity is more than 45%).

# Patients (in complete cohorts of 10)	# Toxicities (inclusive) The trial will be stopped if there are at least this many toxicity
10	8
20	14
30	19
40	25
50	30
60	36
70	41
80	46
90	52
100	57
110	62
120	68
130	Always stop with this many patients

13. SUBSTUDY ABOUT CLONAL EVOLUTION ANALYSIS AND HETEROGENEITY OF MUTATIONAL PROFILES IN MULTIPLE MYELOMA (MM) PATIENTS RECEIVING IMMUNOMODULATORY DRUGS (IMIDS)

Background

Genetic instability plays an important role in oncogenesis by perturbing critical cell signalling pathways, including activation of oncogenes and/or deletion of tumour suppressor genes. Recent studies have shown a marked heterogeneity of mutations in patients with MM. Importantly, the collection of serial sampling at different stages of MM disease revealed diverse patterns of clonal evolution associate with clinical disease progression, including linear evolution, differential clonal response, and branching evolution.

Our hypothesis is that the identification of myeloma sub-clones will provide a better prognostic stratification to detect “high risk” patients. The overall goal of this project is to investigate evolving genomic changes and their significance in MM patients, combining deep sequencing of tumor samples at the serial stages of disease progression through a prospective clinical trial.

Objectives:

- To identify spectrum of genomic lesions and pattern of clonal evolution in uniformly treated patients with MM. We plan to purify MM cells from bone marrow samples at study entry and subsequently at time of relapse (or lack of response) and we will perform Whole Exome Sequencing to identify mutational pattern at the time of progression during lenalidomide and subsequently after progression during pomalidomide. We will evaluate clonal content (37) and identify genomic correlates of response and progression. Peripheral blood samples will be collected at the same BM time-points, and will be used as control or stored for further analysis such as the evaluation of circulating plasma cells levels.
- To evaluate changes in transcriptome parameters, using RNA-seq, to analyze impact of Cereblon (CRBN)/IRF4 pathway on Pomalidomide sensitivity versus resistance and to evaluate evolution of transcriptomes at relapse. Loss of CRBN is clearly associated with resistance to IMiDs and CRBN knockdown confers complete lenalidomide and pomalidomide resistance (38) however this does not appear to be the sole mechanism through which MM cells may

acquire resistance to this class of drugs. Therefore we will evaluate transcriptome parameters using RNA-seq from CD138 sorted cells of paired samples. Whole Genome Sequencing will establish novel markers and potential therapeutic targets, identifying differentially expressed genes and pathways in lenalidomide resistant samples in comparison to pomalidomide related genes. We will also integrate the Exome sequencing data with RNA-seq for an integrative analysis of these correlates.

The samples will be sent to Boston Laboratory to conduct the Whole Exome Sequencing analysis.

The results derived from this research will dissect the factors associated with IMiDs resistance and highlight the importance of assessment of clonality in myeloma patients receiving treatment. This study will eventually lead to the design of new therapeutic approaches for a more targeted and patient-directed therapy.

14. ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Celgene requests that informed consent documents be reviewed by Celgene or designee prior to IRB/IEC submission.
The study will be conducted without prejudice for the scientific and procedural independence of the Investigator according to art. 2 and 6 of the Decree of the Minister of Health dated 17 December 2004 and by no means for the industrial development of the drug and in any case not for profit purposes in respect of the above-said Decree.

14.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

14.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant regulatory authority(ies)

access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Celgene and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Celgene and the regulatory authority(ies) in accordance with the governing regulations.
Any departures from the protocol must be fully documented in the source documents.

14.6 On-site Audits

Regulatory authorities, the IEC/IRB may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14.7 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Celgene or a designee or disposal of the drug (if applicable and if approved by Celgene) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

14.8 Product Complaints

14.8.1 Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Celgene, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Celgene by the terminating party.
Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the drug

14.8.2 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

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16. APPENDIX

16.1 APPENDIX I: NCI-CTCAE VERSION 4.0

Common Terminology Criteria for Adverse Events (CTCAE) of the

National Cancer Institute (NCI) v4.0

Publish Date: May 28, 2009

16.2 APPENDIX II: MULTIPLE MYELOMA DIAGNOSTIC CRITERIA

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcaemia: serum calcium >0,25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2,75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
  - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%
  - Involved:uninvolved serum free light chain ratio§ ≥100
  - >1 focal lesions on MRI studies

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

†Measured or estimated by validated equations.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay. The involved free light chain must be ≥100 mg/L.

¶Each focal lesion must be 5 mm or more in size.

16.3 APPENDIX III: STAGING

DURIE AND SALMON STAGING SYSTEM

Stage I

All of the following:

Hemoglobin>10 g/dl

Normal serum calcium <12 mg/dl

Skeletal survey normal bone structure

Low M component production rates:

IgG < 5 g/dL

IgA < 3 g/dL

Urine light chain M component on electrophoresis < 4 g/24h

Stage II

Overall data not as minimally abnormal as shown for stage I and no single value abnormal as defined for stage III

Stage III

One or more of the following:

Hemoglobin < 8.5 g/dL

Serum calcium value > 12 mg/dL

Advanced lytic bone lesions, three or more

High M component rates:

IgG > 7 g/dL

IgA > 5 g/dL

Urine light chain M component on electrophoresis > 12 g/24h

Subclassification

A = relatively normal renal function (serum creatinine value < 2 mg/dL)

B = abnormal renal function (serum creatinine > 2 mg/dL)

INTERNATIONAL MYELOMA WORKING GROUP STAGING SYSTEM

Stage I

- 2M < 3.5; S. Alb > 3.5

Stage II

- 2M < 3.5; S. Alb > 3.5

  or
- 2M 3.5–5.5

Stage III

- 2M >5.5

16.4 APPENDIX IV: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease 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 (eg, 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, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6): 649-55.

16.5 APPENDIX V: CRITERIA FOR RESPONSE

RESPONSE	CRITERIA FOR RESPONSE (46)
Stringent Complete Response (sCR)	CR as defined below plus Normal Free Light Chain (FLC) ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
Complete response (CR)	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level ≤ 100 mg per 24 h
Partial Response (PR)	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or ≤ 200mg per 24 h If the serum and urine M-protein are unmeasurable[d] 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 the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease (SD) (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 CR, VGPR, PR or progressive disease
Progressive disease[e] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive disease: required one or more of the following: Increase of ≥ 25% from baseline in Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dl)[e] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[f]

	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcemia (corrected serum calcium ≥ 11.5 mg/dl or2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical Relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[e]. It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (411.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ≥ 2 g/dl [1.25 mmol/l] 5. Rise in serum creatinine by 2 mg/dl or more [177 mmol/l or more]
Relapse from CR[e] (To be used only if the end point studied is disease free survival DFS)[g]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥ 5% plasma cells in the bone marrow[f] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

a. All response and relapse 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 if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
b. Confirmation with repeat bone marrow biopsy not needed.
c. Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 44:1 or o1:2.
d. Measurable disease is defined by at least one of the following three measurements:
e. Serum M-protein > 1 g/dl (> 10 gm/l)[10 g/l]
f. Urine M-protein > 200 mg/24 h
g. Serum FLC assay: Involved FLC level > 10 mg/dl (>100 mg/l) provided serum FLC ratio is abnormal
h. For progressive disease, serum M-component increases of >1 gm/dl are sufficient to define relapse if starting M-component is > 5 g/dl.
i. Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

16.6 APPENDIX VI: COCKCROFT-GAULT ESTIMATION OF CREATININE CLEARENCE (Crcl)

Cockcroft-Gault estimation of creatinine clearance (CRcl):

For male

CRcl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]);

or (140 – age) (weight [kg]) / 0.81 (serum creatinine [µmol/L]);

For females

CRcl (mL/min) = 0.85 (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]);

or 0.85 (140 – age) (weight [kg]) / 0.81 (serum creatinine [µmol/L]);

(Cockcroft, 1976; Luke, 1990).

16.7 APPENDIX VII: EORTC QLQ-C30 Quality of Life Questionnaire EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: __ __ __ __

Your birthdate (Day, Month, Year): __ __ __ __ __ __ __ __

Today's date (Day, Month, Year): __ __ __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:

	Not at All	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4

20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

16.8 APPENDIX VIII: EORTC QLQ-MY24 Quality of Life Questionnaire EORTC QLQ-MY24

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past weeks. Please answer by circling the answer that best applies to you.

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had bone pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
47. Were you satisfied with your relationship with your doctors?	1	2	3	4
48. Were you satisfied with the care you received from your doctors?	1	2	3	4
49. Were you satisfied with the information you received about your illness?	1	2	3	4
50. Did you feel that you were being listened to by your doctor/nurse?	1	2	3	4
51. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
52. Have you been thinking about your illness?	1	2	3	4
53. Have you been worried about dying?	1	2	3	4
54. Have you worried about your health in the future?	1	2	3	4

16.9 APPENDIX IX: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe lifethreatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for Females of Childbearing Potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. All FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

Male subjects must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before Starting Study Drug

Female Subjects

All FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Subjects

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During and After Study Participation

Female Subjects

- All FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study drug discontinuation, and at Day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study drug discontinuation, and at Days 14 and 28 following study drug discontinuation.
- At each visit, the investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.
- Pregnancy testing and counselling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.
- Male subjects should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.

Additional Precautions

- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

16.10 APPENDIX X: SKELETAL SURVEY FILMS

The following are the minimum plain radiologic films required for skeletal (bone) survey:

i. Lateral skull
ii. AP and lateral cervical spine
iii. AP and lateral thoracic spine
iv. AP and lateral lumbar spine
v. PA chest
vi. PA pelvis
vii. AP upper extremities, shoulder to elbow
viii. AP lower extremities, hip to knee
ix. Other radiologic film may be necessary to view symptomatic areas or known pre-existing lesions in skeletal regions not included in the films above.

16.11 APPENDIX XI: Risk assessment model for the management of venous thromboembolism in multiple myeloma patients treated with pomalidomide

Actions	
Individual risk factors	
Obesity[a]	If no risk factor or any one risk factor is present:
Previous venous thromboembolism	Aspirin 81–325 mg once daily
Central venous catheter or pacemaker	
Associated disease	If two or more risk factors are present:
Cardiac disease	LMWH (equivalent of enoxaparin 40 mg once daily)
Chronic renal disease	Full-dose warfarin (target INR 2–3)
Diabetes	
Acute infection	
Immobilization	
Surgery	
General surgery	
Any anesthesia	
Trauma	
Medications	
Erythropoietin	
Blood clotting disorders	
Myeloma-related risk factors	
Diagnosis	
Hyperviscosity	
Myeloma therapy	
High-dose dexamethasone[b]	LMWH (equivalent of enoxaparin 40 mg once daily)
Doxorubicin	Full-dose warfarin (target INR 2–3)
Multiagent chemotherapy	

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.

[a] Obesity was defined as body mass index 30 kgm^{-2}.

[b] 480 mg per month.

16.12 APPENDIX XII : FACT/GOG-Neurotoxicity Questionnaire, Vers.4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands.....	0	1	2	3	4
I have numbness or tingling in my feet.....	0	1	2	3	4
I feel discomfort in my hands.....	0	1	2	3	4
I feel discomfort in my feet.....	0	1	2	3	4
I have joint pain or muscle cramps.....	0	1	2	3	4
I feel weak all over.....	0	1	2	3	4
I have trouble hearing.....	0	1	2	3	4
I get a ringing or buzzing in my ears.....	0	1	2	3	4
I have trouble buttoning buttons.....	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand.....	0	1	2	3	4
I have trouble walking.....	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

16.13 APPENDIX XIII: Causality assessment scale

Imputation Causality is a difficult process due to the complex nature of adverse events, multiple treatments and individual clinical variability. Causality inference obtained by the clinical judgment of an expert's panel or global introspection is the most common approach for individual causality assessment of adverse drug reports. As Sponsor, we decide to use the following scale, even if the process of global introspection is subjective and it regard the clinical team of our office.

Naranjo's scale:

Question	YES	NO	DON'T KNOW
Are there previous conclusion reports on this section	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	-1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when the drug was readministered?	+2	-1	0
Are there alternate causes (other then the drug) that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
When the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Assessment schema:
>9 = definite

5-8 = probable

1-4 = possible

0 = unlikely

16.14 APPENDIX XIV: Neurological assessment

Subject number_____ Initials_____ Date of visit_____

For any abnormal finding during exam, Grade should be assigned according to the CTCAE version 4.03 criteria

Motor

		Normal	Abnormal	Not Done	If abnormal, describe		
					CTCAE Grade	Primary relationship	Description
Muscle weakness	Upper extremities						
	Lower extremities						

Muscle weakness grades:
1=Symptomatic, perceived by patient but not evident on physical exam;
2=Symptomatic, evident on physical exam, limiting instrumental activities of daily living (ADL);
3=Limiting self care, ADL, disabling

Sensory

		Normal	Abnormal	Not Done	If abnormal, describe		
					CTCAE Grade	Primary relationship	Description
Deep Tendon Reflexes	Upper extremities						
	Lower extremities						
Paresthesias	Upper extremities						
	Lower extremities						
	Other Location: _____						
Neuropathic Pain	Upper extremities						
	Lower extremities						
	Other Location: _____						
Vibration Assessment (using approx 128 Hz tuning fork)	Upper extremities						
	Lower extremities						

Deep tendon reflexes grades:

1=Asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated;
2=Moderate; minimal, local or nonivasive intervention indicated; limiting age-appropriate instrumental ADL;
3=Severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, disabling, limiting self care ADL
4=Life-threatening consequences; urgent intervention indicated;
5=Death

Paresthesia grades:
1=Mild symptoms;
2=Moderate symptoms, limiting instrumental ADL;
3=Severe symptoms, limiting self care ADL.

Pain grades:
1=Mild pain;
2=Moderate pain, limiting instrumental ADL;
3=Severe symptoms, limiting self care ADL.

Principal or Sub-Investigator Signature: _____ Date_____

Print Name of Principal or Sub-Investigator: _____

16.15 APPENDIX XV: QT drugs by Risk Group

QT-prolonging drugs grouped by risk of torsades, possible risk of torsades, and conditional risk of torsades are included in Tables below.

Table 1: Risk for Torsade de Pointes and/or QT Prolongation

Generic Name	Class/Clinical Use	Comments
Amiodarone	Anti-arrhythmic/abnormal heart rhythm	Females>Males, TdP risk regarded as low
Arsenic trioxide	Anti-cancer/Leukemia	
Astemizole	Antihistamine/Allergic rhinitis	
Bepridil	Anti-anginal/heart pain	Females>Males
Chloroquine	Anti-malarial/Malaria infection	
Chlorpromazine	Anti-psychotic/Anti-emetic/schizophrenia/nausea	
Cisapride	GI stimulant/heartburn	Females>Males
Clarithromicin	Antibiotic/bacterial infection	
Disopyramide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Dofetilide	Anti-arrhythmic/abnormal heart rhythm	
Domperidone	Anti-nausea/nausea	
Droperidol	Sedative; anti-nausea/anesthesia adjunct; nausea	
Erythromycin	Antibiotic; GI stimulant/bacterial infection; increase GI motility	Females>Males
Halofantrine	Anti-malarial/Malaria infection	Females>Males
Haloperidol	Anti-psychotic/schizophrenia, agitation	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases
Ibutilide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Levomethadyl	Opiate agonist/pain control, narcotic dependence	
Mesoridazine	Anti-psychotic/schizophrenia	
Methadone	Opiate agonist/pain control, narcotic dependence	Females>Males
Moxifloxacin	Antibiotic/bacterial infection	
Pentamidine	Anti-infective/pneumocystis pneumonia	Females>Males
Pimozide	Anti-psychotic/Tourette's tics	Females>Males
Probucol	Antilipemic/Hypercholesterolemia	
Procainamide	Anti-arrhythmic/abnormal heart rhythm	
Quinidine	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sotalol	Anti-arrhythmic/abnormal heart rhythm	Females>Males

Sparfloxacin	Antibiotic/bacterial infection	
Terfenadine	Antihistamine/Allergic rhinitis	
Thioridazine	Anti-psychotic/schizophrenia	

Table 2: Possible Risk for Torsades de Pointes and/or QT Prolongation

Generic Name	Class/Clinical Use
Alfuzosin	Alpha 1-blocker/Benign prostatic hyperplasia
Amantadine	Dopaminergic/Anti-viral/Anti-infective/Parkinson's Disease
Atazanavir	Protease inhibitor/HIV
Azithromycin	Antibiotic/bacterial infection
Chloral hydrate	Sedative/sedation/insomia
Clozapine	Anti-psychotic/schizophrenia
Dolasetron	Anti-nausea/nausea, vomiting
Dronedarone	Anti-arrhythmic/Atrial fibrillation
Escitalopram	Anti-depressant/Major depression/Anxiety disorders
Felbamate	Anti-convulsant/seizure
Flecainide	Anti-arrhythmic/abnormal heart rhythm
Foscarnet	Anti-viral/HIV infection
Fosphenytoin	Anti-convulsant/Seizure
Gatifloxacin	Antibiotic/bacterial infection
Gmifloxacin	Antibiotic/bacterial infection
Granisetron	Anti-nausea/nausea, vomiting
Indapamide	Diuretic/stimulate urine & salt loss
Isradipine	Anti-hypertensive/high blood pressure
Lapatinib	Anti-cancer/breast cancer, metastatic
Levofloxacin	Antibiotic/bacterial infection
Lithium	Anti-mania/bipolar disorder
Moexipril/HCTZ	Anti-hypertensive/high blood pressure
Nicardipine	Anti-hypertensive/high blood pressure
Nilotinib	Anti-cancer/Leukemia
Octreotide	Endocrine/acromegaly, carcinoid diarrhea
Ofloxacin	Antibiotic/bacterial infection
Ondasetron	Anti-emetic /nausea, vomiting
Oxytocin	Oxytocic/Labor stimulating
Paliperidone	Antipsychotic, atypical/Schizophrenia
Perflutren lipid microspheres	Imaging contrast agent/Echocardiography
Quetiapine	Anti-psycothic/schizoprenia
Ranolazine	Anti-anginal/chronic angina

Risperidone	Anti-psycothic/schizoprenia
Roxythromycin	Antibiotic/bacterial infection
Sertindole	Anti-psycothic, atypical/Anxiety, schizoprenia
Sunitib	Anti-cancer/RCC, GIST
Tacrolimus	Immunosuppressant/Immune suppression
Tamoxifen	Anti-cancer/breast cancer
Telithromycin	Antibiotic/bacterial infection
Tizanidine	Muscle relaxant
Vardenafil	Phosphodiesterase inhibito/vasodilator
Venlafaxine	Anti-depressant/depression
Voriconazole	Anti-fungal
Ziprasidone	Anti-psycothic/schizoprenia

Table 3: Conditional Risk for Torsades de Pointes and/or QT Prolongation

Generic Name	Class/Clinical Use
Amitriptyline	Tryciclic Antidepressant/depression
Ciprofloxacin	Antibiotic/bacterial infection
Citalopram	Anti-depressant/depression
Clomipramine	Tryciclic Antidepressant/depression
Desipramine	Tryciclic Antidepressant/depression
Diphenydramine	Antihistamine/allergic rhinitis, insomnia
Doxepin	Tryciclic Antidepressant/depression
Fluconazole	Anti-fungal
Fluoxetine	Anti-depressant/depression
Galantamine	Cholinesterase inhibitor/Demenatia, Alzheimer's
Imipramine	Tryciclic Antidepressant/depression
Itraconazole	Anti-fungal
Ketoconazole	Anti-fungal
Nortriptyline	Tryciclic Antidepressant/depression
Paroxetine	Anti-depressant/depression
Protriptiline	Tryciclic Antidepressant/depression
Ritonavir	Protease inhibitor/HIV
Sertraline	Anti-depressant/depression
Solifenacin	Muscarinic receptor antagonist/treatment of overactive bladder
Trazodone	Anti-depressant/depression, insomnia
Trimethoprim-Sulfa	Antibiotic/bacterial infection
Trimipramine	Tryciclic Antidepressant/depression