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A Phase II Clinical Trial for Untreated Patients with Multiple Myeloma Eligible for Stem Cell Transplant: Lenalidomide (Revlimid®) plus Low-dose Dexamethasone (Ld x 4 cycles) Then Stem Cell Collection Followed by Randomization to Continued Ld or Stem Cell Transplantation (SCT) Plus Maintenance L

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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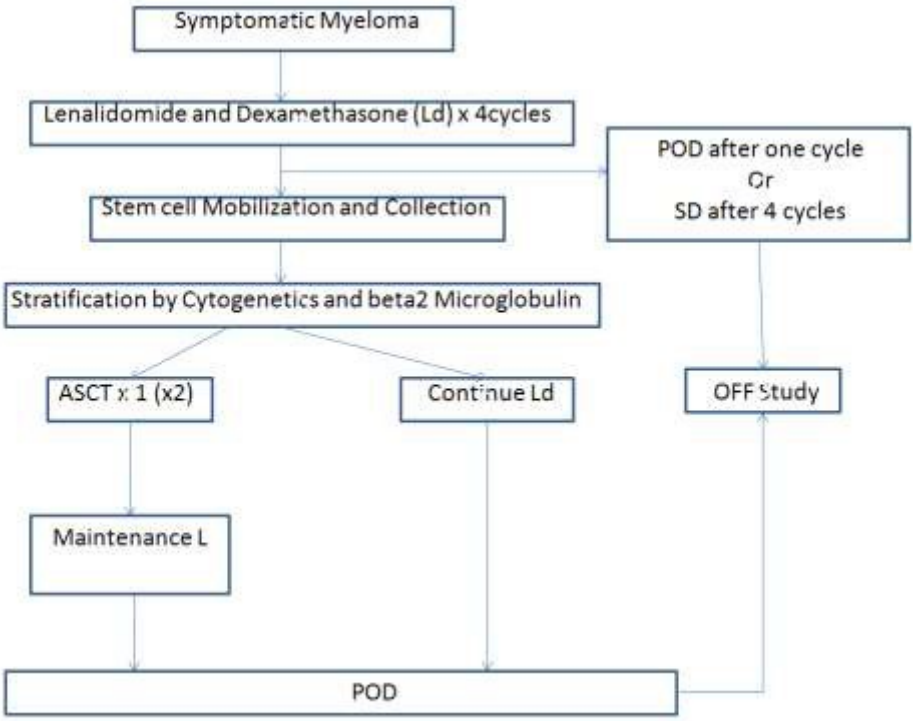


1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Figure 1. Protocol Schema

"The need for early ASCT in an era of new drugs is the most important clinical question in myeloma today." Robert A. Kyle and Vincent Rajkumar, Blood 2008; 111:2962

This is a phase II clinical trial for newly diagnosed patients with symptomatic multiple myeloma eligible for stem cell transplant (SCT). In this trial we ask whether the regimen of lenalidomide and dexamethasone achieves a response profile 2 and 3 years into the disease that is similar to the response profile achieved with the more conventional approach of initial therapy followed by early high-dose melphalan with stem cell transplant. In this randomized phase II trial, neither arm can be considered standard therapy because there is no established standard initial therapy for myeloma at this time, nor is there an established role for maintenance therapy with lenalidomide. Lenalidomide and low-dose dexamethasone are acceptable, effective and widely used initial therapy based on phase II and III trial data but there have been no direct comparisons of thalidomide and dexamethasone, bortezomib and dexamethasone, and lenalidomide and dexamethasone as initial therapies. Therefore, there is no established standard initial therapy. This phase II trial is designed so that results from the two treatment arms will be compared directly to each other using a “pick-the-winner” approach.

Lenalidomide is initially dosed at 25mg/day for 21 of 28 days. Dexamethasone is dosed at 40mg weekly. Dexamethasone dosed in this fashion (4 days per cycle) is considered low-dose (d) while dexamethasone given in pulses on days 1-4, 9-12 and 17-20 is considered high dose (D). Lenalidomide and low-dose dexamethasone (Ld) is the standard dose-schedule based on a recent phase III trial and is the dose-schedule we use in this trial.

Newly diagnosed untreated patients with myeloma will receive Ld for 4 cycles and then undergo conventional stem cell mobilization with cyclophosphamide and G-CSF (10ug/kg/day) or plerixafor and G-CSF and stem cell collection. Mobilization with cyclophosphamide is preferred, but plerixafor is also allowed. Then all patients will be stratified into high- and standard-risk groups. High-risk patients are those who have baseline high-risk cytogenetics or FISH (hypodiploidy, presence of t(4;14) or del 17p) or baseline β2-microglobulin > 3.5. All other patients will be designated as standard-risk. After stratification, patients will be randomized either to continue Ld or to undergo standard high-dose melphalan and SCT.

On the Ld arm, patients will resume Ld with prophylactics and dose reductions as indicated.

On the SCT arm, patients will undergo up to 2 SCT. Achievement of at least a 90% reduction in myeloma from baseline (very good partial response, VGPR) after the 1st SCT will determine the need for a second SCT. Patients who do not achieve a VGPR after the 1st SCT will undergo a 2nd SCT. Patients who do not achieve a VGPR after the 2nd SCT will receive lower-dose Ld (L=10mg/day on days 1-28 every 28-day cycle, d=20mg flat dose weekly on days 1, 8, 15, and 22 every 28-day cycle) beginning 3 months after the 2nd SCT. Patients who are high-risk will also receive lower-dose Ld after the 1st or 2nd SCT.

All patients will continue on those arms of therapy until progression of disease.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

To determine the progression free survival (PFS) at 2 years after enrollment in untreated patients with multiple myeloma who receive initial therapy with four cycles of Ld, undergo stem cell collection and storage, and then are stratified into high- and standard-risk groups and randomized either to continue Ld or to undergo SCT with additional Ld for those not achieving VGPR or for those having high-risk disease.

Secondary objectives:

To assess the CR+VGPR rate at 2 and 3 years
To assess overall myeloma response rates at 2 and 3 years
To assess overall survival

3.0 BACKGROUND AND RATIONALE

Multiple Myeloma (MM)

MM is an incurable plasma cell malignancy with over 16,000 new cases and 11,000 deaths estimated in the U.S. in 2006.[1] It accounts for 10-15% of all hematologic malignancies, with a median age at diagnosis of 63 years. Median overall survival remains 4-5 years and long-term myeloma-free survivors are rare. Age and race influence the incidence of MM. MM rarely occurs before the age of 40.[2] Its incidence increases rapidly with age and is lowest among Asian peoples, intermediate among Caucasians in America and Europe, and highest among blacks in the USA. The differences in the incidence of MM in different countries appear to be due to genetic rather than environmental factors.

The numerous clinical manifestations associated with MM result from bone marrow replacement by myeloma plasma cells and the pathologic effects resulting from their overproduction of a monoclonal immunoglobulin molecule ("M protein"), which include bone destruction, anemia, hypercalcemia, immunodeficiency and renal dysfunction.[3] A number of chemotherapeutic regimens are employed to treat myeloma. Decades ago prednisone added to oral melphalan became the mainstay of therapy (MP) although complete response (CR) was rare (< 5%) and median survival did not exceed 3 years.[4] The addition of other alkylating agents, anthracyclines and vinca alkaloids to MP did not improve survival. Until recently, regimens employed as standard initial therapy included VAD and single-agent dexamethasone with response rates that ranged from 40-70% with uncommon complete responses.[5]

Over the past 15 years autologous stem cell transplantation (SCT) has been shown in several phase III studies to provide higher CR and survival rates than historical alkylator-based therapy.[6,7] Although neither achievement of CR nor SCT is a cure, SCT likely adds 1 year to survival compared to historical therapy. For over a decade, the importance of achieving a CR (or $\geq$ VGPR) has been well established with respect to overall survival. In the IFM 90 trial, the 5-year overall survival was significantly higher in those with CR or VGPR (72%) 3 months post-SCT than in those with PR (39%).[6] This point was driven home with the results of the IFM 94 trial in which patients not achieving at least a VGPR after the first SCT had a survival advantage with a second SCT. The CR+VGPR with tandem SCT on IFM 94 was 50%.

Because the new agents available to treat myeloma are so effective, many patients and physicians are questioning the role of high-dose melphalan with SCT in the treatment of the disease. They question the need for the morbidity and investment of time associated with 1 or 2 SCT when the response rates with the new agents, lenalidomide and bortezomib in initial therapy, for example, are as high as those achieved with historical therapies and high-dose melphalan with SCT. In addition to being supported by the improved response rates noted with

recently approved novel agents, these concerns are supported by several large studies that have demonstrated no difference in overall survival with SCT early or late in the course of disease, and by retrospective evaluations showing that patients achieving complete responses with standard therapy have similar survivals to those achieving complete response (CR) with SCT. This trial asks whether continued combination therapy with the new agent lenalidomide and low-dose dexamethasone (Ld) is as effective as initial therapy with Ld followed by SCT. In the initial phase II trial of lenalidomide and high-dose dexamethasone (LD) investigators at Mayo Clinic reported a progression-free survival of about 3 years in myeloma patients of various ISS stages. (It is important to note that patients continuing on long-term lenalidomide therapy on that trial received low-dose dexamethasone).

Although the median progression-free survival after high-dose melphalan with SCT is 30 months, two large SCT trials have clearly demonstrated no difference in overall survival between patients receiving early or delayed SCT. Therefore, delay of high-dose melphalan will not put patients at risk.

Novel agents and response rates

Over the past 5 years the FDA has approved thalidomide, bortezomib and the thalidomide-analogue lenalidomide for the treatment of myeloma.[8] The effectiveness of these new agents combined with dexamethasone and other traditional medications has changed the treatment of myeloma. Phase III trials have shown higher response and survival rates with thalidomide combined with MP (MPT) versus MP or two cycles of intermediate-dose melphalan (100mg/m^2) with SCT.[9,10] Similarly, thalidomide when combined with pulse dexamethasone (TD) was superior to D alone as initial therapy in a transplant-eligible population.[11] With thalidomide as part of a tandem SCT strategy in a recent large phase II trial, median overall survival was 6.5 years.[12]

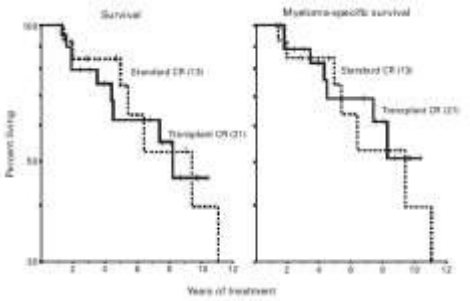
Phase II trials of bortezomib-based regimens in initial therapy have also shown very high complete and overall response rates.[13-16] One can now expect complete and near complete response rates with initial therapy for myeloma at levels previously attained only with high-dose therapy and SCT. The Spanish intergroup (PETHEMA) recently reported results of a phase III trial of VMP (bortezomib+MP) versus MP for patients who were not stem cell transplant candidates. The CR+VGPR rates were 45% in the VMP and 10% in the MP arm. Both VMP and MP contain pulse oral melphalan, a leukemogenic agent; the long-term effects of combining it with bortezomib are not known and it is not advisable to use VMP in a young patient who is a candidate for SCT because of the risk of leukemia and the deleterious effects of oral melphalan on hematopoietic stem cells. Stem cell mobilization and collection are impaired in patients receiving more than 200mg of prior oral melphalan.

In a phase II trial of LD in newly diagnosed MM patients, those who received LD as their primary therapy and continued on it (with reduction in the dexamethasone dose) until progression of disease had a 24% CR and 43% VGPR (CR+VGPR = 67%) best response rate. Median time to progression of disease was 32 months.[17] At 1 year, the CR+VGPR rate was 56%,

indicating continued responsiveness in years 2 and 3. There was no difference in response rate based on ISS stage. A phase III ECOG trial comparing lenalidomide with high-dose (LD) versus low-dose dexamethasone (Ld) was halted because of significantly better survival in the Ld arm at one year (96% vs 88%). Best overall response rates at 1 year were different in the arms, however, with CR+VGPR of 52% in the LD versus 42% in the Ld arm. Whether continued use of Ld for an additional year increased the CR+VGPR rates is currently unknown.

With these improvements in response, the significance of attaining CR in myeloma and the definition of CR have become critical issues in therapy. The latter has undergone several iterations over the past 20 years and now is defined as normalization of the marrow, of the serum and urine immunofixation studies and of the free light chain levels and ratio also.[18] The significance of CR has recently been re-examined in a retrospective evaluation of 721 consecutive patients treated at MD Anderson from 1/87 to 5/06. Patients achieving CR with initial therapy, those achieving CR after SCT (with PR or NR to initial therapy) and those undergoing SCT in CR from initial therapy all had similar long-term median survivals of 10 to 14 years as is shown in Figure 2.[19] The MD Anderson investigators state that these results suggest "that high-dose therapy provided no further benefit after CR had been achieved with initial therapy. A randomized trial may be useful to clarify this question." In the light of such results and statements, patients, their physicians and myeloma specialists are questioning the role of high-dose melphalan and SCT. Not surprisingly, SCT physicians are responding to these concerns. Jean-Luc Harrousseau, a pioneer in MM SCT trials, has written "SCT is being challenged again by the introduction of novel agents such as bortezomib, thalidomide, and lenalidomide."[20] Another pioneer, Bart Barlogie, has written “Although high CR rates may translate into extended survival for MEL treatment of patients with good-risk (*sic*) myeloma, this may not hold true following treatment with the newer non-genotoxic agents.”[21]

Figure 2. OS with CR after initial therapy or after SCT
(MD Anderson experience)



A trial conducted at MSKCC (IRB 00-077) contributed to the trend towards better responses with initial therapy.[22] On that phase II trial, newly diagnosed Durie-Salmon (DS) stage II and III myeloma patients received doxorubicin and dexamethasone (AD) followed by thalidomide and dexamethasone (TD). (NB: The DS staging system, not the ISS, was used for IRB 00-077.) Based on intent-to-treat the overall response rate was 84.4% (38/45) and the CR+VGPR rate 36% (16/45). The AD/TD schedule was developed after calling attention to the risk of thromboembolic complications when thalidomide was simultaneously used with doxorubicin.[23] The rate of thromboembolic complications in the final version of IRB 00-077 was 10%,

equivalent to the rate with VAD. There were no treatment-related deaths and the incidence of neuropathy was nil.
All patients on the MSKCC clinical trial IRB 00-077 had DS stage II or III myeloma. The DS staging system was used for 30 years, despite the fact that newer staging systems were developed. The continued use of DS staging was based upon the need to clearly describe and in some cases stratify the patients enrolled on clinical studies. The majority of DS stage I patients, for example, did not need to be treated at diagnosis and would not be appropriate for aggressive initial therapy trials.

The International Staging System (ISS) for myeloma was developed and validated several years ago and has been integrated into clinical research here and elsewhere.[24] It has supplanted the DS staging system and represents a major advance in staging because it does not require inclusion of skeletal survey findings, the most inaccurate and confusing component of the DS system, and because of its objectivity and ease of application. ISS stage I patients have a serum albumin level $\geq$ 3.5g/dl and β2 microglobulin (B2M) < 3.5mg/dl while ISS stage III patients have B2M > 5.5mg/dl. ISS stage II patients are neither stage I nor III.

After assessing all of the patients enrolled on all versions of MSKCC clinical trial IRB 00-077 (n=64) for response and survival by ISS stage, we learned that the response rate to therapy was similar in all ISS groups but that ISS stage II and III patients, and patients with extramedullary disease (EMD) regardless of stage, had poorer overall survival. ISS stage II and III patients had a median survival of 3.5 years while the median survival of ISS stage I patients had not been reached with a median follow-up of 4 years. Patients with EMD had a median survival of 1.8 years. Based on this analysis, we defined ISS stage II or III patients, and those patients with EMD, as high risk. Patients with ISS stage I myeloma without EMD were defined as standard risk. A subsequent clinical trial at MSKCC (IRB 06-067) was designed for patients with high-risk myeloma defined as ISS stage II or III or having EMD. The CR+VGPR rate is 53% in the first 27 patients treated. (Landau H, Comenzo RL, unpublished observation). Of note, one responder on that trial (not a SCT candidate) relapsed within 6 months of completing therapy on 06-067 and has responded to 3 cycles of Ld.

Since the phase II clinical trial 06-067 was designed, the cytogenetic data on risk profiles in MM have been more cogently assessed. For many years the presence of deletion 13q (del 13q) was considered a marker of high-risk MM; we did not find it to be such a marker in patients on 00-077 and therefore discounted it and other cytogenetic findings in the design of 06-067. Current thinking, however, based on large numbers of patients treated similarly, views hypodiploidy and the presence of the t(4;14) or del 17p by FISH, as well as an elevated β2 microglobulin (> 3.5; i.e., ISS stage II and III), as markers of high risk.[25] A recent retrospective evaluation of over 1000 cases of myeloma evaluated by FISH supported this view and put the prior significance of del 13q in a better perspective.[26] Del 13q is easily appreciated on standard karyotype. The identification of del 13q on karyotype was a reflection of the proliferative rate of the myeloma and of the ease with which that particular abnormality could be visually appreciated with traditional metaphase spreads and Giemsa banding.

In this trial, then, we use a newer definition of risk: after stem cell collection and prior to randomization patients will be stratified into high-risk and standard-risk groups based on the criteria of high-risk cytogenetics or FISH (hypodiploidy, t(4;14) or del 17p) or β2 microglobulin (B2M) > 3.5. All others will be considered standard risk. The response rates to treatment with Ld or with tandem SCT are not different in these groups. A recent study from the University of Calgary, Canada, has found that patients with and without t(4;14) responded equally well to lenalidomide plus dexamethasone treatment, with little difference between the patient groups in either the response rate (CR + PR) or event-free survival.[27] However, with conventional treatment and SCT, although the response rates are not different in those with t(4;14), the median progression-free survival in those patients after SCT may be as short as 9 months and is different than that of patients without the t(4;14).[28] We do not know yet whether the use of Ld before and after SCT, as we propose, will modify that outcome. Since the fraction of newly diagnosed patients with t(4;14) or del 17p is about 20% of patients, and effective therapy (e.g., thalidomide, SCT, bortezomib) is available at progression of disease (i.e., removal from study), it does not make sense to exclude these patients from this trial.

Stem cell transplant

There have been two large prospective trials in France (IFM 90) and in UK (MRC 9), and one large retrospective study of myeloma patients in Nordic countries, showing a survival benefit for SCT compared to conventional chemoptherapy.[6,7,29] In IFM 90, patients less than 65 years of age with DS stage II or III MM were randomized to either SCT after up to 6 cycles of VMCP alternating with BCNU, vincristine, Adriamycin and prednisone (BVAP) or to conventional chemotherapy with 18 cycles of VMCP alternating with BVAP. The SCT regimen was MEL 140 mg/m^2 and TBI, and recombinant interferon alpha (IFNα) was administered to patients in both groups until relapse. By intent-to-treat, SCT patients had a significantly higher response rate than those receiving conventional chemotherapy (CR+VGPR 38% versus 14%). At a median follow-up of 37 months in the chemotherapy group and 41 months in the SCT group, the latter had significantly longer PFS and OS. Multivariate analysis of prognostic factors demonstrated that low B2M and treatment-group assignment were significantly related to prolonged EFS and only a low B2M was significantly related to prolonged OS.

Recent reports of 2 other trials have cast doubt on the benefit of SCT compared with conventional chemotherapy. In a multi-center trial conducted in Spain, patients whose myeloma responded to initial chemotherapy were randomized to SCT or continued standard chemotherapy.[30] The CR rate was significantly higher in the SCT arm (30% vs. 11%) but no difference was seen in EFS and OS. However, randomization did not occur at diagnosis, introducing a selection bias, and only three-quarters of the patients enrolled were randomized. SCT is a useful salvage treatment for patients with primary refractory multiple myeloma; hence, those patients would have been excluded by the trial design. In addition, the median PFS was higher in the SCT arm (42 months vs. 33 months), a difference that might have achieved statistical significance had the size of the patient groups been larger.

In a large intergroup trial in the United States, patients under 70 (n=516) received initial therapy with VAD and were then randomized to SCT or to vincristine/carmustine/melphalan/ cyclophosphamide/prednisolone (VBMCP).[31] There was selection bias in this trial also. Of 813 patients registered and assigned to treatment arms, only 516 were randomized and then only 424 were treated as planned. There were no differences seen in response rate, PFS and OS between the arms.

Simply comparing conventional chemotherapy with SCT is not as salient an issue, however, because the results of SCT have improved with the use of melphalan alone at 200mg/m^2 (less morbidity) and with tandem MEL 200 SCT. Patients not achieving a VGPR after the 1st SCT benefit from a 2nd SCT, based on the results of the IFM 94 trial.[32] In this randomized trial 1 and 2 SCT were compared in 399 patients up to 60 years of age. The 7-year EFS and OS were significantly improved in the tandem SCT arm (20% vs. 10% and 42% vs. 21%, respectively). In the IFM 94 trial, 75% of patients underwent the 2nd SCT and treatment-related mortality was less than 5%.

Because of concerns about the cost and risk of tandem SCT, defining the patients who benefited from tandem SCT was important. In the IFM 94 trial, the only factor that distinguished patients who benefited from tandem SCT was response to the 1st SCT. Patients with < 90% reduction of the M-protein (i.e., those not achieving a VGPR) after the 1st SCT had a longer OS in the tandem SCT arm. Patients experiencing CR or VGPR after the 1st SCT had the same OS with or without the 2nd SCT. Therefore, in this trial, comparing continued Ld to early SCT, patients randomized to SCT will receive a second MEL 200 SCT if their response to the 1st SCT is not at least a VGPR with respect to the baseline M-protein studies.

Early versus delayed stem cell transplant

In addition to the important trials described above, there have been two trials examining the question of early versus delayed SCT in newly diagnosed patients.[33,34] In the first trial, conducted at Mayo Clinic in the early 1990's, 118 patients with multiple myeloma had stem cells mobilized and collected within 6 months of diagnosis, followed by transplantation only at progression of disease.[33] Eleven had transplants early due to progressive disease. Overall, with 7 years of follow-up at the time of the report, 67 had had SCT, 9 had died of progressive disease before SCT, and 42 were alive in plateau phase. Median survival of the group was 58.5 months. Predictors of survival were markers of the biology of the myeloma and not treatment-related variables: B2MG, bone marrow labeling index (S phase), and hemoglobin level predicted overall survival. The investigators concluded "early cryopreservation of blood stem cells followed by transplantation at progression is a feasible approach to therapy in patients with myeloma. The underlying biology of the disease has a greater impact on survival than the timing of transplantation. A prospective randomized trial is required to answer definitively the question of the optimal timing of blood cell transplantation."

In the mid-1990's Jean-Paul Fermand and his colleagues in the Group ''Myelome Autogreffe'' performed a multi-center prospective randomized trial comparing early and delayed timing of autologous SCT for newly diagnosed untreated patients with MM.[34] After enrollment, all patients received 1 to 2 cycles of intensified CHOP (cyclophosphamide, Adriamycin, vincristine and prednisone; the second cycle also included G-CSF) followed by stem cell collection and then randomization to early versus late SCT. The early transplantation group (n = 91) received 3 to 4 cycles of VAMP (V, A and methylprednisolone) followed by autologous SCT with lomustine, etoposide, cyclophosphamide, MEL 140 and TBI. Patients in the late transplantation group (n = 94) received VMCP as induction therapy until a stable plateau phase was reached. Once patients showed either disease progression while receiving VMCP, disease resistance (no response or < PR after 6 courses of VMCP), or relapsed after responding (n = 81), they then received monthly VAMP followed by autologous SCT as rescue therapy. At a median follow-up of 58 months, there was no significant difference in OS with an estimated median OS in the early group of 64.6 and in the late group of 64 months. There was a significant difference in EFS (medians of 39 and 13 months in the early and late groups respectively). Treatment-related mortality in both groups was notable -- 10% and 14% in the early and late groups -- and not surprising given the intensity of the regimen.

In this trial, comparing continued Ld to Ld and SCT, the optimal SCT strategy (tandem MEL 200) will be available to all patients, either on study for those randomized to SCT or off-study at progression of disease for those randomized to continued Ld. At the three collaborating centers treatment-related mortality in autologous SCT for myeloma is < 1% in all categories of MM patients. In the last 3 ASCT trials at MSKCC (IRB # 98-107, 04-024, 05-080) over 100 patients have been treated and there has been 1 treatment-related death (on IRB # 98-107) due to transfusion-related bacterial sepsis. At TMC, there has been no treatment related death among the more than 60 myeloma patients who have received an ASCT in the past 4 years.[35] In addition, the Ld regimen is likely more effective than the combination chemotherapy regimens used on these historical trials and less toxic as well.

Lenalidomide and multiple myeloma

Lenalidomide (Revlimid®, CC-5013) is a thalidomide analog and a proprietary IMiD® compound of Celgene Corporation. Its anti-neoplastic activity stems from several potential mechanisms of action, including direct induction of apoptosis, inhibition of angiogenesis, inhibition of pro-survival signals to tumor cells, and stimulation of host anti-tumor immunity.[36] Lenalidomide is FDA-approved for the treatment of low- or intermediate-1-risk myelodysplastic syndrome (MDS) with deletion 5q cytogenetic abnormality and transfusion-dependent anemia, based on a 64% rate of achieving transfusion-independence (including 33% achieving a cytogenetic complete response) in this population of MDS patients in a multi-center phase II trial.[37] Lenalidomide is also approved in combination with dexamethasone for relapsed/refractory multiple myeloma.

In pre-clinical studies, lenalidomide has been shown to have direct anti-myeloma activity, inducing apoptosis or G1growth arrest in multiple myeloma cell lines and in primary patient myeloma cells resistant to melphalan, doxorubicin and dexamethasone.[38] A close analog of lenalidomide, CC-4047, decreased the binding of myeloma cells to bone marrow stromal cells, and decreased the production of pro-myeloma survival factors such as IL-6 and TNF-α within the bone marrow environment.[39] Thalidomide, lenalidomide, and CC-4047 all increase T cell proliferation following T cell receptor-mediated activation, leading to increased IL-2 and IFN-γ secretion.[40-42] These cytokines in turn can augment natural killer (NK) cell activation and strengthen NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) against myeloma cell lines and primary patient myeloma cells.[43,44]

In clinical studies, lenalidomide has demonstrated significant activity in both relapsed/refractory and untreated multiple myeloma. Two phase I trials enrolled a total of 44 patients with relapsed/refractory myeloma at lenalidomide doses of 5, 10, 25, and 50mg daily. Grade 3 or 4 neutropenia and thrombocytopenia occurred in almost all patients in the highest dose cohort after 28 days of therapy, requiring dose reductions to 25 mg/day, which was determined to be the MTD. One patient had thromboembolism; other toxicities were generally mild and included rash, leg cramps, fatigue, and lightheadedness. Clinical responses were noted in both trials.[45,46]

A phase II multicenter study randomized 101 relapsed/refractory myeloma patients to lenalidomide 15mg BID or 30mg daily for days 1-21 of every 28 days. Dexamethasone could be added for progressive disease (PD) at 4 weeks or stable disease (SD) at 8 weeks. Thirty-eight percent achieved a minimal response (≥25% reduction in paraprotein) or better, including 6% CR, and another 47% had stable disease. An additional 10 of 30 (33%) achieved a PR or better after the addition of dexamethasone. Median time to progression (TTP) was 6 months. Grade ≥3 neutropenia and thrombocytopenia were seen in 28% and 18% of patients, respectively, more commonly in the BID dosing cohort.[47] A larger multicenter study examined the efficacy of lenalidomide monotherapy in relapsed/refractory myeloma at 30mg daily for 21 of every 28 days. A greater than 50% reduction in paraprotein levels was required for response. Of 222 patients enrolled, 53 (25%) achieved a response (PR or CR) and 152 (71%) had SD, with median TTP of 6 months. Neutropenia (40%) and thrombocytopenia (23%) were the most common grade 3/4 adverse events in this heavily pretreated population.[48]

In two double-blind multicenter international phase III clinical trials (MM-009, North American, 353 patients; MM-010, Europe, Australia, and Israel, 351 patients), patients with relapsed or refractory MM not resistant to dexamethasone (D) were treated with D 40 mg daily on days 1-4, 9-12, and 17-20 every 28 days and were randomized to receive either lenalidomide (L) 25mg daily orally on days 1-21 every 28 days or placebo.[49,50] At a median follow-up from randomization of 17.1 months (MM-009) and 16.5 months (MM-010), both studies showed significant improvement with LD compared to D in overall response (OR) (MM-009: 61% vs 20.5%, p<.001; MM-010: 59.1% vs. 24%, p<.001, respectively), time to progression (TTP) (MM-009: 11.1 months vs. 4.7 months, p<.001; MM-010: 11.3 months vs. 4.7 months, p<.001, respectively), and overall survival (OS) (MM-009: 29.6 months vs. 20.5 months, p<.001; MM-010: not estimable vs 20.6 months, p<.001, respectively). In a subgroup analysis on patients with

impaired creatinine clearance, no significant difference in response rate, TTP, or OS was observed in patients with creatinine clearance above or below 50 ml/min who were treated with LD; however, for 16 patients with creatinine clearance <30ml/min, median TTP and OS was shorter than for those with creatinine clearance >30ml/min, but still significantly longer than for patients treated with D. Lenalidomide in combination with dexamethasone received FDA approval in the use of relapsed/refractory multiple myeloma on June 29th, 2006.

LD has also been examined as a first-line therapy for multiple myeloma. In a phase II study, investigators from Mayo clinic treated 34 newly diagnosed myeloma patients with LD on the same schedule used in the phase III trials.[17] In follow-up presented in 12/07 at the American Society of Hematology annual meeting, the data on this trial were up-dated.[51] At 1 year, 31 of 34 (91%) patients had objective responses (≥50% paraprotein reduction), with 6 (18%) CR and 13 (38%) VGPR (CR+VGPR = 56%). No patients experienced progression of disease within the first 5 months of therapy. Forty-seven percent experienced grade 3/4 non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Of the 34 patients on the trial, 21 received LD (4 cycles) as their primary therapy and continued on Ld to progression of disease. In those patients, best overall responses were 24% CR and 43% VGPR (CR+VGPR = 67%) and the median time to progression was 32 months.

On the ECOG phase III trial the one-year survival of 96% with Ld is the highest ever reported for an initial therapy trial in multiple myeloma.[52] On that trial there was a 9% incidence of thromboembolic complications despite prophylaxis with aspirin (325mg). Ld has now become a frequently used initial therapy for myeloma because the toxicity and safety profile is better than LD and likely better than that of thalidomide and dexamethasone. In addition, the availability of bortezomib as well as SCT give options for second-line therapies should Ld be ineffective.

In this trial we have chosen to use lenalidomide at the starting dose of 25mg QD on days 1-21 every 28 days, with built-in dose reductions for toxicity, because this is the regimen studied in the largest number of patients and is the FDA-approved dose. We also will use low-dose dexamethasone based on superior survival in the ECOG phase III trial. In addition, for thromboembolic prophylaxis, we will use aspirin for those with no risk factors for thromboembolic complications and prescribe prophylactic low-molecular weight heparin (LMWH) for those with risk factors (prior deep vein thrombosis or pulmonary embolus > 6 months prior to enrollment, obesity (body mass index greater than 30), history of vascular disease, documented coronary artery disease, pacemaker, or insulin-dependent diabetes). For patients whose insurance will not cover LMWH, full-dose Coumadin can be used. Patients who experience thromboembolic complications on this trial will be fully anticoagulated and continue on therapy.

On this trial then, we are comparing treatment approaches in which the response data indicate near parity. On this trial, at 1-year in the Ld arm, the CR+VGPR rate is likely to be in the 45% range. Cyclophosphamide (used for mobilization) may increase the response rate. It is difficult to know what the 2-year CR+VGPR rate will be but on the Mayo Clinic phase II trial patients continuing to receive Ld showed improved responses as noted above with CR+VGPR of 67%

and median time to progression of almost 3 years. Of note, continuing lenalidomide in responding patients until progression of disease is standard practice at this time.[53]

In the SCT arm the CR+VGPR rates will be in the 50% range but adding maintenance low-dose Ld for those failing to achieve VGPR after two SCT and for those with high-risk disease may increase those rates. It is important to note that patients experiencing progression of disease in either arm of this trial will be able to receive effective second-line therapy with bortezomib-based treatment and for those in the Ld arm with SCT.

There is no patient jeopardy attached to being in either arm of this trial. It is also important to note that this trial uses a "pick-the-winner" trial design that provides a challenge to Ld to show equivalence to SCT.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Newly diagnosed patients with symptomatic multiple myeloma eligible for SCT will receive Ld for 4 cycles and be evaluated for response after every cycle. Patients with progressive disease after at least one cycle of treatment, and patients with stable disease after 4 cycles will be removed from study. Since the rate of progressive disease on Ld was 0% in the Mayo Clinic phase II trial described above, we expect that patients who experience progression of disease after 2 or 4 cycles of Ld will be extremely rare.

After completion of 4 cycles of Ld, all patients will then undergo conventional stem cell mobilization with cyclophosphamide and G-CSF (10ug/kg/day), or plerixafor and G-CSF, and stem cell collection. Mobilization with cyclophosphamide is preferred, but plerixafor is also allowed.

After stem cell mobilization and collection, patients will be stratified. Stratification will be based on baseline cytogenetics, FISH and β-2 microglobulin. High-risk patients are those with hypodiploidy, t(4;14) or del 17p, or β-2 microglobulin greater than 3.5, while all others will be considered standard risk.

Patients will then be randomized to continued Ld or high-dose melphalan with SCT.

On the SCT arm, patients not achieving VGPR by 3 months after the 1st SCT will undergo a 2nd SCT. All patients, after one or two SCT, will receive maintenance L as described below.

On the continued Ld arm (or non-transplant arm), patients will continue Ld as described below.

Clinical and myeloma status will be evaluated every month during the initial 4 cycles of Ld and every 3 months thereafter as described in Section 12 below. Beyond 3 years of treatment, the patients will be followed yearly for PFS and OS. At progression of disease patients will come off

study and be treated with alternative therapies. Patients on the Ld arm may have high-dose melphalan with SCT at progression of disease.

Evaluation of the disease will occur according to the schedule outlined in table 7, section 10.

4.2 Intervention

In the initial 4 cycles of therapy, patients will receive oral lenalidomide at the starting dose of 25mg on days 1-21 every 28 days (one cycle) with dose adjustments for creatinine clearance and dose reductions for toxicity as described below. Patients will receive low-dose oral dexamethasone at 40mg weekly on days 1, 8, 15 and 22 of each 28-day cycle with dose reductions as below for toxicity (the weekly dose could be split over 2 days in the week i.e. 20mg on days 1, 4, 8, 11, 15, 18, 22, and 25 for better tolerance).

For thromboembolic prophylaxis, patients with no risk factors for thromboembolic complications will receive aspirin (325mg or 81mg). Risk factors include prior deep vein thrombosis or pulmonary embolus (> 6 months prior to enrollment), obesity, history of vascular disease, documented coronary artery disease, pacemaker, or insulin-dependent diabetes. Those with one or more risk factors will be prescribed prophylactic low-molecular weight heparin (LMWH). For patients whose insurance will not cover LMWH, Coumadin (INR 2-3) can be used. Patients who experience thromboembolic complications on this trial will receive Coumadin (INR 2-3) and continue on therapy.

Patients will be evaluated by their physician monthly during the first 4 cycles of Ld and patients will have response of the myeloma assessed with serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay. Patients with non-secretory myeloma will not have bone marrow assessment repeated if they are clinically stable. Patients with progression of disease after at least one cycle of treatment with Ld and patients with stable disease after 4 cycles will be removed from study.

After 4 cycles of Ld, eligible patients will undergo stem cell mobilization and collection with standard-of-care cyclophosphamide and Neupogen (G-CSF), or with plerixafor and G-CSF. Mobilization with cyclophosphamide is preferred, but plerixafor is also allowed. Ld will be held for at least 2 weeks prior to stem cell mobilization.

Within 2 weeks after stem cell mobilization and collection has been completed, patients will be stratified and randomized by the biostatistician working with the Clinical Trials Office at the registration center of MSKCC to either continued Ld or SCT.

For continued Ld, patients will resume Ld at the last dose tolerated during the initial 4 cycles, with prophylactics and dose reductions as indicated. Treatment on the continued Ld arm will resume at the treating physician's discretion. Lenalidomide will be continued until progression of disease or as tolerated. Low-dose dexamethasone will be continued for 1 year, as tolerated. Dose

adjustments will follow guidelines detailed in section 9.2. Patients will be seen every 3 months by their physician and their disease will be reassessed for the first 3 years on study. Patients will also have a CBC and pregnancy test performed monthly as long as they remain on treatment. Beyond 3 years of treatment, the patients will be followed yearly for PFS and OS.

For SCT, patients are admitted to the hospital. High-dose melphalan is administered in a single dose on day -2 or split dose on days -3 and -2, through a central venous catheter. Melphalan dose-adjustments are made for age and creatinine clearance. Patients with creatinine clearance $\geq$ 51ml/min receive melphalan at 200mg/m^2. Patients with creatinine clearance < 51ml/min (to be evaluated within 2 weeks of SCT) will receive 140mg/m^2. Patients > 70 years old receive 140mg/m^2 also. Each SCT in a tandem SCT is a clinically discrete event and these rules of dose adjustment apply to each SCT. Therefore, it is possible, that patients will get different doses of melphalan in tandem SCT.

Patients will receive standard supportive care measures in SCT as previously described except that Neulasta (PEG-filgrastim) and not Neupogen is used after SCT on day +1 to aid hematopoietic recovery.[35,73,74]

Post-SCT after discharge patients are followed on a regular basis as per standard of care and as deemed necessary by their treating physician. At 3 months after the first SCT patients will have response of the myeloma assessed with serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, serum free light chain assay and bone marrow studies. Patients with non-secretory myeloma will have a bone marrow assessment at 3 months post-SCT.

Patients with less than a VGPR at 3 months post-SCT will undergo a second SCT. At 3 months after the 1st or 2nd SCT, all patients will begin maintenance L(L=10mg/day on Days 1-28 of every 28 days cycle escalated to 15 mg after 3 cycles, if tolerated). Lenalidomide will be continued until progression of disease, as tolerated. Dose adjustments will follow guidelines detailed in section 9.2.

For 12 months post-SCT all patients will receive prophylactic acyclovir 400mg PO twice a day adjusted for renal function and a daily proton-pump inhibitor.

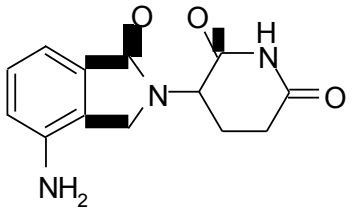
During the first 3 years on study, patients are seen and evaluated every 3 month by their physician and will have response of the myeloma assessed with serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay. Patients with non-secretory myeloma will not routinely have bone marrow assessment repeated if clinically stable.

Beyond 3 years on study, patients will be seen every once a year with disease assessments at those visits for PFS and OS assessment.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Lenalidomide (Revlimid®)

Lenalidomide (L) (REVLIMID®, CC-5013), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Formulation

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Lenalidomide is available in 5 mg, 10 mg, 15 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Supporter: Celgene Corporation will provide lenalidomide free of charge through the Revlimid REMS® program to enrolled patients.

Mechanism of Action

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. It inhibits production in the bone marrow of cytokines (IL-6, TNF-α, VEGF) important for growth and survival of myeloma cells, inhibits COX-2 expression, and decreases tumor angiogenesis. Lenalidomide can directly induce G1 cell cycle arrest and apoptosis in some but not all myeloma cell lines. It also stimulates T cell proliferation and cytokine secretion and NK cell cytotoxic activity.

Storage

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

Pharmacokinetics and Drug Metabolism

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers. In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

Administration

Lenalidomide is an analogue of thalidomide, a known human teratogen that causes severe life-threatening human birth defects. Because of this toxicity, and to limit potential fetal exposure to lenalidomide, patients must follow the birth control guidelines outlined in Appendix C. All women of childbearing potential must follow the protocol-dictated timelines for pregnancy testing.

Lenalidomide is administered orally. It may be taken with or without food at approximately the same time each day.

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the Revlimid REMS® program. All physicians who prescribe lenalidomide for research subjects enrolled into this trial and all research subjects enrolled into this trial must be registered in and must comply with all requirements of the Revlimid REMS® program.

Packaging

Lenalidomide will be shipped directly to patients. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

Accurate records will be kept of all study drug administration, including dispensing and dosing, in the source documents.

5.2 Dexamethasone (D)

Formulation: Supplied as 4 mg tablets.

5.3 Cyclophosphamide

General Information

Mechanism of action: Activation by hepatic microsomal enzymes forming 2 major intermediates, aldophosphamide and 4-hydroxycylophosphamide, which act as powerful alkylating agents and prevent cross linking of DNA strands.

Formulation

Available in both oral and parenteral forms. The parenteral formulation is available as white crystals with sodium chloride as an excipient. The 100 mg dose is provided in a 10 mL vial and a 500 mg dose in a 30 mL vial. For high dose intravenous therapy there are 1 and 2 gram vials which are reconstituted in 50-100 mL of sterile water containing a solution of 20 mg/mL.

In this protocol, cyclophosphamide is administered at a dose of 3000mg/m^2 based on adjusted ideal body weight. This is the standard-of-care dose employed for stem cell mobilization at MSKCC.

Supplier: Mead Johnson

Preparation

The drug may be given by intravenous push or as a slow infusion. Adequate hydration of the patient before and 72 hours after high-dose therapy is recommended to reduce the incidence of hemorrhagic cystitis.

Storage

Solutions reconstituted as described have 24-hour stability at room temperature.

5.4 Melphalan

General information

Generic name: Melphalan, L-phenylalanine mustard
Commercial name: Alkeran
Chemical name: 4-[bis(chloroethyl)-amino]-L-phenylalanine
Melphalan is an alkylating agent coupled to an amino acid.

Formulation

The drug is supplied in a sterile 50 mg vial, prepared as a lyophilized powder with 20 mg of povidone per vial. Ten ml of special diluent is provided for reconstitution. The composition of the diluent is sodium citrate (0.20 g), Propylene glycol (6.00 ml), ethanol (95%) (0.5 ml) and sterile water. The constituted solution is further diluted with 0.9% sodium chloride injection USP to a final concentration of 0.45 mg/ml.

Supplier: Celgene.

ALKERAN for Injection is supplied in a carton containing one single-use
clear glass vial of freeze-dried melphalan hydrochloride equivalent to 50mg melphalan and one 10 ml clear glass vial of sterile diluent.

Administration

The dose is administered intravenously and IV fluids may be given before and after melphalan administration. Furosemide may be given 1 hour after IV melphalan. Intravenous melphalan will be used at doses of 140 and 200 mg/m2. It will be administered in a single dose on 1 day.

5.5 Pegfilgrastim (Neulasta(TM))

Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim.

Formulation

6 MG/0.6 ML SOL. A single fixed dose of 6 milligrams (mg) subcutaneously, given once per chemotherapy cycle, is effective and is recommended.

Supplier: Amgen, Inc

Storage

The manufacturer recommends storage of Neulasta(TM) syringes at 2 to 8 degrees C (36 to 46 degrees F), avoidance of freezing or shaking, and leaving syringes in the carton provided until time of use to protect from light (Prod Info Neulasta(TM), 2002).

Contraindications

Prior hypersensitivity to Escherichia coli-derived proteins, filgrastim, or pegfilgrastim.

5.6 Recombinant human granulocyte-colony stimulating factor (NEUPOGEN®, G-CSF)

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. NEUPOGEN® is the Amgen Inc. trademark for Filgrastim, recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF). NEUPOGEN® is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, Filgrastim, or any component of the product.

The only consistently observed clinical toxicity described with Neupogen® is medullary bone pain. Other clinical toxicities that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.
If required, NEUPOGEN® may be diluted in 5% dextrose. NEUPOGEN® diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by addition of Albumin (Human) to a final concentration of 2 mg/mL.

Do not dilute with saline at any time; product may precipitate.

NEUPOGEN® should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, NEUPOGEN® may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room

temperature for greater than 24 hours should be discarded.

Commercial NEUPOGEN® is available in 1 mL and 1.6 mL vials at a concentration of 300 mcg/mL. Discard unused portions. Use only one dose per vial; do not reenter the vial. Do not save unused drug for later administration.

5.6 Plerixafor (Mozobil)

General Information

Mechanism of Action: Plerixafor is an inhibitor of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α). SDF-1α and CXCR4 are recognized to play a role in the trafficking and homing of human hematopoietic stem cells (HSCs) to the marrow compartment. Once in the marrow, stem cell CXCR4 can act to help anchor these cells to the marrow matrix, either directly via SDF-1α or through the induction of other adhesion molecules.

Formulation

Mozobil (plerixafor injection) is a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution for subcutaneous injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 1.2 mL of the sterile solution that contains 24 mg of plerixafor and 5.9 mg of sodium chloride in Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

Preparation

Vials should be inspected visually for particulate matter and discoloration prior to administration and should not be used if there is particulate matter or if the solution is discolored.

The recommended dose of Mozobil is 0.24 mg/kg body weight by subcutaneous (SC) injection. Use the patient's actual body weight to calculate the volume of Mozobil to be administered. Each vial delivers 1.2 mL of 20 mg/mL solution, and the volume to be administered to patients should be calculated from the following equation:
0.012 X patient's actual body weight (in kg) = volume to be administered (in mL)

Recommended Concomitant Medications: Administer daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first evening dose of Mozobil and on each day prior to apheresis.

Begin treatment with Mozobil after the patient has received G-CSF once daily for four days. Administer Mozobil approximately 11 hours prior to initiation of each apheresis for up to 4 consecutive days.

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

Each vial of Mozobil is intended for single use only. Any unused drug remaining after injection must be discarded.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

Age ≥18 and ≤ 75

Histologic and serologic findings from MSKCC confirming the diagnosis of multiple myeloma. Standard diagnostic criteria for multiple myeloma will be used, as per the revised International Myeloma Working Group diagnostic criteria.[79]

Patients must have symptomatic multiple myeloma without advanced organ damage (such as multiple fractures or advanced bone disease causing immobilization, renal failure, spinal cord compression, or organ compromise due to soft tissue plasmacytoma). If immediate therapy with radiation and high-dose steroids (eg, for cord compression) or with bortezomib-based therapy (eg, for renal failure) is required, the patient is not eligible for this trial.

Patients may have received 1 cycle of prior therapy with dexamethasone for multiple myeloma

Adequate organ function is required, defined as follows:

- ANC ≥ 1,500/µl and platelets≥100,000/µl (unless low ANC and platelets are due to multiple myeloma)
- Serum bilirubin ≤ 2.0 mg/dl
- AST, ALT and alkaline phosphatase < 3 times the upper limit of laboratory normal
- Adequate renal function as assessed by calculated creatinine using Cockcroft-Gault estimation of CrCl (see Appendix H): Subjects must have calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula.

Performance status (ECOG) ≤ 2 (Appendix D).

Eligible for SCT with LVEF ≥ 50% by MUGA or ECHO, and diffusing capacity > 50% predicted by pulmonary function testing

Ability to understand the investigational nature of this study and to give informed consent

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS® program.

Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree not to father a child and agree to use a latex condom during sexual contact with females of child bearing potential even if they have had a successful vasectomy. See Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Able to take aspirin 325mg or 81mg daily as prophylactic anticoagulation (patients intolerant to ASA may use Coumadin or low molecular weight heparin).

6.2 Subject Exclusion Criteria

Prior treatment for myeloma except for one cycle of dexamethasone

History of thromboembolic disease within the past 6 months regardless of anti-coagulation

Myocardial infarction within 6 months prior to enrollment, or New York Hospital Association (NYHA) Class III or IV heart failure (see APPENDIX F), uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

Pregnant or breast-feeding women are excluded due to the potential teratogenicity of lenalidomide.

Concurrent active malignancy other than non-melanoma skin cancers or carcinoma-in-situ of the cervix, or presence of myelodysplastic or myeloproliferative disease. Patients with prior malignancies with a disease-free interval of ≥5 years are eligible. Patients who have had prior malignancies within the past 5 years but are considered to

[†] A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

be “cured” with a low likelihood of recurrence may be eligible at the discretion of the Principal Investigator.

Active hepatitis B or C infection

HIV 1 or 2 positivity

Any other medical condition or laboratory evaluation that, in the treating physician’s or principal investigator's opinion, makes the patient unsuitable to participate in this clinical trial

7.0 RECRUITMENT PLAN

Patients seen in the in-patient or out-patient setting who meet eligibility criteria will be recruited to this study. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. All co-investigators agree to follow the treatment protocol and to conduct the proposed investigation according to recognized principles of good clinical practice.

All participants will be required to sign statements of informed consent and research authorization that conform to FDA, IRB and HIPPA guidelines. All prescribing investigators and study participants must also be registered in Revlimid REMS®. Informed consent will be documented by the use of a written consent form approved by the MSKCC IRB.

Previously, a total of 2 patients were recruited and treated at Tufts Medical Center and The Lahey clinic. These sites were closed in 2012.

8.0 PRETREATMENT EVALUATION

The following tests must be performed prior to patient enrollment:

Within 42 days of enrollment:

History and physical exam

Assessment of ECOG performance status. See Appendix E for ECOG Performance Status

CBC, PT/PTT

Electrolytes (Na, K, Cl, CO_2, Ca), BUN, creatinine, LDH, total bilirubin, AST, ALT, alkaline phosphatase, albumin, β2-microglobulin, TSH

Serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay

24 hour urine collection for total protein, immunofixation (IF), protein electrophoresis, and creatinine clearance

Serum β-HCG (sensitivity of at least 50mIU/ml) for females of childbearing potential (must be done within 10-14 days before and again within 24 hours before prescribing lenalidomide)

Hepatitis A, B, C serologies and HIV 1/2 antibody test (unless previously negative within the last six months)

If possible a core biopsy of any suspected site of soft-tissue plasmacytoma with specimen sent for cytogenetics and FISH as below

Within 56 days of enrollment:

Skeletal survey

Pulmonary function test (including DLCO)

Bone marrow assessment, defined as:

- Biopsy to be stained for CD138, CD20 and kappa/ lambda.
- Aspirate will be sent for the following tests:
  - Routine staining and cell counts.
  - 1 to 3 ml of marrow for flow cytometry for myeloma markers, if indicated, as per standard procedures of the pathology department.
  - 1 to 3 ml of marrow for FISH analysis / myeloma panel, as per standard procedures of the pathology department.

Echocardiogram or MUGA scan, and electrocardiogram (EKG)

MRI of the spine or PET/CT

9.0 TREATMENT/INTERVENTION PLAN

9.1 Administration of therapy

Lenalidomide and Dexamethasone as initial therapy

Patients with newly diagnosed symptomatic multiple myeloma deemed candidates for SCT will be enrolled if they sign the informed consent and are eligible.

Lenalidomide (L) is administered orally at a dose of 25mg daily for days 1-21 of each 28-day cycle. Dexamethasone (d) will begin at 40mg weekly on days 1, 8, 15 and 22 of each 28-day cycle (the weekly dose could be split over 2 days in the week i.e. 20 mg on days 1, 4, 8, 11, 15, 18, 22, and 25 for better tolerance). Dose modifications for toxicity will be performed as described below

Ld increases the risk of thrombotic events. All patients with no risk factors for thromboembolic complications will begin thromboembolic prophylaxis with aspirin 325mg or 81mg daily at the start of treatment. [Aspirin-intolerant patients should receive prophylactic daily low molecular weight heparin (LMWH) or anticoagulation with Coumadin (INR 2-3).] Risk factors include prior deep vein thrombosis or pulmonary embolus (> 6 months prior to enrollment), obesity (body mass index greater than 30), history of vascular disease, documented coronary artery disease, pacemaker, or insulin-dependent diabetes. Those with one or more risk factors will be prescribed prophylactic low-molecular weight heparin (LMWH). For patients whose insurance will not cover LMWH, Coumadin (INR 2-3) can be used. Patients who experience thromboembolic complications on this trial will receive Coumadin (INR 2-3) and continue on therapy.
Concurrent use of recombinant erythropoietin is discouraged due to reports of increased thromboembolic events in patients receiving Ld with erythropoietin. For information on the risk of venous thromboembolism with combined oral contraception see Appendix B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
Concurrent use of erythropoietin requires full anticoagulation of patients with therapeutic doses of LMWH or Coumadin. Anticoagulation should be managed as per MSKCC anticoagulation guidelines for platelet counts <50,000/mm^3. Anti-microbial prophylaxis is not required and is left to the discretion of the treating physician.
Prednisone to treat lenalidomide-related rashes is permitted in small doses of no more than 10mg per day.
Standard supportive care measures may be used at the discretion of the treating physician.

The lenalidomide starting dose will be based on baseline calculated creatinine clearance as follows:

Lenalidomide Starting Dose Based on Renal Function at Study Entry

Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)	Starting Lenalidomide Dose
≥ 60 ml/min	25mg daily on Days 1 - 21 of each 28-day cycle
≥ 30 and < 60 ml/min	10mg daily on Days 1 - 21 of each 28-day cycle

At investigator discretion, patients started with a reduced lenalidomide dose due to baseline calculated creatinine clearance ≥ 30ml/min but < 60ml/min, may have their lenalidomide dose gradually increased in a step-wise manner at the start of Cycle 2 or at the start of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. Lenalidomide dose titrations are permitted in 5mg increments on the same dosing schedule (daily on Days 1-21 of each 28-day cycle) up to the maximum allowable target dose of 25mg daily on

Days 1-21 of each 28-day cycle. The lenalidomide dose may only be increased at the start of a new cycle of therapy, may only be increased once every 28 days (or less frequently), and may only be increased if the prior treatment cycle was completed without requiring dose modifications, interruptions or delays due to toxicity.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Response to Ld as initial therapy will be assessed after every cycle of therapy. Patients with progression of disease after at least one cycle, or patients with stable disease after 4 cycles will be removed from study and offered other therapies including SCT. After 4 cycles of therapy, patients with a response to Ld will have Ld held for at least 2 weeks prior to stem cell mobilization.

Stem cell mobilization and collection

All patients will have blood stem cells mobilized according to institutional practices. This may include either cyclophosphamide or plerixafor based on AIBW as below and in Appendix G) and G-CSF (Neupogen) given at 10ug/kg subcutaneous daily based on actual body weight with leukapheresis beginning as per institutional practices. Mobilization with cyclophosphamide is preferred, but plerixafor is also allowed. Patients will receive prophylaxis antibiotics according to institutional practices.

Once stem cell collection begins, a target of 10 x 10^6 CD34+ cells per kg will be sought, allowing the collection of adequate stem cells for up to 3 stem cell transplants in a patient's lifetime. We will seek a minimal acceptable collection of 4 x 10^6 CD34+ cells per kg, allowing two SCT with the minimum acceptable dose of 2 x 10^6 CD34+ cells per kg per SCT.

Patients failing to collect the minimum dose may be mobilized as per institutional guidelines a second time. Patients who are mobilized twice and have less than 4 million stem cells (CD34+ cells) collected per kg will be removed from study. The likelihood of this happening is less than 2%.

Blood stem cells will be cryopreserved according to institutional practices.

Then all patients will be stratified into high- and standard-risk groups. High-risk patients are those who have baseline high-risk cytogenetics or FISH (hypodiploidy, presence of t(4;14) or del 17p) or baseline β2-microglobulin > 3.5. All other patients will be designated as standard-risk. After stratification, patients will be randomized either to continue Ld or to undergo standard high-dose melphalan and SCT.

Continued Lenalidomide and Dexamethasone

Patients who are randomized to receive continued Ld will be treated as described above, but with dexamethasone at 20 mg weekly on days 1, 8, 15, and 22 (the weekly dose could be split over 2 days in the week i.e. 10 mg on days 1, 4, 8, 11, 15, 18, 22, and 25 for better tolerance). Lenalidomide (L) will remain at a dose of 25mg (or at the last tolerated dose) daily for days 1-21 of each 28-day cycle. Lenalidomide will be continued until progression of disease, as tolerated. Low-dose dexamethasone will be continued for 1 year (from the start of initial treatment), as tolerated. Dose adjustments will follow guidelines detailed in section 9.2.

Pregnancy tests must be performed as in Table 7, footnote 4, during the initial 4 cycles of Ld, all breaks in therapy including the break between completing the initial 4 cycles of Ld through stem cell mobilization and collection, randomization and resumption of Ld.

Dose reductions of lenalidomide will be made as described below.

Stem cell transplantation

For SCT, patients are admitted to hospital.

High-dose melphalan is administered in a single dose on day -2 or a split dose on days -3 and -2, through a central venous catheter. Melphalan will be administered at a dose of 140 or 200 mg/m^2. Melphalan dose-adjustments are made for age and creatinine clearance. Patients > 70 years of age receive 140mg/m^2. Patients with creatinine clearance < 51ml/min (to be evaluated within 2 weeks of SCT) receive 140mg/m^2. Each SCT in a tandem SCT is a clinically discrete event and these rules of dose adjustment apply to each SCT. Therefore, it is possible that patients will get different doses of melphalan in tandem SCT.

Melphalan will be given based on ideal body weight (IBW- Appendix G) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW).

Ideal Body Weight Formulas:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet
Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet
For patients less than 5 feet, subtract 2.3 kg/inch

Adjusted Ideal Body Weight Formula:
AIBW = IBW + [(0.40) x (Actual BW - IBW)]

Patients will receive standard supportive care measures in SCT as per MSKCC institutional practices.

Post-SCT after discharge patients are followed on a regular basis as per standard of care and as deemed necessary by the treating physician through month 3 post-SCT. This applies to all SCT.

Patients may then be seen and evaluated monthly.

Patients will be assessed for disease response 3 months after the 1st SCT.

Patients will receive a 2nd SCT 3 to 6 months after the 1st SCT if the response to the first stem cell transplant is less than a VGPR, provided they have fully recovered from the 1st SCT.

Recovery from the 1st SCT (i.e., from high-dose melphalan and SCT) is defined by achievement of the following clinical criteria:

- Mucositis and gastrointestinal symptoms resolved, off hyperalimentation and intravenous hydration.
- Liver and renal function tests within the inclusion criteria for initial autograft.
- Off antibiotics and Amphotericin B formulations or voriconazole for proven, probable or possible infections (defined in accordance with the EORTC/MSG criteria).[75] Patients who have been treated for an infection but are continuing antibiotics, Amphotericin B or voriconazole for prophylaxis are eligible to continue on protocol with approval of the Principal Investigator.
- Completed administration of any radiotherapy.
- Patients who developed symptoms of cardiac insufficiency after initial enrollment will require repeat cardiac testing and must meet the same criteria as for initial study entry.
- Pulmonary function tests must meet initial study entry criteria.

Patients will be assessed for myeloma response every 3 months beginning 3 months after the 2nd SCT for the first 3 years.

Beginning 3 months post 1st or 2nd SCT, all patients will receive maintenance L (L=10mg/day on Days 1-28 every 28 day cycle, escalated to 15 mg after 3 cycles, if tolerated). Lenalidomide will be continued until progression of disease, as tolerated. Dose adjustments will follow guidelines detailed in section 9.2.

Beyond 3 years, patients will be observed until progression of disease on a yearly base.

9.2 Dose Continuation, Modification and Interruption

Patients will be assessed for toxicity at each visit using the NCI CTCAE v3.0 for the grading of severity.

A) Lenalidomide dose reduction steps:

Table 1: LENALIDOMIDE Dose Reduction Steps	
Starting Dose	**25mg daily**
Dose Level -1	20mg daily
Dose Level –2	15mg daily
Dose Level –3	10mg daily
Dose Level -4	5mg daily
Dose Level -5	2.5mg daily
Dose Level -6	2.5 mg every other day

B) Dexamethasone dose reduction steps

Table 2: Dexamethasone Dose Reduction Steps	
Starting Dose	**40mg weekly on days 1, 8, 15 and 22 of each 28-day cycle**
Dose Level -1	20mg weekly on days 1, 8, 15 and 22 of each 28-day cycle
Dose Level –2	12mg weekly on days 1, 8, 15 and 22 of each 28-day cycle
Dose Level -3	4mg weekly on days 1, 8, 15 and 22 of each 28-day cycle

Note that for the starting dose level and levels -1and -2, the weekly dexamethasone dose could be split over 2 days in the week as detailed in the text and given on days 1, 4, 8, 11, 15, 18, 22, and 25)

C) Instruction for initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle **of initial therapy or continued Ld therapy** if:

The ANC is ≥ 1,000/μL
The platelet count is ≥ 50,000/μL
Hemoglobin is ≥ 8g/dL

Any drug-related rash, allergic reaction/hypersensitivity, sinus bradycardia/ other cardiac arrhythmia adverse event, dyspepsia, gastritis, gastric or duodenal ulcer or confusion or mood alterations that may have occurred has resolved to ≤ grade 1 severity;

Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

A new course of treatment may begin on the scheduled Day 1 of a new cycle of **lenalidomide maintenance therapy** if:

The ANC is ≥ 500/μL
The platelet count is ≥ 50,000/μL
Hemoglobin is ≥ 8g/dL
Any drug-related rash, allergic reaction/hypersensitivity, sinus bradycardia/ other cardiac arrhythmia adverse event, dyspepsia, gastritis, gastric or duodenal ulcer or confusion or mood alterations that may have occurred has resolved to ≤ grade 1 severity;
Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If the toxicity does not resolve within four weeks, the patient will discontinue the treatment. If discontinuation of the treatment occurs before randomization, the patient will be taken off study; if after randomization, the patient will remain on study until progression of disease. If dosing of lenalidomide or dexamethasone was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. If dosing of lenalidomide or dexamethasone was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with dose modifications as described in Section 9.2, Tables 1, 2, 3, 4, 5, and 6.

The investigator retains the discretion to delay or hold treatment if safety concerns arise and if clinically indicated (e.g. surgical procedure or severe infection).

D) Instructions for dose modifications or interruption during a cycle

See Tables 3, 4, 5, and 6 below for detailed dose modification guidelines.

Table 3: Dose Modification for Lenalidomide during Initial Therapy or Continued Ld Therapy

Instructions for Hematologic Toxicities		
NCI CTC v3.0 Toxicity Grade	**Day 2 – 14 of Cycle**	**≥ Day 15 of Cycle**
Grade 3 neutropenia (ANC <1000-500/mm^3) associated with fever , (temperature ≥ 38.5°C) or Grade 4 neutropenia(<500/mm^3)	Hold (interrupt dose) Follow CBC weekly If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of the cycle G-CSF may be used and the dose may be maintained for the next cycle at the treating physician's discretion
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm^3)	Hold (interrupt dose) Follow CBC weekly If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of cycle
Anemia ≥ Grade 3 (Hgb < 8g/dL	Hold (interrupt dose) Follow CBC weekly If anemia resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of cycle

Table 4: Dose Modification for Lenalidomide during Lenalidomide Maintenance Therapy

Instructions for Hematologic Toxicities	
NCI CTC v3.0 Toxicity Grade	**Days 2-28 of Cycle**
Grade 3 neutropenia (ANC <1000-500/mm^3) associated with fever , (temperature ≥ 38.5°C) or Grade 4 neutropenia(<500/mm^3)	Hold (interrupt dose) Follow CBC weekly If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide G-CSF may be used and the dose may be maintained for the next cycle at the treating physician's discretion
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm^3)	Hold (interrupt dose) Follow CBC weekly If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart lenalidomide The dose may be maintained for the next cycle at the treating physician's discretion
Anemia ≥ Grade 3 (Hgb < 8g/dL	Hold (interrupt dose) Follow CBC weekly If anemia resolves to ≤ grade 2 prior to Day 21, restart lenalidomide The dose may be maintained for the next cycle at the treating physician's discretion

Table 5: Dose Modification for Lenalidomide for Non-Hematologic Toxicities during Initial Therapy, Continued Ld Therapy and Lenalidomide Maintenance Therapy

NCI CTC v3.0 Toxicity Grade	Day 2 – 14 of Cycle	≥ Day 15 of Cycle
Non-blistering rash Grade 3	Hold (interrupt dose) Follow weekly If the toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of cycle
Non-blistering rash Grade 4	Discontinue lenalidomide study drug	Discontinue lenalidomide study drug
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide study drug	Discontinue lenalidomide study drug
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide study drug	Discontinue lenalidomide study drug
Sinus bradycardia/other cardiac arrhythmia Grade 2	Hold (interrupt) dose Follow at least weekly If toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of cycle
Sinus bradycardia/other cardiac arrhythmia ≥ Grade 3	Discontinue lenalidomide study drug	Discontinue lenalidomide study drug
Allergic reaction or hypersensitivity Grade 2-3	Hold (interrupt) dose Follow at least weekly If toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of cycle
Allergic reaction or hypersensitivity Grade 4	Discontinue lenalidomide study drug	Discontinue lenalidomide study drug

Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt dose) and start anticoagulation; restart at investigator's discretion (maintain dose level)	Omit lenalidomide for remainder of cycle
Other non-hematologic toxicity assessed as Lenalidomide-related ≥ Grade 3	Hold (interrupt dose) Follow at least weekly If toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle	Omit lenalidomide for remainder of cycle
Hyperthyroidism or hypothyroidism	Omit lenalidomide for remainder of cycle, evaluation etiology, and initiate appropriate therapy See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level	Omit lenalidomide for remainder of cycle, evaluation etiology, and initiate appropriate therapy See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level

Table 6: Dose Modification for Dexamethasone

Dyspepsia	≥ Grade 3	Hold (interrupt) dexamethasone until ≤ grade 1 Reduce dexamethasone by 1 dose level and restart
Gastritis, gastric or duodenal ulcer	≥ Grade 3	Hold (interrupt) dexamethasone until ≤ grade 1 Reduce dexamethasone by 1 dose level and restart
Edema	≥ Grade 3	Reduce dexamethasone by 1 dose level Use diuretics, as needed
Confusion or mood alternations	≥ Grade 2	Hold (interrupt) dexamethasone until ≤ grade 1 Reduce dexamethasone by 1 dose level and restart
Muscle weakness	≥ Grade 3	Reduce dexamethasone by 1 dose level If symptoms persist, continue to reduce dexamethasone by 1 dose level, as needed
Hyperglycemia	≥ Grade 3	Reduce dexamethasone by 1 dose level

		Treat with insulin or oral hypoglycemics, as needed
Acute pancreatitis	≥ Grade 3	Discontinue dexamethasone and take patient off study
Other non-hematologic toxicity assessed as dexamethasone-related	≥ Grade 3	Hold dexamethasone for remainder of cycle Reduce dexamethasone by 1 dose level

Note that if a dose reduction has occurred for lenalidomide due to toxicity, AND if the toxicity has completely resolved to less than grade 1, AND the ANC > 1,000 and the platelet count is > 75,0000, dose re-escalation is allowed one step per cycle to a maximum level of 25 mg during induction or continuous treatment, and 15 mg during maintenance after transplantation.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

During the initial 4 cycles of Ld, a patient history, physical exam, Revlimid REMS® requirements and toxicity assessments will be performed every month. Complete blood counts (CBC) will be performed every two weeks during the first 4 cycles (16 weeks).

For all patients response assessment as described in Section 12 will be performed after every cycle of initial Ld therapy and will include a bone marrow biopsy after completion of 4 cycles, as is shown in Table 7 below. The response of patients who receive SCT will be assessed as in Table 7 beginning 3 months after the 1st SCT. Patients not achieving a VGPR will undergo a 2nd SCT within 6 months of the 1st SCT and be followed for response as in Table 7. The response of patients who receive tandem SCT will be assessed as in Table 7 beginning 3 months after the 2nd SCT.

The toxicities of continued Ld and maintenance L will be assessed in both arms.

While on study assessment for adverse events will be done using NCI version 3.0 CTC criteria as such events occur and at each monthly follow-up visit.

Patients will be removed from study at the time of progression of disease. The end-of-study evaluation will be within 1 month of discontinuation of Ld or of documenting progression of disease and will include the assessment as described in Table 7.

All patients will undergo annual assessments of myeloma status as described below in Table 7.

Table 7. Schedule of Study Assessments

Tests and Studies	Baseline[2]	On day 1 of every Cycle Before Randomization[11]	Every 12 Weeks (+/- 2 weeks) Once Randomized in the first 3 years		Annually while on study And at End of Study[12]
			ASCT[10]	Ld only	
History and physical exam[1]	X	X	X	X	X
ECOG PS	X		X	X	X
CBC [7]	X	X[7]	X[7]	X[7]	X
PT/PTT	X				
COMP	X	X	X	X	X
TSH	X	X	X	X	X
LDH, B2MG	X	X	X	X	X
SPEP, SIF, Quant Ig, serum FLC	X	X	X	X	X
24 hr urine for UPEP, UIF, TP, Creatinine clearance	X	X	X	X	X
Pregnancy test[3]	X[4]	X[4]	X[4]	X[4]	X[4]
Register patient into Revlimid REMS® program	X				
Hepatitis and HIV serologies	X				
Biopsy of EM disease if suspected	X		X	X	X
Skeletal survey[2a]	X				X[13]
MRI spine or PET/CT[2a]	X				
Bone marrow assessment[2a, 6]	X[6]	X[6]	X[6]		X[6]
Echocardiogram or MUGA[2a]	X				
EKG[2a]	X				
PFTs including DLCO[2a]	X				
Assess for adverse events and review medication diary [5, 9]	X	X[9]	X	X	X[9]
Prescribe lenalidomide via Revlimid REMS® [8]	X	X	X[8]	X[8]	

1. Baseline history and exam must include all prior and current medications, all prior anti-cancer therapies, vital signs, height and weight.
2. Within 42 days of enrollment;
   a. 56 days of enrollment
3. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24

consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

4. Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). Breaks in therapy include the period after completing the initial 4 cycles of LD through stem cell mobilization and collection, randomization and resumption of LD.
5. See APPENDIX B for medication diary
6. See Section 8.0. To be performed at baseline, after first 4 cycles of Ld, 3 months post ASCT, annually and at End of Study visit. For transplant patients, the physician may forgo the bone marrow biopsy at 12 months from initiation of treatment if the post transplant biopsy was performed within 3 months of the annual assessment. For patients who have completed 3 years on study bone marrow assessment will be left to MD discretion.
7. Complete blood counts (CBC) will be performed every 2 weeks during the first 16 weeks and monthly thereafter while on Lenalidomide, with a window of +/- 3 days.
8. Lenalidomide must be prescribed every 4 weeks through and in compliance with the Revlimid REMS® program. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned by the patient for disposition in accordance with the Revlimid REMS® program.
9. An additional safety assessment will be done approximately 28 days following the last dose of lenalidomide.
10. Schedule of Assessments to be followed with or without Ld treatment
11. These assessments may be done within one week preceding day 1 of every cycle.
12. Testing should occur annually +/- 4 weeks; For patient that have completed 5 years of study treatment, annual assessments will be at the MD discretion.
13. For patients who have completed 3 years of study treatment Skeletal Survey will be left to MD discretion

11.0 TOXICITIES/SIDE EFFECTS

Toxicity scoring will be done using NCI CTCAE v3.0.

Lenalidomide

Thalidomide is teratogenic. Lenalidomide is a structural analog of thalidomide and it must be treated as if it were a known teratogen. Women of childbearing potential must have a negative pregnancy test before and during therapy, and sexually active men and women must agree to use adequate contraceptive practices while on study (see Appendix B).

Side-effects include:

Likely

Fatigue or feeling tired
Lack or loss of strength
Anemia or a decrease in red blood cells that can cause tiredness (which may require transfusion)
Thrombocytopenia or a decrease in platelets which can cause you to bruise or bleed easily
Leukopenia and neutropenia or a decrease in white blood cells that can make you more prone to infections
Constipation or difficulty moving your bowels
Diarrhea or loose/frequent bowel movements
Bone pain
Pain in extremity
Upper respiratory infection
Bronchitis
Nasopharyngitis
Rhinitis
Pneumonia or an infection of the lungs
Blurred vision
Urinary tract infection
Hypokalemia
Dysgeusia
Hypoesthesia
Peripheral neuropathy
Tremor
Epistaxis or nosebleeds
Pharyngitis

Less Likely

Febrile neutropenia
Lymphopenia
Blood clots
Pancytopenia
Acute myocardial infarction

Respiratory distress
Atrial fibrillation or irregular heartbeat
Cardiac failure
Cardiac failure congestive
Myocardial ischemia
Palpitations
Tachycardia
Chest pain
Sepsis or an infection of the blood
Bacteremia or presence of bacteria in the blood
Dehydration
Renal failure (which may require dialysis or may cause swelling)
Granulocytopenia
Cataracts
Abdominal pain
Joint pain
Back pain
Dry mouth
Dyspepsia
Diabetes mellitus
Gastrointestinal motility disorder
Toothache
Fall
Abnormal liver function tests
Alanine aminotransferase increased
Gamma-glutamyltransferase increased
Erysipelas
Pyroderma gangrenosum
Gastroenteritis
Herpes simplex
Herpes zoster
Influenza
Lower respiratory tract infection
Sinusitis
Hyperglycemia
Hyperuricemia
Hypocalcemia
Hypophosphatemia
Hypomagnesemia
Hyponatremia
Hypothyroidism
Iron overload

Muscular weakness
Muscle cramps/spasms/pain
Cerebrovascular accident
Lethargy
Paresthesia
Nausea
Vomiting
Chills
Weight loss, anorexia
Syncope
Dizziness
Headache
Insomnia
Pruritus
Cough
Dyspnea
Depression
Altered mood
Hyperhidrosis
Night sweats
Hematoma
Edema
Hypertension
Hypotension
Peripheral ischemia
Thrombosis
Peripheral sensory neuropathy

The following events have been reported from clinical studies and post-marketing experience:

Inflammation of the pancreas, which causes increase in pancreatic enzymes (lipase), which could result in abdominal pain and discomfort and could require hospitalization and intravenous treatment

Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Kidney damage which may require dialysis

Severe skin rash with blisters that can involve the inside of the mouth and other parts of the body

Brain damage which may cause headache, seizure, blindness

Rare treatment-emergent adverse events of angioedema (an allergic skin disease which includes small areas of swelling involving the skin and/or the lining of the nose, mouth, stomach, and intestines) and serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to separation of the top layer of skin (could be body-wide) which have been reported with lenalidomide during commercial use. These events have the potential to result in death. Medical journals have reported patients with allergic skin reaction with thalidomide who also developed the same type of reaction with lenalidomide.

Tumor lysis syndrome (TLS) and tumor flare reaction (TFR) have commonly been observed in patients with Chronic Lymphocytic Leukemia (CLL), and uncommonly in patients with other lymphomas, who were treated with lenalidomide. There have been rare reports of TLS in patients with Multiple Myeloma (MM) treated with lenalidomide, and no reports in patients with Myelodysplastic Syndrome (MDS) treated with lenalidomide. Tumor lysis syndrome is a metabolic complication caused by the break-down products of dying cancer cells. Complications include hyperkalemia (high potassium), hyperphosphatemia (high phosphorus), hyperuricemia and hyperuricosuria (high uric acid in blood and urine), hypocalcemia (low calcium), and consequent acute uric acid nephropathy and acute renal failure (kidney damage). Tumor lysis syndrome can occur with or without treatment of cancer. Tumor flare reaction is a condition that involves any of the following: increase in size of the cancerous lymph nodes, rash and slight fever.

The rare adverse event of rhabdomyolysis has been seen with lenalidomide treatment. This is a serious condition involving destruction of skeletal muscle that can lead to kidney damage. Signs and symptoms include dark, red or cola colored urine, muscle tenderness and stiffness, aching (myalgia) or weakness.

An immune system disorder known as graft versus host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation. This disorder is defined as damage to organs in the body when donor cells attack host organs which may cause yellowing of the eyes and skin, itchy dry skin, or muscle weakness.

Hematological Toxicity

Lenalidomide is associated with significant neutropenia (decrease in white blood cells that help fight infection) and thrombocytopenia (decrease in platelets that help with blood clotting). You will have your blood counts checked frequently when starting treatment with lenalidomide.

Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide, in combination with dexamethasone, has been associated with an increased incidence in thrombotic or thromboembolic events, including DVT, pulmonary embolism, thrombosis, and thromboembolism, particularly among patients with MM receiving concomitant therapy with an erythropoietic agent and, to a lesser extent, in patients with MDS treated with lenalidomide monotherapy. Prophylaxis to reduce the risk of thrombosis should be considered in

accordance with study protocols, particularly in patients with additional underlying risk factors, such as prior history of a thrombotic event.

Patients with MM taking lenalidomide and dexamethasone, and to lesser extent patients with MDS or lymphomas taking lenalidomide monotherapy, as well as patients taking combined oral contraceptives or hormone replacement therapy have an increased risk of venous thromboembolic events. Physicians should discuss the risk/benefit of contraceptive methods or hormonal replacement with their patients. Effective measures to avoid pregnancy must be taken.

Second new cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers. Cancers such as acute myeloid leukemia, B-cell lymphoma, basal cell carcinoma, and squamous cell carcinoma of the skin have been seen, as well as tumor flare.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Reports of progression to acute myeloid leukemia (AML) have been received from MDS studies. It is unclear whether lenalidomide indeed increases the risk of AML or if progression merely reflects the natural course of the disease. AML is the rapid multiplication of abnormal cells which accumulate in the bone marrow and interfere with the production of normal blood cells. AML is a very serious condition which may result in death.

Other Risks

Patients taking lenalidomide and dexamethasone for multiple myeloma should be careful taking drugs that may increase chance of having blood clots (for example drugs to increase red blood cell count or hormone replacement therapy).

Cases of transient (for a short time) liver laboratory abnormalities were reported in subjects treated with lenalidomide. Your doctor will monitor laboratory tests closely and recommend treatment interruption until improvement in laboratory results.

Lenalidomide has been shown to increase the level of digoxin in the blood in some patients; please tell your doctor if you are taking digoxin.

Dexamethasone

Side-effects include:

Likely

- Weight gain
- Stomach upset or ulcers
- Insomnia and mood changes
- Fluid retention

Less likely
- Increased blood sugar level
- Increased blood pressure
- Thinning of the bones
- Alterations in hair growth
- Decreased muscle mass (myopathy)
- Anxiety

Rare but serious
- Cataracts
- Skin changes
- Aseptic necrosis of the hip
- Susceptibility to infections

Cyclophosphamide

The maximum dose of cyclophosphamide that can be given without bone marrow transplantation is 7 gm/m^2 resulting in severe myelosuppression. The pharmacokinetics of high dose cyclophosphamide do not differ from that of low doses and there is no evidence that enzymes responsible for cyclophosphamide biotransformation and detoxification are saturated.

Side-effects include:

Likely
- A drop in blood counts leading to an increased risk of infection and bleeding
- Fatigue
- Hair loss
- Nausea and vomiting
- Bleeding from the wall of the bladder
- Male infertility

Rare but serious
- Heart inflammation and damage
- Lung problems
- Changes in plasma sodium levels
- Bladder cancer
- Serious skin reactions

• Secondary leukemia

Plerixafor (Mozobil)

Likely
• Nausea
•Vomiting
•Stomach pain
•Diarrhea
•Gas
•Dizziness
•Headache
•Excessive tiredness
•Difficulty falling asleep or staying asleep
•Joint pain
•Pain, redness, hardness, swelling, irritation, itching, bruising, bleeding, numbness, tingling, or rash in the place where plerixafor injection was injected

Rare but serious
•Pain in the left upper part of the stomach or in the shoulder
•Easy bruising or bleeding
•Swelling around the eyes
•Difficulty breathing
•Hives
•Fainting

Melphalan

The major systemic toxicity of IV melphalan is bone marrow depression with secondary anemia, leukopenia and thrombocytopenia. This side-effect is exacerbated by prior chemotherapy or radiotherapy.

Side-effects include:

Likely
Low blood cell counts (bone marrow suppression) that can lead to anemia that requires red blood cell transfusions; a decreased number of white blood cells that increases the risk of infections and is treated with G-CSF injections and with stem cells; and low platelets that increases the risk of bruising and bleeding and is treated with platelet transfusions.
• Fatigue
• Nausea, vomiting
• Hair loss (temporary)
• Mouth sores

• Pain in the mouth requiring pain medicines
• Pain with swallowing requiring pain medicines
• Diarrhea and cramping

Less likely
• Liver damage
• Allergic reactions (which could make you feel short of breath and/or have a skin rash)

Rare but serious
• Secondary leukemia 5 to 10 years after exposure
• Lung damage
• Blood vessel damage
• Red blood cell damage due to an immune reaction
• Death

Neulasta and Neupogen (G-CSF)

Side-effects of Neulasta include:

Likely:
• Bone pain
• Exacerbation of preexisting autoimmune disorders
• Transient and reversible changes in alkaline phosphatase, uric acid and LDH
• Minor local discomfort associated with subcutaneous injection (temporary)

Side-effects of Neupogen include:

Likely
• Body aches
• Pain, swelling and redness at the site of injection
• Bone pain
• Fever
• Muscle cramps and pain in your back or legs (relieved by taking Tylenol)

Less likely
• Inflammation, psoriasis or arthritis may get worse

Rare but serious
• Decreased blood pressure and risk of falling
• Enlargement of the spleen that may lead to rupture
• Hair thinning
• Decreased blood platelets which may increase your risk of bruising or bleeding
• Enlargement of the liver

- Allergic reactions

Stem cell mobilization and collection

Central Venous Catheter

The patients may need to have central venous catheter placed to have stem cells collected. Patients with small stature or small arm veins will likely need a catheter placed for stem cell collection. A central venous catheter is a flexible sterile tube that will be placed into a large vein that runs under your collarbone so that blood can be withdrawn and medications given to you more easily and with less discomfort. This tube is usually placed under local anesthesia. There is a lot of experience with the use of these catheters.

The most common complications are clotting and local infection that sometimes lead to a general infection in the blood. Clotting may require the removal of the catheter or treatment of the clot by medicines that dissolve blood clots. Infections will be treated with antibiotics and sometimes removal of the catheter may be required. There is also a small risk of puncturing the lung at the time of the catheter insertion. If this occurs, placement of a temporary chest tube to re-inflate the lung may be required and there are no long-term effects once it has resolved.

Side-effects can include:

Likely

Clotting
Local infection

Less Likely

General infection of blood

Rare but serious

Puncturing of lung upon catheter insertion

Stem cell mobilization

Patients will have stem cells mobilized. Mobilization with cyclophosphamide is preferred, though Mozobil is also allowed. Following chemotherapy for stem cell mobilization, they will receive G-CSF (filgrastim or pegfilgrastim) as per institutional practices. Neupogen will help to move the stem cells out of the bone marrow into the bloodstream. Once the number of stem cells in the blood stream is high enough, patients will be collected over 2-5 days, while still receiving the Neupogen injections. A procedure called leukapheresis will be done to collect the stem cells. During this procedure, blood will be collected either through your central venous catheter or from a vein in one arm, processed through a machine to remove the white blood cells (stem cells), and then the rest of the blood will be returned to the patient through the catheter or a vein

in the other arm. The leukapheresis procedure will last several hours each time. Patients will be asked to sign a separate consent form for the leukapheresis procedure. Enough stem cells will be collected for at least two autologous stem cell transplants. The stem cells will be frozen (cryopreserved) until the time when they will be given back to the patient.

Stem cell transplant

A couple of weeks after the stem cells have been collected, patients randomized to stem cell transplant will undergo an autologous stem cell transplant using high-dose chemotherapy with melphalan given through a central venous catheter. Since this high-dose treatment destroys the normal bone marrow in addition to the myeloma cells, blood stem cells must be given back to the patient. The previously collected stem cells will be thawed and given back to the patient through the central venous catheter, similar to a blood transfusion; two days after the patient received the melphalan. On the day after that, the patient will be given Neulasta by injection under the skin. Neulasta helps the bone marrow to produce new white blood cells and needs to be given only once. After completion of the stem cell transplant, the patient will be followed in the out-patient clinic.

At 2 and 4 months after the transplant the response of the patient's myeloma will be evaluated. If the patient has not had a greater than 90% reduction in myeloma since the start of treatment, the patient will undergo a second stem cell transplant with stem cells already collected. If the patient has had a greater than 90% reduction in myeloma, the patient will not have a second stem cell transplant.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Responses will be determined according to the IMWG Response Criteria (that have supplanted the older European Group for Blood and Marrow Transplantation (EBMT) criteria)[76,77] using standard electrophoretic and immunofixation tests of blood and urine for a monoclonal protein (M protein), the serum free light chain assay, and the bone marrow aspirate and biopsy with immunohistochemical staining. A Response Review group that includes Pathology, Clinical Chemistry, and Hematology will formally score responses. The group meets every Tuesday in the early afternoon in Pathology. Research study assistants prepare patient data for review and record response decisions.

For all patients, responses will be assessed after every cycle of initial Ld therapy, including a bone marrow aspirate and biopsy after the initial 4 cycles. Patients will have response of the myeloma assessed with serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay. Patients with non-secretory myeloma will have the bone marrow assessment repeated after 4 cycles of initial Ld therapy if they have been otherwise clinically stable (i.e., without new lytic lesions, soft-tissue plasmacytomas or hypercalcemia). Bone marrow assessment is defined in Section 8.0.

For patients randomized to continued Ld, responses will be scored at least every 3 months for the first 5 years (and every 6 months beyond 5 years) until progression of disease. For patients randomized to SCT, responses will be scored at 3 months after the first and, if performed, 3 months after the second SCT, including a bone marrow aspirate and biopsy, and then every 3 months for the first 5 years (and every 6 months beyond 5 years) until progression of disease. Testing for response assessment will include serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay. Patients with non-secretory myeloma will not have bone marrow studies performed if they have been clinically stable as described above.

Annually during the first 5 years after enrollment, and at the time of end-of-study evaluation for progression of disease, patients will have response of the myeloma assessed with serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, serum free light chain assay and bone marrow assessment (see table 7 for schedule of bone marrow biopsies). Patients in either arm who experience progression of disease will undergo end-of-study assessments and will be removed from study to receive other therapy in consultation with their physicians. They will continue to be followed for overall survival.

Response criteria are as follows for patients with measurable M protein or free light chains: Adapted from Durie et al, "International uniform response criteria for multiple myeloma, Leukemia 2006; 20:1467-73" [78].

Stringent Complete Response (sCR) = CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

Complete Response (CR) = Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow.

Unconfirmed Complete Response (uCR) = All criteria for CR are met, except a bone marrow biopsy is not available.

Near Complete Response (nCR) = Normalization of M-protein as detected by Serum Protein Electrophoresis, but M-protein is still detectable by immunofixation.

Very Good Partial Response (VGPR) = 90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 hours

Partial Response (PR) = ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is requires in place of the M-protein criteria. If serum and 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 meeting criteria for sCR, CR, nCR, VGPR, PR, or POD.

Progressive Disease (PD) = Laboratory/Biochemical Relapse or Progressive Disease: Required any one or more of the following:

- 1) Increase of ≥25% from lowest response level in:
  - a) Serum M-component (the absolute increase must be ≥0.5 g/dl) **and/or**
  - b) Urine M-component (the absolute increase must be ≥200 mg/24h **and/or**
  - c) The difference between involved and uninvolved FLC levels (only in patients without measurable serum and urine M-protein levels). The absolute increase must be >10mg/dl **and/or**
  - d) Bone marrow plasma cell percentage (the absolute % must be ≥10%).
- 2) Definite development of new bone lesions or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- 3) Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

Clinical Relapse (i.e., progressive disease requiring re-treatment or alternate treatment) = Clinical relapse or progressive disease requires one or more of:
Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival, but is listed here 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 1cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion.
- 3) Hypercalcemia (>11.5 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 μmol/l or more]

Complete response requires confirmation by bone marrow assessment.

Special considerations in assessing response

Low-level urinary M proteins may vary from measurement to measurement. For an increase in urinary M protein to be considered progression of disease it must be an absolute increase of at least 200 mg/day.

In quantitative immunoglobulin serum studies, the levels of heavy and light chain are often discrepant for technical reasons. If the discrepancy leads to equivocal response values, the heavy-chain value will be used since the heavy-chain value is usually a more reliable indicator because of its longer half-life and non-renal metabolism.

In 2% of patients, only the serum free light chain level can be measured as the M protein. In these patients, the response criteria are based on changes in the involved free light chain levels, and remain statistically the same except that the ratio of kappa-to-lambda in the free light chain assay should also be normal in CR.

In 1% of patients, no marker for the M protein exists. In those patients, the response criteria are:

Partial Response (PR) = A reduction of $\geq$ 50% in marrow plasma cells with no progressive disease by skeletal survey or other imaging modality.

Very good partial response (VGPR) = A reduction of $\geq$ 90% in marrow plasma cells with no progressive disease by skeletal survey or other imaging modality.

Complete Response (CR) = Normalization of the bone marrow biopsy, including $\leq$5% total plasma cells and lack of clonal excess by kappa/lambda staining, with no progressive disease by skeletal survey or other imaging modality.

Stable disease (SD) = An increase in marrow plasma cells by < 25% from baseline or a decrease in marrow plasma cells by < 50% from baseline with no progressive disease by skeletal survey or other imaging modality.

Progressive Disease (PD) = An increase in marrow plasma cells of $\geq$ 25% from baseline after therapy, and/or the occurrence of new hypercalcemia or new lytic lesions by skeletal survey or new soft-tissue plasmacytomas.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Treatment with study drugs is to be discontinued when any of the following occurs:

Progressive disease at any point in time during the treatment after at least 1 cycle of Ld
Stable disease after 4 initial cycles of Ld
Adverse event(s) that, in the judgment of an Investigator, may cause severe or permanent harm or which rule out continuation of study drug

Major violation of the study protocol
Withdrawal of consent
Patient is lost to follow-up
Death

Suspected or confirmed pregnancy

If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB, regulatory authorities, etc.).

14.0 BIOSTATISTICS

The protocol has been amended to change the endpoint to 2-year progression free survival (PFS) rather than the 2-year response rate.

After initial therapy with 4 cycles of Ld, patients will have stem cells mobilized and collected and then will be stratified and randomized as described in Section 15.2 to either SCT or continued Ld. We propose declaring treatment in either arm a success if the 2-year PFS is at least 65%. This 2-year PFS rate was seen in patients receiving induction lenalidomide and dexamethasone followed by transplant which is considered the standard of care. A single stage design that differentiates between 2-year PFS rates of 65% and 87% will be used to assess the efficacy of the current regimen. This design has type I and type II error rates both set to 10%. A total of 25 patients will be accrued in each arm. If 20 or more patients are progression free at 2 years in a treatment arm, then the arm will be considered to have sufficient activity to be of interest for further study. In order to reach a number of 50 randomized patients, we estimate that approximately 62 patients will need to be enrolled, taking into account patients who do not respond or do not tolerate the induction treatment, and who are therefore not randomized.

Results from the two treatment arms will be compared directly to each other using a "pick-the-winner" approach. If both arms are declared desirable by demonstrating at least 20 patients progression free by 2 years in their 25 patient cohorts, then the choice of which arm will be suitable for further study will be based on the absolute number of responses. In such a case, if the treatment arm with a higher number of responses is also associated with more toxicity, then the investigators will weigh both the absolute number of responses and toxicity in selecting which arm is suitable for further study. If the difference in the true response rates of the treatment arms is 10% then the chance that the regimen with the higher response rate will be picked is over 73%. If the difference in the true response rates of the treatment arms is 15% then the chance that the regimen with the higher response rate will be picked is over 85%.

Progression-free survival from date of randomization will be estimated using the method of Kaplan-Meier. Secondary endpoints include CR+VGPR and overall response rates at 2 and 3 years. Estimates of the CR+VGPR and overall response rates will be calculated along with 95% confidence intervals.

15.0 RESEARCH PARTICIPANT REGISTRATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2Randomization

Prior to randomization patients will be stratified into high-risk or standard-risk groups using the baseline marrow aspirate cytogenetic and FISH findings and the baseline β-2 microglobulin. The high-risk group includes patients with hypodiploidy by karyotype, t(4;14) or del 17p, or β-2 microglobulin > 3.5. All others are standard risk.

Patients will be randomized to EITHER continued Ld OR SCT within 2 weeks after stem cell mobilization and collection are completed using the Clinical Research Database (CRDB) by calling the MSKCC PPR registry at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday - Friday. Randomization will be accomplished by the method of random permuted block.

16.0 DATA MANAGEMENT ISSUES

All patients will be enrolled on protocol at MSKCC.

A Research Study Assistant (RSA) will be assigned to the study at MSKCC. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database (CRDB) by the assigned MSKCC RSA. Source documentation will be available to support the computerized patient record.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRDB. Relevant source documentation to be maintained throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

16.1 Quality Assurance

Investigator responsibilities: Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

The Investigator will permit study-related audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

Retention of Records: All documentation pertaining to the conduct of the study and the distribution of the study drug, source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]), and all IRB correspondence will be retained for at least 2 years after the investigation is completed.

16.1.1 Response Review

Since therapeutic efficacy is a stated primary objective, patients' responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology,

additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained for MSKCC TRRC review and confirmation of response assessment.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms at MSKCC by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB).

16.3.1 Amendments

Any amendment to this protocol must be agreed to by the MSKCC Principal Investigator and reviewed by Celgene Corporation. Amendments should only be submitted to the IRB after consideration of Celgene review. Each change to the protocol document must be organized and approved by the MSKCC IRB/PB.

16.3.2 Additional IRB Correspondence

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC, approval from the MSKCC IRB/PB is required prior to the action. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. Protocol violations that are identified after they occur should be reported to the MSKCC IRB/PB as soon as possible. Protocol violations that are identified after they occur should report to MSKCC IRB/PB as soon as possible.

16.3.3 Document maintenance

The MSKCC PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC's IRB guidelines.

Patients will be eligible for this trial regardless of gender or racial/ethnic background. All patients must follow the guidelines for pregnancy testing birth control and counseling related to the risk of fetal exposure to lenalidomide as outlined in appendix C.

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Potential risks and benefits

The potential risks of this therapy may outweigh the potential benefit in an individual patient. The potential risks to patients are related to drug induced adverse effects and are outlined in Section 11.0. Appropriate exclusion criteria for patients are listed in Section 6.0: Patient Eligibility. Appropriate exclusion of patients with significant organ dysfunction or infection will help avoid treatment-related toxicity. Careful monitoring of laboratory parameters and

patient symptoms, along with serial assessment for disease recurrence, will be carried out routinely in order to minimize the risk of adverse effects during this study.

Alternatives/Options for treatment

Patients with newly diagnosed standard-risk multiple myeloma have many treatment options. Alternative therapy for patients who choose not to enroll on this study include standard chemotherapy, autologous or allogeneic stem cell transplant, thalidomide, steroids, bortezomib, lenalidomide, some combination of the above, other clinical trials, observation, or supportive care.

Costs

Patients will be responsible for all costs related to treatment and complications of treatment, including all hospitalizations. Patients will not be responsible for the cost of lenalidomide.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit their representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

17.2 Serious Adverse Event (SAE)

An adverse event is considered serious if it results in ANY of the following outcomes:

Death

A life-threatening adverse event

An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

A congenital anomaly/birth defect

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:
For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered**:**

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject's condition

- Indication if the subject remains on the study

If an amendment will need to be made to the protocol and/or consent form
If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.3 Reporting of SAEs to Study Supporter (Celgene Corporation)

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of that event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day of learning of the event by MSKCC RSA. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. The Celgene tracking number (RV-MM-PI-0287) and the institutional product number should be included on the SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information:

Treatment regimen (dosing frequency, combination therapy)
Protocol description (and number, if assigned)
Description of event, severity, treatment, and outcome if known
Supportive laboratory results and diagnostics
Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

The investigator will determine which events are associated with the use of the study drugs.

For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

There is a clinically plausible time sequence between onset of the AE and study drug administration; and/or
There is a biologically plausible mechanism for the study drug causing or contributing to the AE; and

The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

Follow-up information may be added to a previously submitted report by any of the following methods:

Adding to the original report and submitting it as follow-up
Adding supplemental summary information and submitting it as follow-up with the original form
Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

17.4 Safety Reports

Reporting SAE to the FDA
Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse Drug Reaction Reporting
Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

Pregnancies

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 lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Prenancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferable one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. 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 to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report 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 IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

In the case of a live "normal" birth, Celgene Drug Safety should be advised as soon as the information is available.

Male Subjects

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

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

Adverse event updates/IND safety reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB, on file.

Annual Reports to Celgene

This study meets requirements for IND exemption. Annual report must be submitted to Celgene for review/approval:

Celgene Corporation
Attn: Medical Development
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

APPENDIX A:	Schedule of Study Assessments
APPENDIX B:	Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods
APPENDIX C:	Diagnostic and Staging Criteria for Multiple Myeloma
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APPENDIX A: SCHEDULE OF STUDY ASSESSMENTS

Tests and Studies	Baseline[2]	On day 1 of every Cycle Before Randomization[11]	Every 12 Weeks (+/- 2 weeks) Once Randomized in the first 3 years		Annually while on study And at End of Study[12]
			ASCT[10]	Ld only	
History and physical exam[1]	X	X	X	X	X
ECOG PS	X		X	X	X
CBC [7]	X	X[7]	X[7]	X[7]	X
PT/PTT	X				
COMP	X	X	X	X	X
TSH	X	X	X	X	X
LDH, B2MG	X	X	X	X	X
SPEP, SIF, Quant Ig, serum FLC	X	X	X	X	X
24 hr urine for UPEP, UIF, TP, Creatinine clearance	X	X	X	X	X
Pregnancy test[3]	X[4]	X[4]	X[4]	X[4]	X[4]
Register patient into Revlimid REMS® program	X				
Hepatitis and HIV serologies	X				
Biopsy of EM disease if suspected	X		X	X	X
Skeletal survey[2a]	X				X[13]
MRI spine or PET/CT[2a]	X				
Bone marrow assessment[2a, 6]	X[6]	X[6]	X[6]		X[6]
Echocardiogram or MUGA[2a]	X				
EKG[2a]	X				
PFTs including DLCO[2a]	X				
Assess for adverse events and review medication diary [5, 9]	X	X[9]	X	X	X[9]
Prescribe lenalidomide via Revlimid REMS® [8]	X	X	X[8]	X[8]	

1. Baseline history and exam must include all prior and current medications, all prior anti-cancer therapies, vital signs, height and weight.
2. Within 42 days of enrollment; For patients who have completed 5 years of study treatment the end of study Skeletal Survey is at MD discretion if clinically indicated
   a. 56 days of enrollment

3. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
4. Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). Breaks in therapy include the period after completing the initial 4 cycles of LD through stem cell mobilization and collection, randomization and resumption of LD.
5. See APPENDIX B for medication diary
6. See Section 8.0. To be performed at baseline, after first 4 cycles of Ld, 3 months post ASCT, annually and at End of Study visit. For transplant patients, the physician may forgo the bone marrow biopsy at 12 months from initiation of treatment if the post transplant biopsy was performed within 3 months of the annual assessment. For patients who have completed 3 years on study bone marrow assessment will be left to MD discretion.
7. Complete blood counts (CBC) will be performed every 2 weeks during the first 16 weeks and monthly thereafter while on Lenalidomide, with a window of +/- 3 days.
8. Lenalidomide must be prescribed every 4 weeks through and in compliance with the Revlimid REMS® program. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned by the patient for disposition in accordance with the Revlimid REMS® program.
9. An additional safety assessment will be done approximately 28 days following the last dose of lenalidomide.
10. Schedule of Assessments to be followed with or without Ld treatment
11. These assessments may be done within one week preceding day 1 of every cycle.
12. Testing should occur annually +/- 4 weeks; For patient that have completed 5 years of study treatment, annual assessments will be at the MD discretion
13. For patients who have completed 3 years of study treatment Skeletal Survey will be left to MD discretion

APPENDIX B: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

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

Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide

A male patient taking lenalidomide acknowledges that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with 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

intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. 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 patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method 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 patients with neutropenia.

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. Patients and physicians must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

Before starting lenalidomide

Female Patients:

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

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.

At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.

If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.

Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.

Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

Patients should be instructed never to give lenalidomide to another person.

Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.

Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

APPENDIX C: Diagnostic and Staging Criteria for Multiple Myeloma

International Staging System (ISS)

Stage	Criteria
I	**β2-microglobulin < 3.5 mg/dL**
	Serum albumin ≥ 3.5 g/dL
II	**Neither stage I nor stage II**
III	**β2-microglobulin ≥ 5.5 mg/dL**

APPENDIX D: ECOG Performance Status

Grade	Description
0	Normal activity, fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but fully ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	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	Capable of only limited self-care, Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

APPENDIX E: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX F: Ideal Body Weight Formulas

Males IBW = 50 kg + 2.3 kg/inch over 5 feet
Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

For patients less than 5 feet, subtract 2.3 kg/inch

Adjusted Ideal Body Weight Formula:
AIBW = IBW + [(0.40) x (Actual BW - IBW)]

APPENDIX G
ABBREVIATIONS

AE	Adverse event
AIBW	Adjusted ideal body weight
B2M	Beta-2 microglobulin
CBC	Complete blood count
COMP	Comprehensive panel (SMA-12)
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-ray
D	Dexamethasone
DLCO	Diffusing Capacity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EM	Extramedullary myeloma (soft-tissue disease)
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
IBW	Ideal body weight
IL-6	Interleukin-6
IRB	Institutional Review Board ISS International Staging System
KPS	Karnofsky Performance Status
L	Lenalidomide
LVEF	Left Ventricular Ejection Fraction
MEL	Melphalan
MM	Multiple Myeloma
MP	Melphalan and Prednisone MRI Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition scan
NR	No response
OS	Overall Survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free Survival
PFT	Pulmonary Function Tests
PLT	Platelet count
PR	Partial response

PT/PTT	Prothrombin time/ Partial thromboplastin time
SAE	Serious adverse event
SCT	Stem cell transplant
TBI	Total body irradiation
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of the normal range
VGPR	Very Good Partial Response
WBC	White blood cell count

Appendix I: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \quad (\textbf{Males})$$

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85 \quad (\textbf{Females})$$