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1. Study Design, endpoints, and definitions

Trial Title: Randomized Phase III Trial of Bortezomib, L**EN**alidomide and Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide and Dexamethasone (KRd) Followed by Limited or Indefinite **DUR**ation Lenalidomide Mainten**ANCE** in Patients with Newly Diagnosed Symptomatic Multiple Myeloma (**ENDURANCE**)

Original Design of the Study

This two-stage randomized study is designed and powered to investigate both a maintenance and an induction question: (#1) following induction with a proteasome inhibitor–IMiD combination, whether indefinite versus limited lenalidomide maintenance therapy is superior; and (#2) whether KRd versus VRd induction treatment is superior. To implement these two comparisons, 756 patients are first randomized (R1) equally to either 12 cycles of VRd induction (Arm A) or 9 cycles of KRd induction (Arm B). Patients who have completed induction without experiencing disease progression or being withdrawn will be randomized again (R2) equally to 24 cycles of R maintenance and then observation (Arm C) or indefinite R maintenance until disease progression (Arm D). Patients will be stratified by intent for transplant at disease progression (R1) and by induction arm (R2).

Maintenance Overall Survival: The primary endpoint is overall survival for the maintenance analysis defined as the time from the maintenance randomization (R2) to death due to any cause or, censored at the date last known alive. Kaplan-Meier (KM) methods will be used to describe the overall survival function by arm. All patients in the maintenance randomization (R2) will be classified according to their randomized treatment assignment irrespective of actual treatment received (ITT: intent-to-treat). The power calculation for the maintenance comparison of overall survival assumes no interaction between induction and maintenance therapies. We estimate 85% of patients would be eligible to begin maintenance, based largely on progression-free survival assumptions. Assuming exponential distribution and a median PFS of 3 years corresponding with 12 cycles of VRd + 24 cycles of lenalidomide versus a median PFS of 4 years for 9 cycles of KRd + 24 cycles of lenalidomide, the PFS rates at end of induction (8.3 months) are 85% and 89%. The study is designed with a target improvement in median OS of 50% [Hazard Ratio (HR) = 0.667] with an annual hazard rate reduced from limited R maintenance (Arm C) of 0.1386 to 0.0924 on R indefinite maintenance (Arm D). Assuming exponential distribution of failures from the start of maintenance randomization, this corresponds to a median OS of 5 years versus 7.5 years, respectively (4-y OS rate of 57% vs. 69%). There is 80% power using a stratified log-rank test to detect this HR given 9 years of follow-up from R2, a 1-sided 0.025 alpha, 360 patients and 198 events. To account for progression and dropout during the first 2 years of maintenance after R2 (i.e. patients

randomized to indefinite R essentially crossing over), we inflate the sample size according to Lachin-Foulkes non-compliance adjustment. Assuming 25% non-compliance, the sample size for the maintenance comparison increases to n=640 patients and full information to 356 deaths. Backing into the induction comparison assuming 15% progression/drop-out before R2, the overall sample size is 756 patients. The table below outlines expectations which will be monitored around number of cases censored at various time points prior to the cutoff date of 9 years and after full accrual (accrual duration estimated to be 3.5 years).

Year from R2	No. Censored Cases	No. Deaths
4	494	146
5	440	200
6	392	248
7	351	289
8	315	325
9	284	356

A stratified Cox proportional hazards (PH) regression model will be used to estimate the hazard ratio (HR) [Arm D/Arm C] and 95% confidence interval; however, the assumption of proportional hazards is not valid given there is no difference in maintenance treatment for the first 24 cycles. Thus, absolute difference in OS rates at 2-, 3- and 4- years from R2 will be estimated. Accrual duration is expected to be 3.5y (42m) with an accrual rate target of 18 patients per month. Given the uncertainty around the number of patients that will enroll onto maintenance, we will build in sample size re-estimation if the yield is too low or shorten follow-up duration if the yield is above expectations.

Interim analyses for superiority of R indefinite maintenance (Arm D) are planned coincident with ECOG-ACRIN DSMC meetings. Critical values at the interim analyses will be determined using a truncated version of the Lan-DeMets error spending function corresponding to the O'Brien-Fleming boundary, preserving overall Type I error of 2.5%.[1] Under the accrual and failure rate assumptions above, interim analyses (IA) are expected to occur at years 4 through 8 after R2 corresponding with information times of 41%, 56%, 70%, 81% and 91%. The final analysis occurs after 9 years of follow-up. There is also monitoring for inefficacy using a linear inefficacy boundary (LIB) described by Freidlin et al.[2] which enables stopping the study if there is not at least a small trend in favor of the alternative hypothesis based on the observed hazard ratio. The boundary starts with a hazard ratio of 1.0 at the 1st IA and gradually decreases to approximately 20% of the targeted benefit (0.92) at full information. If the observed HR exceeds the cutoff value at the corresponding information proportion, the study may be stopped for inefficacy provided the two-sided 95% confidence interval does not contain the design alternative HR 0f 0.667.

Induction Progression-Free Survival: Progression-free survival comparing induction arms is a key secondary analysis. Induction PFS is defined as the time from the induction randomization (R1) until the earlier of progression or death due to any cause. Patients alive without disease progression will be censored at date of last disease evaluation. Only deaths that occur within 3 months of the last disease evaluation are considered events. The main analysis dataset for induction PFS comparison will be all patients randomized (R1). The Kaplan-Meier method will be used to describe the progression-free survival function by arm using all data while ignoring maintenance.[3] PFS distributions between induction arms will be compared with the stratified log-rank test. Median PFS on VRd (Arm A) is expected be 3 years. Assuming exponential distribution of events, this corresponds to an annual hazard rate of 0.231. With 756 patients randomized at induction, there is 80% power at a 1-sided 0.025 significance level to detect a 25% reduction in the hazard rate to 0.1733 on the KRd arm (33% improvement in median PFS to 4 year; hazard ratio=0.75). Full information under the alternative hypothesis is 392 PFS events expected after 5.5 years. A stratified Cox regression model will be used to estimate the hazard ratio [B/A], where all patients (regardless of maintenance treatment) will be combined by induction arm.

There will be two interim analyses at 30% and 68% of full information expected at 2.5 and 4 years from R1 to evaluate efficacy and futility. Similar to the primary endpoint, to preserve the overall type I error rate, critical values at the interim will be determined using Lan-DeMets error spending rate function corresponding to the O'Brien Fleming boundary (truncated at 0.0005). The final analysis will occur after 5.5 years of follow-up. A conditional power approach will be used for futility monitoring. Early termination of the induction randomization would be considered if at a given IA the calculated conditional power that the trial would reject the null hypothesis if completed is less than 10%. Although unlikely, if this occurred, the protocol would be amended to directly assign patients to VRd induction to complete the accrual for the maintenance comparison.

Toxicity: Both Grade 3 and higher overall and non-hematologic toxicity rates during the induction, active maintenance and observation phases will be calculated with 2-sided 95% confidence intervals. Grade 3 and higher non-hematologic toxicity rates will be compared between arms. Using the Fisher's exact test, with 378 treated patients per induction arm, there is 85% power to detect a difference in toxicity rates of 11.0%. There is one formal interim analysis for toxicity planned when 100 patients on the KRd arm have received 6 cycles of treatment. The endpoint is a composite toxicity rate of grade 4-5 cardiac, pulmonary or renal toxicity either directly or at least probably related to treatment. The current KRd regimen would be acceptable if the toxicity rate is no worse than 25%. If 32 or more patients experience this level of toxicity, consideration will be given to modifying the treatment regimen. Under this monitoring rule,

there is less than 7% probability of meeting this boundary if the true rate is 25% but 96% probability of meeting the boundary if true rate is unacceptable (40%).

Quality of Life: Assessing quality of life (QoL) utilizing PRO measures is deemed of critical importance to the evaluation of the overall benefit of each particular therapeutic strategy and its clinical utility. Therefore, QoL assessments are planned for all phases of the study (induction, active maintenance, observation). The primary QoL instrument will be the FACT-Neurotoxicity Trial Outcome Index (FACT-Ntx TOI), which is the sum of the physical, functional and neurotoxicity instruments (25 questions, score 0-100). We will also assess patient reported outcomes using the disease-specific FACT-MM. The QoL analysis cohort will comprise a subset of patients randomized to induction approximating 70% of the target study sample size (n=530 of 756 patients). Compliance will be monitored semi-annually and submission of quality of life forms will be stopped for enrolling patients when adequate sample size for QoL analyses has been achieved. There are 4 primary QOL treatment group comparisons as follows. The 2-sided significance level will be 0.05/4=0.0125 for these analyses. Differences in mean change score that can be detected with satisfactory power are plausible and reasonable within the context of associated hypotheses.

Treatment Comparison: Transition to Active Maintenance: For the transition to active maintenance question, the FACT-Ntx TOI mean change from end of induction to the end of 6 cycles of maintenance will be compared between induction treatment arms.

Treatment Comparison: Maintenance versus Observation- Short Term: For the short-term comparison of the two strategies of lenalidomide maintenance of limited duration versus indefinite maintenance therapy until disease progression, the health-related QoL endpoint is the FACT-Ntx TOI change from the end of 24 cycles of maintenance randomization to month 36 post R2.

Treatment Comparison: Maintenance versus Observation – Long Term: For the long-term comparison of the two strategies of lenalidomide maintenance of limited duration versus indefinite maintenance therapy until disease progression, the health-related QoL endpoint is the FACT-Ntx TOI change from the end of 24 cycles of maintenance randomization to month 60 post R2.

Treatment Comparison: Induction: The mean change in health-related QoL measured by the FACT-Ntx TOI from registration to end of induction will be compared between induction treatment arms.

Revised Design (Addendum #11)

The final redesign submitted as Addendum #11 and Addendum #12 which was in response to a lenalidomide Action Letter (dated June 25, 2018) were activated June 27, 2018. The redesign approved as Addendum #11 covers two main objectives: (1) addressing the S2 enrollment yield problem and (2)

amplifying the primary induction objective. For the latter, it was resolved that induction PFS will become a co-primary endpoint with maintenance OS. In both analyses, assumptions regarding effect size, Type I error and power are unchanged. Overall sample size is increased by 324 to 1,080 patients while S2 sample size is increased by 64 to 704 patients given the assumed S2 enrollment yield drops from 85% to 65%. Addendum #11 also has measures expected to enhance S2 enrollment yield including the following: expanding the window for S2 registration from 28 days to 6 weeks and allowing both patients who have completed induction without experiencing disease progression *and* patients who received at least 6 cycles on Arm A and 4 cycles on Arm B but withdrew early due to adverse events to be eligible for S2.

Maintenance Overall Survival: The OS power calculation still targets a 50% improvement (HR=0.667) in median OS of 5 years on limited R maintenance (Arm C) versus 7.5 years on R indefinite (Arm D). There is 80% power using a stratified logrank test to detect this improvement given 9 years of follow-up from R2, a 1-sided 0.025 alpha, 395 patients and 204 events. Assuming the same Lachin-Foulkes non-compliance adjustment of 25%, the sample size for the maintenance comparison increases to n=704 patients and full information to 364 deaths. Backing into the induction comparison assuming 35% progression/drop-out before R2 as opposed to 15%, the overall sample size is 1,080 patients. As before, interim analyses are conducted annually starting at an estimated 4 years from R2 [information times (n deaths): 32% (n=116), 48% (n=173), 64% (n=232), 77% (n=282), 89% (n=326)]. While the approach for monitoring efficacy was unchanged, there was a slight modification for futility. Specifically, the inefficacy rule based on LIB20 will be implemented starting at the 2nd IA and there is a check for harm at the 1st IA. At 32% information, the DSMC may consider stopping the maintenance component of the study if the lower bound of a 95% CI for the maintenance OS HR is above 1.0. Additionally, the table below outlines revised expectations with respect to event information per planned interim analyses.

Year from R2	No. Censored Cases	No. Deaths
4	447	116
5	531	173
6	472	232
7	422	282
8	378	326
9	340	364

Induction Progression-Free Survival: The analysis dataset for the co-primary endpoint of the induction PFS comparison will be all patients randomized to Step 1 (R1). The Kaplan-Meier method will be used to describe the progression-free survival function by arm using all data while ignoring maintenance. A stratified logrank test will be used to compare PFS distributions between induction arms. The effect size for induction PFS remains a HR=0.75 which corresponds to a median PFS on VRd (Arm A) of 3 years

versus 4 years on KRd (Arm B). With 1,080 patients randomized at induction, accrued over 5 years and followed up to 5 years, there is 80% power at a 1-sided 0.025 significance level to detect a 25% reduction in the hazard rate. Full information under the alternative hypothesis is 399 PFS events. There will be three interim analyses at 54% (n=215 events), 68% (n=272 events) and 84% (n=333 events) of full information expected at 3.5, 4 and 4.5 years from R1 to evaluate efficacy and futility of the PFS comparison. In response to a major issue identified by CTEP upon initial review of Addendum #11, the futility monitoring plan was revised. Specifically, the original conditional power calculation with a 10% threshold was replaced with the Wieand rule and the 1st planned IA was shifted to occur later (from 25% to 54% of total information). According to the Wieand rule, if the HR estimate [B/A] from the Cox regression model equals or exceeds 1, the stopping rule for futility with respect to the induction PFS comparison is met.

Projected Accrual: Accrual duration is assumed to be approximately 5 years with the revised accrual target of 1,080 patients assuming an accrual rate of 18 patients per month.

Endpoints and definitions

Primary endpoint

Progression-free survival for the induction analysis: Defined as the time from the induction randomization (R1) until the earlier of progression or death due to any cause. Patients alive without disease progression will be censored at date of last disease evaluation. Only deaths that occur within 3 months of the last disease evaluation are considered events.

Secondary endpoints

1. Overall survival for the induction analysis: Defined as the time from induction randomization (R1) to death due to any cause or censored at the date last known alive.
2. Overall response rate: Includes partial response (PR), very good partial response (VGPR), immunofixation negative complete response (IF-CR) and complete response (CR) at 2.8 and 8.3 months after induction randomization (R1).
3. Time to progression (TTP) for the induction analysis: Defined as the time from the induction randomization (R1) to progression or censored at the date of last disease evaluation for those without progression reported.
4. Duration of response (DOR) for the induction analysis: Defined as the time from first objective response (partial response or better) since induction randomization (R1) until progression or censored at date of last disease evaluation for those without progression.

5. Incidence of overall grade 3 or higher non-hematologic toxicity and by type during induction.
6. Incidence of grade 3 or higher peripheral neuropathy and cardiac-renal-pulmonary toxicity during induction phase.
7. MRD negative rates at 8.3 months after induction randomization (R1).

Quality of Life Endpoints

1. Change for the transition to maintenance analysis: Defined as the change in the FACT-Ntx TOI from the end of induction therapy to the end of cycle 6 maintenance.
2. Change for the end of induction analysis: Defined as the change in the FACT-Ntx TOI from the induction randomization (R1) to the end of induction therapy (month 8.3).
3. Change for the early induction analysis: Defined as the change in the FACT-Ntx TOI from the induction randomization (R1) to 2.8 months of induction therapy.
4. Levels and changes in the FACT-Ntx TOI and FACT-MM during induction.
5. Time to worsening of FACT-Ntx TOI for the induction analysis; Defined as the time from the baseline assessment at induction randomization (R1) to a decrease of 7 points. Patients with at least one post-baseline assessment are censored at the date of last assessment. Patients without a baseline assessment or a post-baseline assessment are censored at date of maintenance randomization.

Correlative Endpoints

1. MRD negative rates at 2.8 months after induction randomization (R1).
2. Mutation status at pre-registration, disease progression and suspected complete response.
3. Gene expression levels at pre-registration, disease progression and suspected complete response.

Minimal residual disease assessment by flow cytometry: For each sample, one milliliter whole bone marrow was washed in PBS (phosphate buffered saline) and lysed in ammonium chloride buffer (ACK). The cells were counted, and the concentration was adjusted to 10 million cells per ml. Two million cells were added to each of the four MRD (minimal residual disease) panel tubes. CD38 APC, CD45 APC-H7 and CD138 percp cy5.5 were included in each tube for gating purposes. Tubes 2 and 3 contained additional phenotyping markers (CD27 FITC, CD19 PE, CD56 V450 with CD28 FITC and CD117 PE respectively) while tube 4 contained isotype control reagents. After 15 minutes incubation in the dark the tubes were washed one time with PBS. Tube one was further fixed and permeabilized (Caltag Fix and Perm kit), then stained with kappa FITC and lambda PE in order to determine the light chain restriction of the gated plasma cells. The samples were resuspended in 0.5 ml of BD Biosciences stabilizing fixative and held at 4 degrees in the dark until run on the Canto II flow cytometer. Acquisition was done in a single step with the instrument set to collect 2 million events or stop at three minutes of collection.

2. Complete trial eligibility criteria

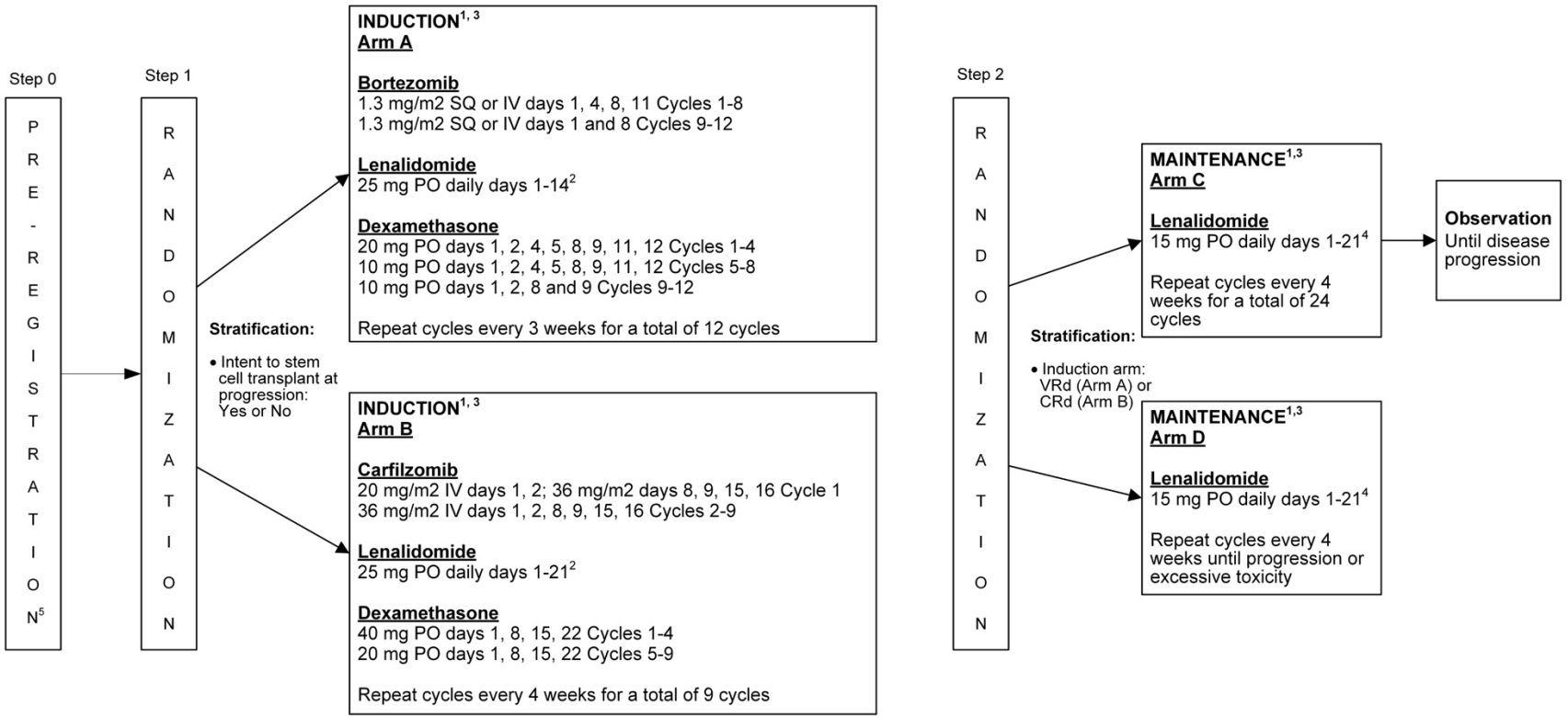
1. Age ≥ 18 years.
2. Patients must be diagnosed with symptomatic standard-risk multiple myeloma (SR-MM) as defined by all of the following:
    a. No evidence of t(14;16), t(14:20) or deletion 17p by FISH testing on bone marrow
    b. Standard Risk GEP70 signature within the past 90 days (only if GEP has been done and results are available).
    c. Serum LDH ≤ 2 x ULN within the past 28 days
    d. No more than 20% circulating plasma cells on peripheral blood smear differential or 2,000 plasma cells/microliter on WBC differential of peripheral blood within the past 90 days
3. Patients must have measurable or evaluable disease as defined by having one or more of the following, obtained within 28 days prior to randomization:
    a. ≥ 1g/dL monoclonal protein (M-protein) on serum protein electrophoresis
    b. ≥ 200 mg/24 hours of monoclonal protein on a 24-hour urine protein electrophoresis
    c. Involved free light chain ≥ 10 mg/dL or ≥ 100 mg/L AND abnormal serum immunoglobulin kappa to lambda free light chain ratio (< 0.26 or > 1.65)
    d. Monoclonal bone marrow plasmacytosis ≥ 30% (evaluable disease)
4. The following laboratory levels must be obtained within 28 days prior to randomization:
    a. Hemoglobin ≥ 8 g/dL.
    b. Untransfused platelet count ≥ 75,000 cells/mm3.
    c. Absolute neutrophil count ≥ 1000 cells/mm3.
    d. Calculated creatinine clearance ≥ 30 mL/min
    e. Bilirubin ≤ 1.5 mg/dL.
    f. SGPT (ALT) and SGOT (AST) < 2.5 times the upper limit of normal.
5. Patients must have received no more than one cycle (4 weeks or less) of prior chemotherapy and no more than 160mg of prior dexamethasone (or equivalent dose of prednisone) for treatment of symptomatic myeloma. They should not have been exposed to lenalidomide, bortezomib or carfilzomib for treatment of symptomatic myeloma. Prior radiation therapy to symptomatic lesions is allowed provided there are no residual toxicity related to radiation and blood counts that meet the study requirements.

6. Prior systemic glucocorticoid use for the treatment of non-malignant disorders is permitted. Prior or concurrent topical or localized glucocorticoid therapy to treat non-malignant comorbid disorders is permitted.
7. Patients must not have active, uncontrolled seizure disorder. Patients must have had no seizures in the last 6 months.
8. Patients must not have uncontrolled intercurrent illness including uncontrolled hypertension, symptomatic congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, uncontrolled psychiatric illness or social situation that would limit compliance with the study, or a prior history of Stevens Johnson Syndrome.
9. ECOG performance status 0, 1, or 2. (PS 3 allowed if secondary to pain)
10. Patients with monoclonal gammopathy of undetermined significance or asymptomatic multiple myeloma are not eligible.
11. Patients must not have Grade 2 or higher peripheral neuropathy by CTCAE 4.0.
12. Patients must not have active, uncontrolled infection.
13. Patients may have a history of current or previous deep vein thrombosis or pulmonary embolism but must be willing to take some form of anti-coagulation as prophylaxis if they are not currently on full-dose anticoagulation.
14. Patients should not have New York Heart Association classification III or IV heart failure or myocardial infarction within the previous 6 months.
15. Patients with a history of prior malignancy are eligible provided they were treated with curative intent and do not require active therapy (currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast are not excluded).
16. 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 of starting lenalidomide 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, throughout the entire duration of study treatment, and for 28 days after the last dose of lenalidomide.
17. Sexually active males must be willing to use a condom (even if they have undergone a prior vasectomy) while having intercourse, while taking lenalidomide and for 28 days after stopping lenalidomide. Male subjects must also agree to abstain from donating blood,

semen, or sperm during study participation and for at least 28 days after discontinuation from lenalidomide, and for 90 days after discontinuation of carfilzomib.

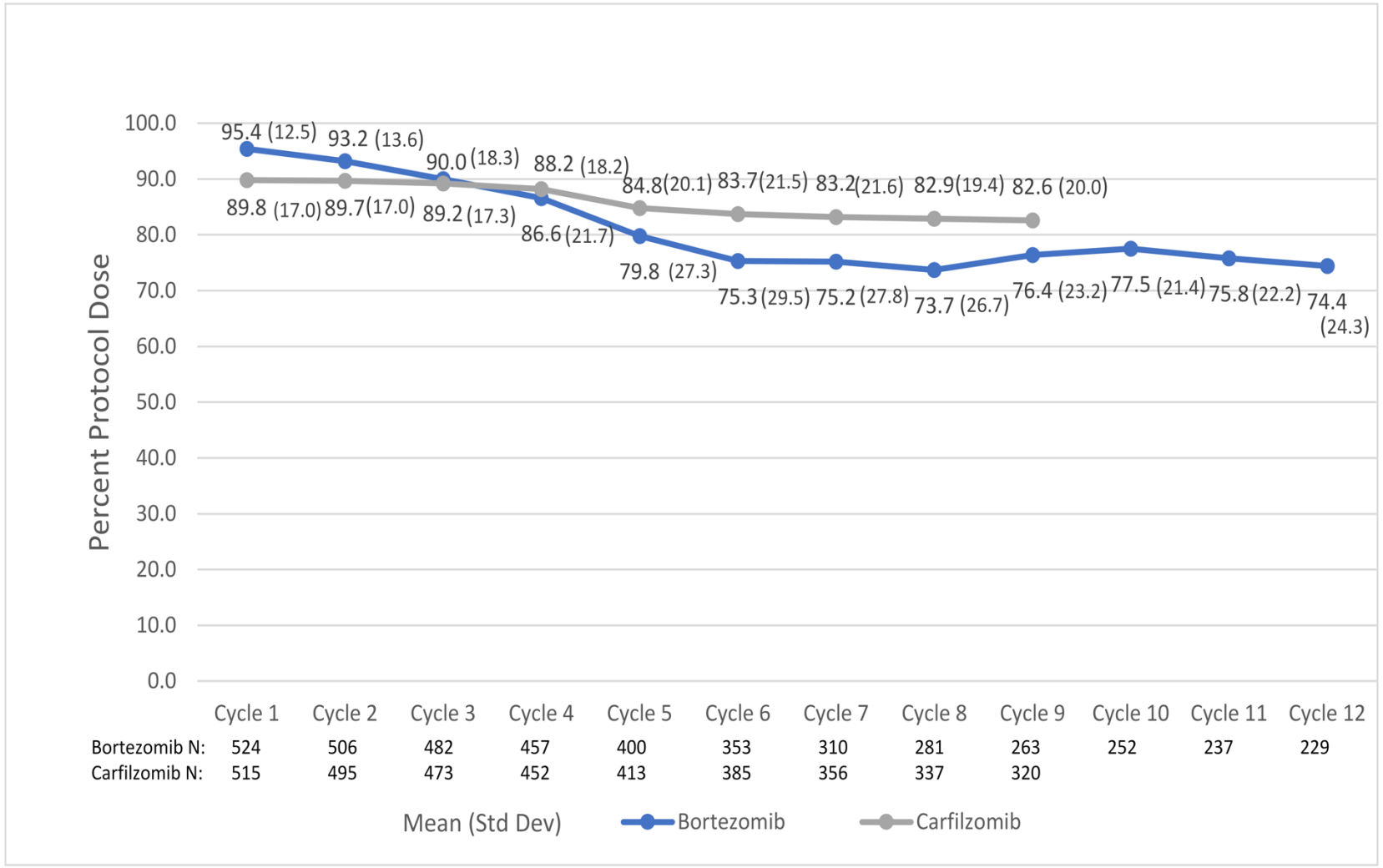
18. The following patients will be excluded as this study involves an agent that may have genotoxic, mutagenic and teratogenic effects.
    a. Pregnant women
    b. Nursing women
19. HIV infection is not excluded. Known HIV positive patients must meet the following criteria:
    a. CD4 cell count ≥ 350/mm3
    b. No history of AIDS-related illness
    c. Not currently prescribed zidovudine or stavudine
20. Patient enrolling to this study must agree to register to the mandatory RevAssist® program and be willing and able to comply with the requirements of RevAssist®.

3. Figure S1: Trial Design

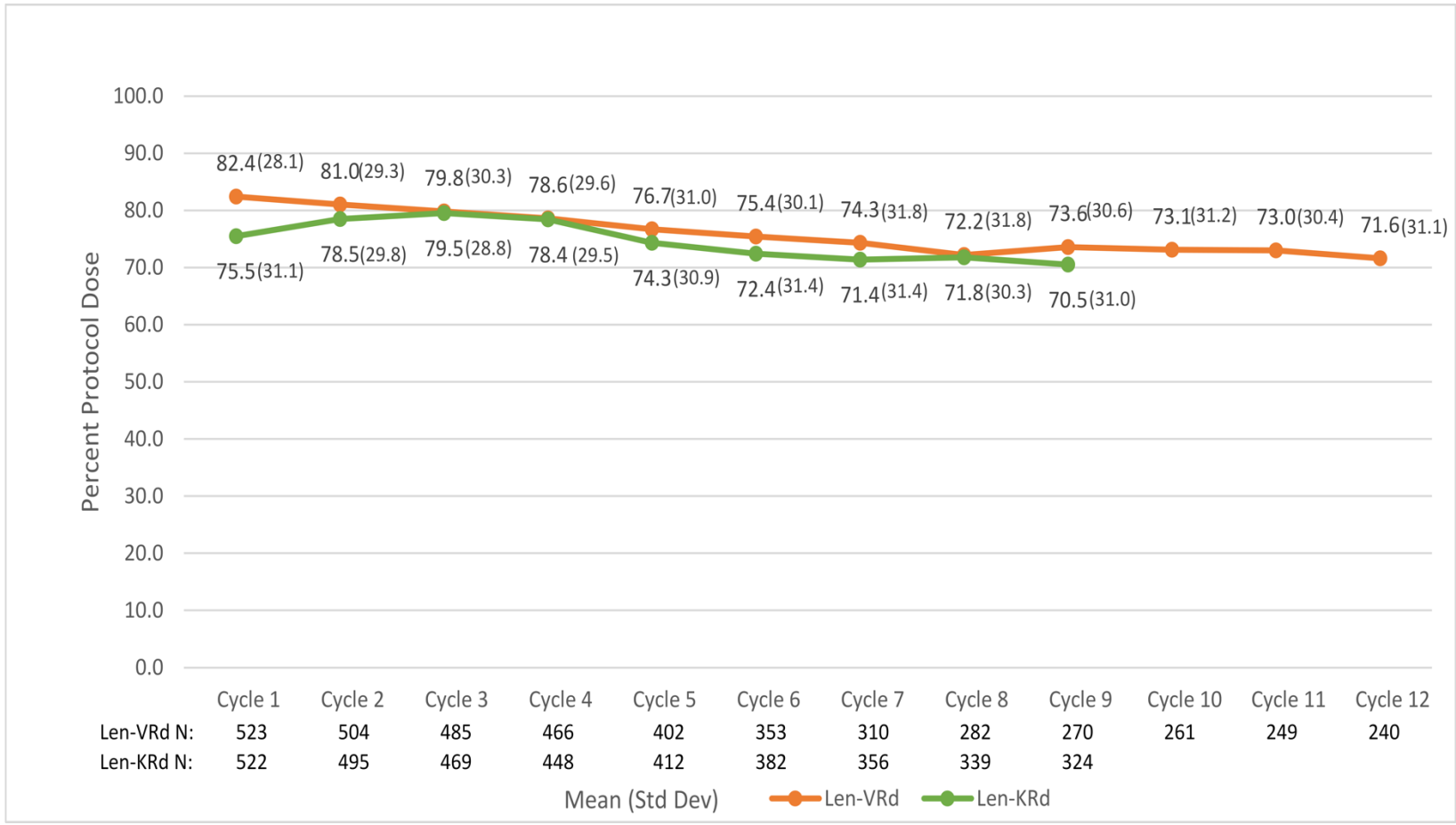


1. Patients can mobilize stem cells any time following 4 cycles (Arm A) or 3 cycles (Arm B) of induction therapy. If stem cells are harvested, interruption of treatment cycles for up to 35 days is allowed for completion of stem cell collection. While stem cell collection is strongly encouraged for transplant eligible patients, it is not required for protocol participation.
2. In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥60 ml/min, the dose can be increased to 25 mg provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.
3. At discretion of enrolling MD if considered appropriate, patients randomized to Arm A (VRd) can receive bortezomib injections under care of a local oncologist, returning to the enrolling institution only at the beginning of each cycle. Patients randomized to Arm B (CRd) are required to receive Carfilzomib injections at the enrolling institution. During maintenance and observation (Arms C and D), patients will have to be seen at the enrolling institution once every three months.
4. In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 15 mg provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.
5. Submission of pre-study specimens per patient consent.

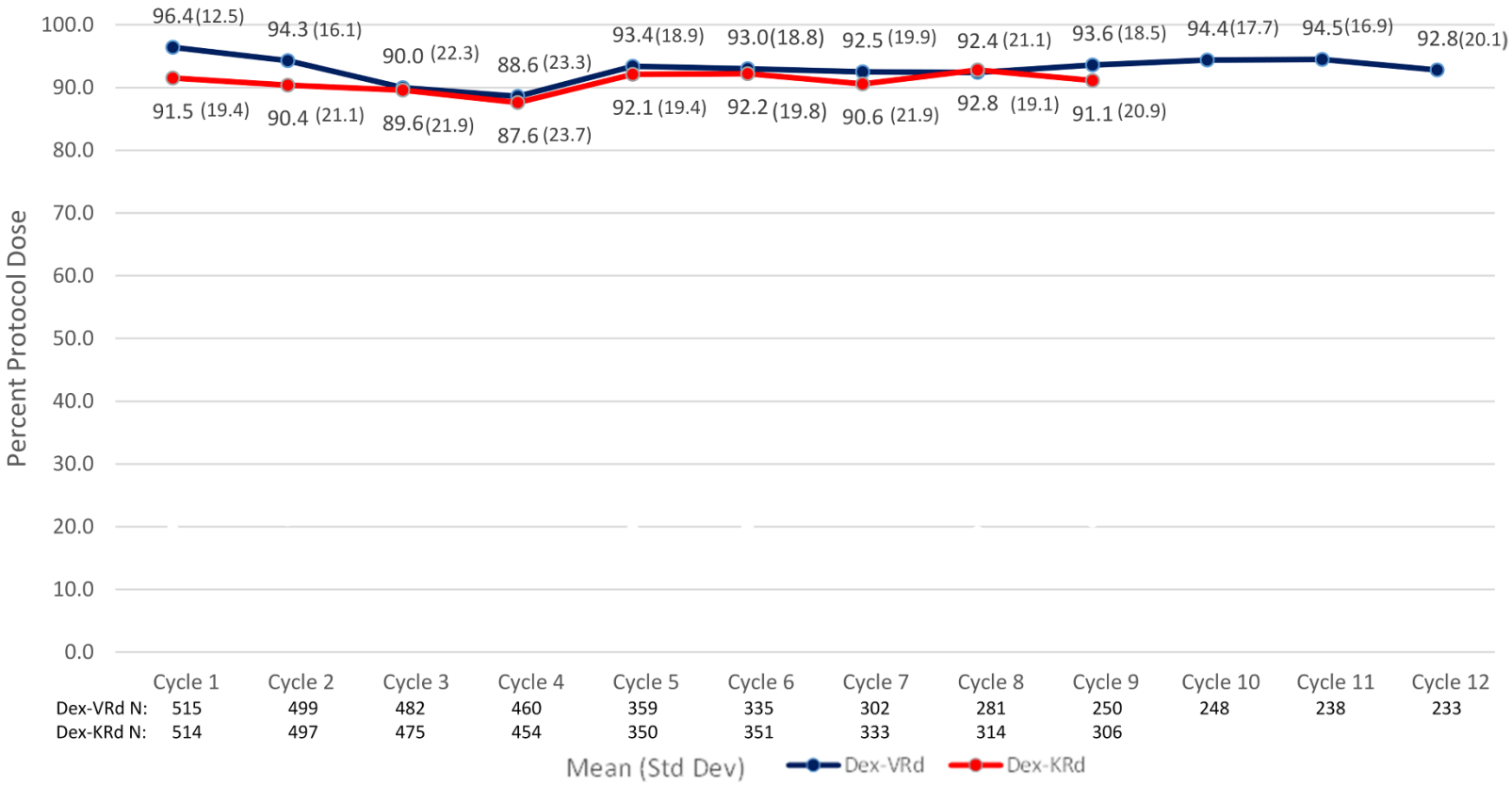
4. Figure S2: Percent Protocol Dose per Cycle-bortezomib and carfilzomib



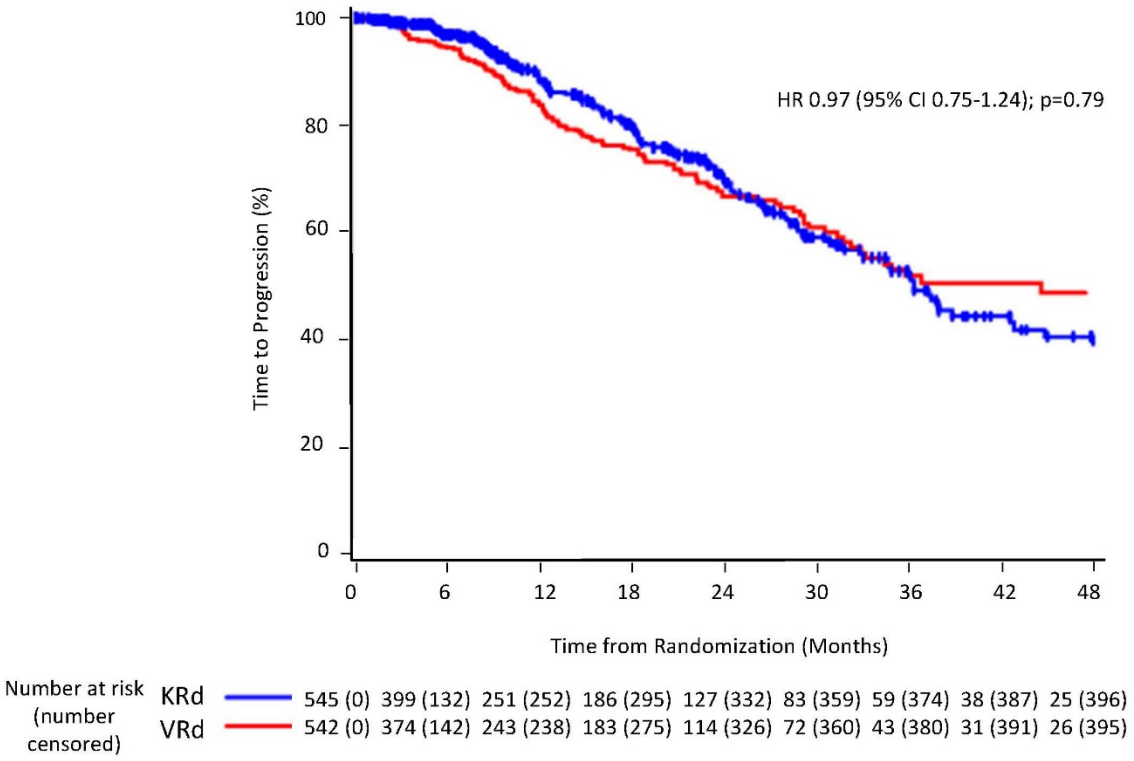
5. Figure S3: Percent Protocol Dose per Cycle-lenalidomide



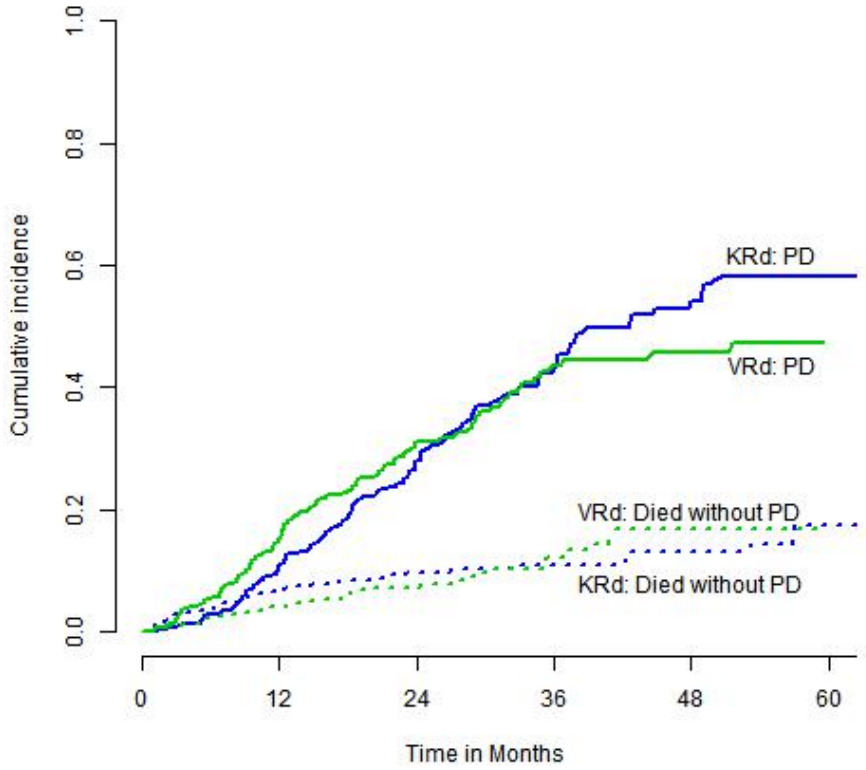
6. Figure S4: Percent Protocol Dose per Cycle-dexamethasone



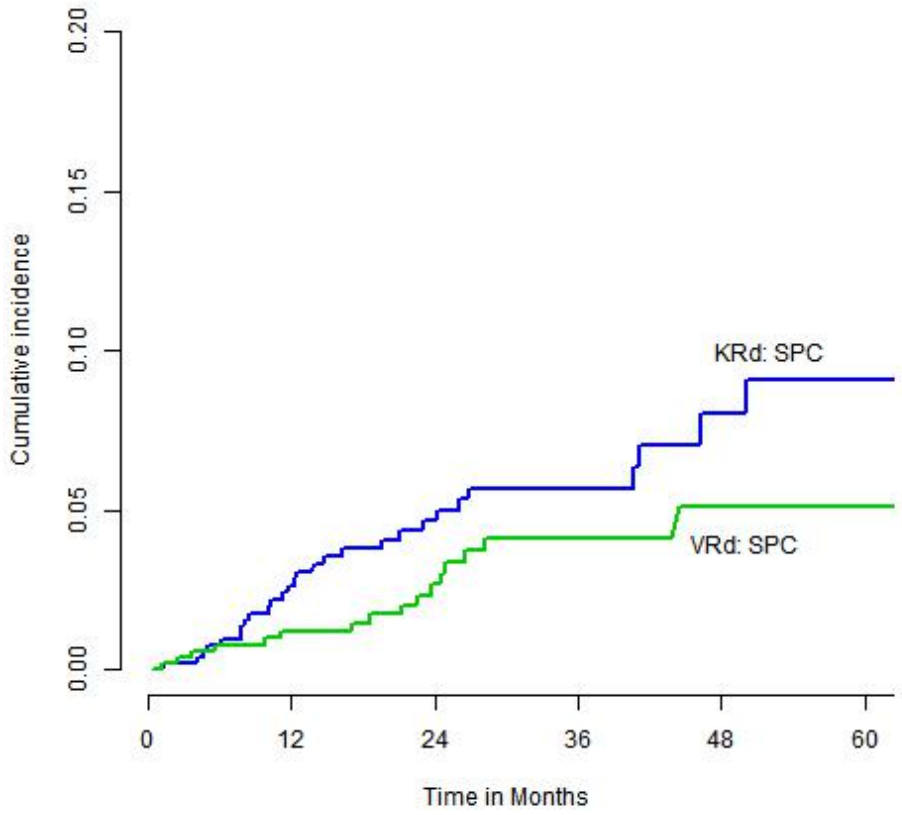
7. Figure S5: Time to Progression



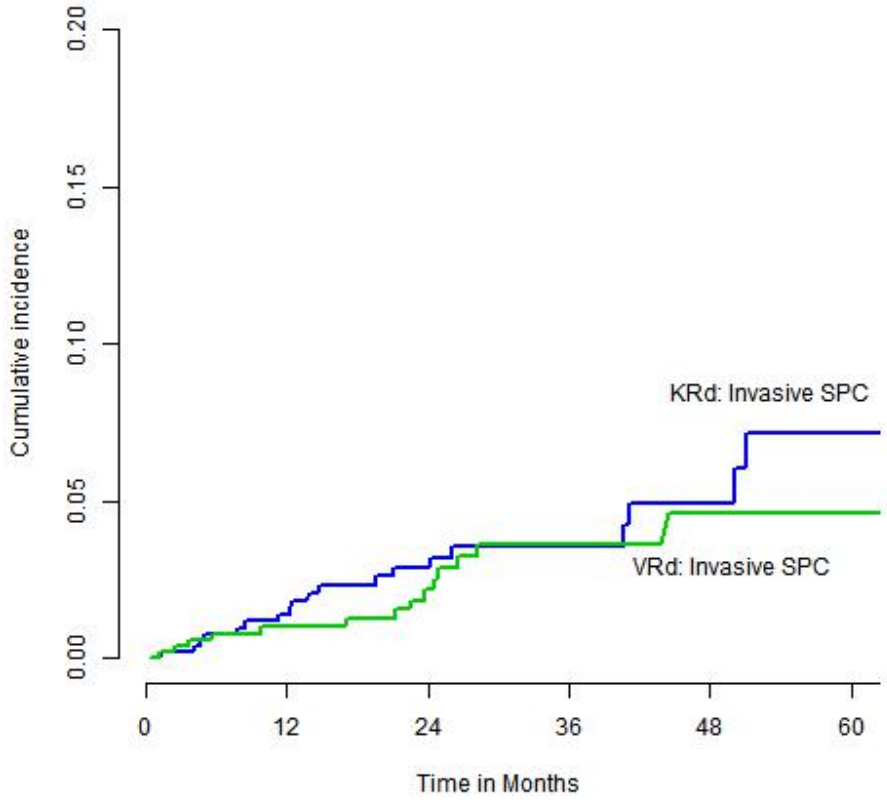
8. Figure S6: Cumulative Incidence of Progression (death as a competing event)



9. Figure S7: Cumulative Incidence Second Primary Cancers (death as a competing event)



10. Figure S8: Cumulative Incidence Invasive Second Primary Cancers (death as a competing event)



11. Figure S9: QoL Measurements

Figure S9a. FACT-Ntx (neurotoxicity) Trial Outcomes Index (TOI) Scores over Induction [Score 0-100]

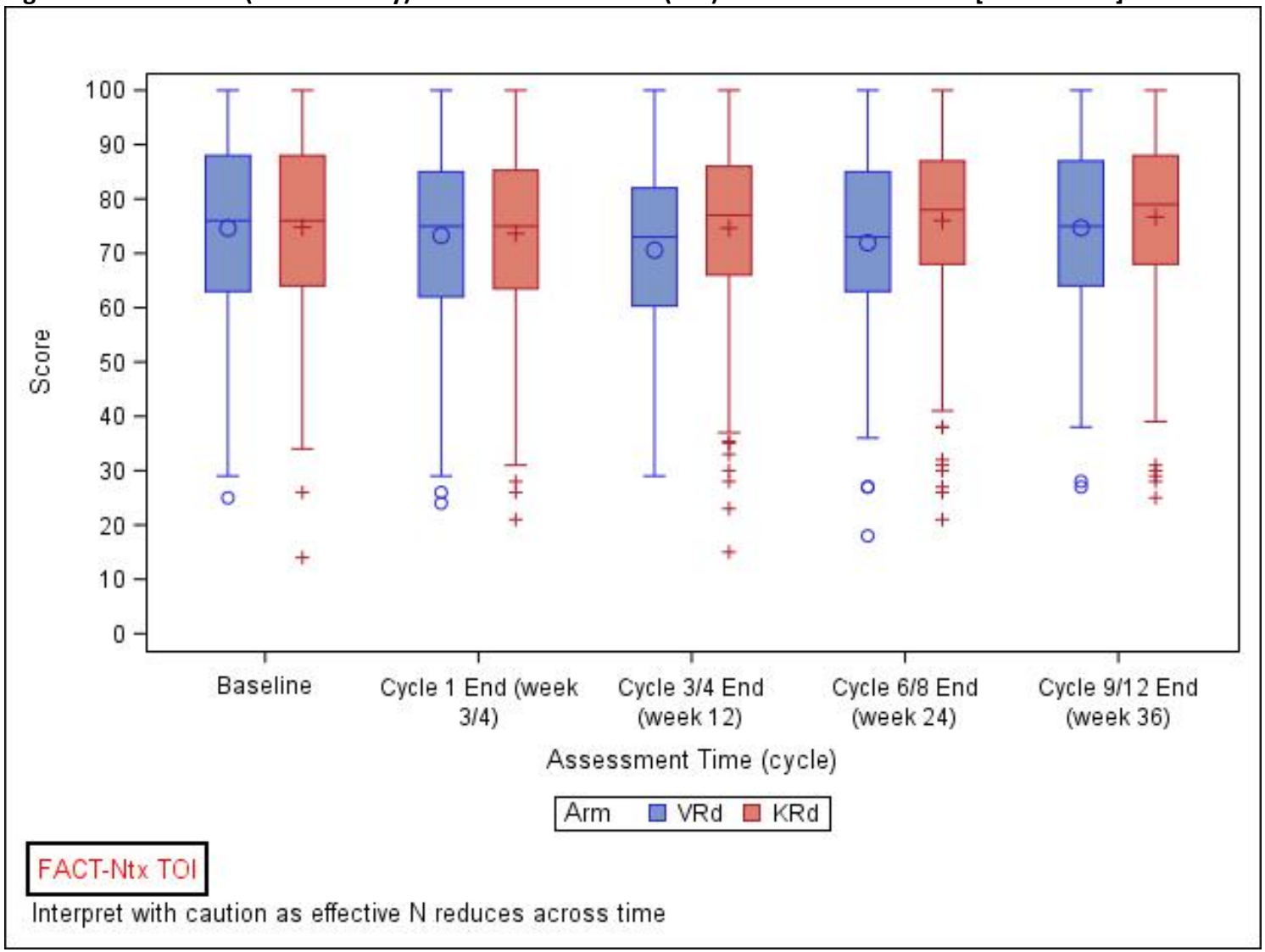


Figure S9b. FACT-Ntx (neurotoxicity) Scores over Induction [Score 0-44]

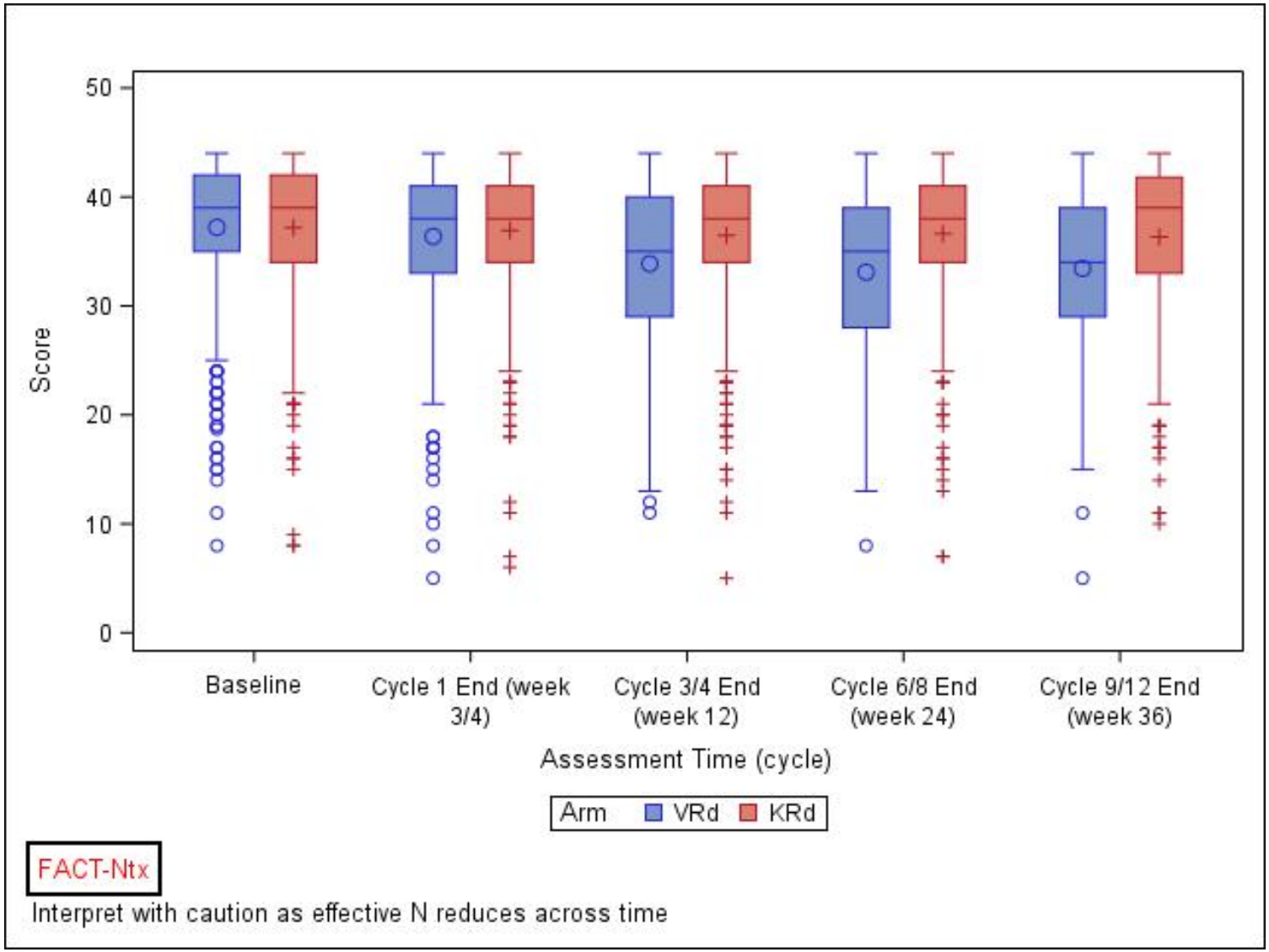


Figure S9c. FACT-F (functional well-being) Scores over Induction [Score 0-28]

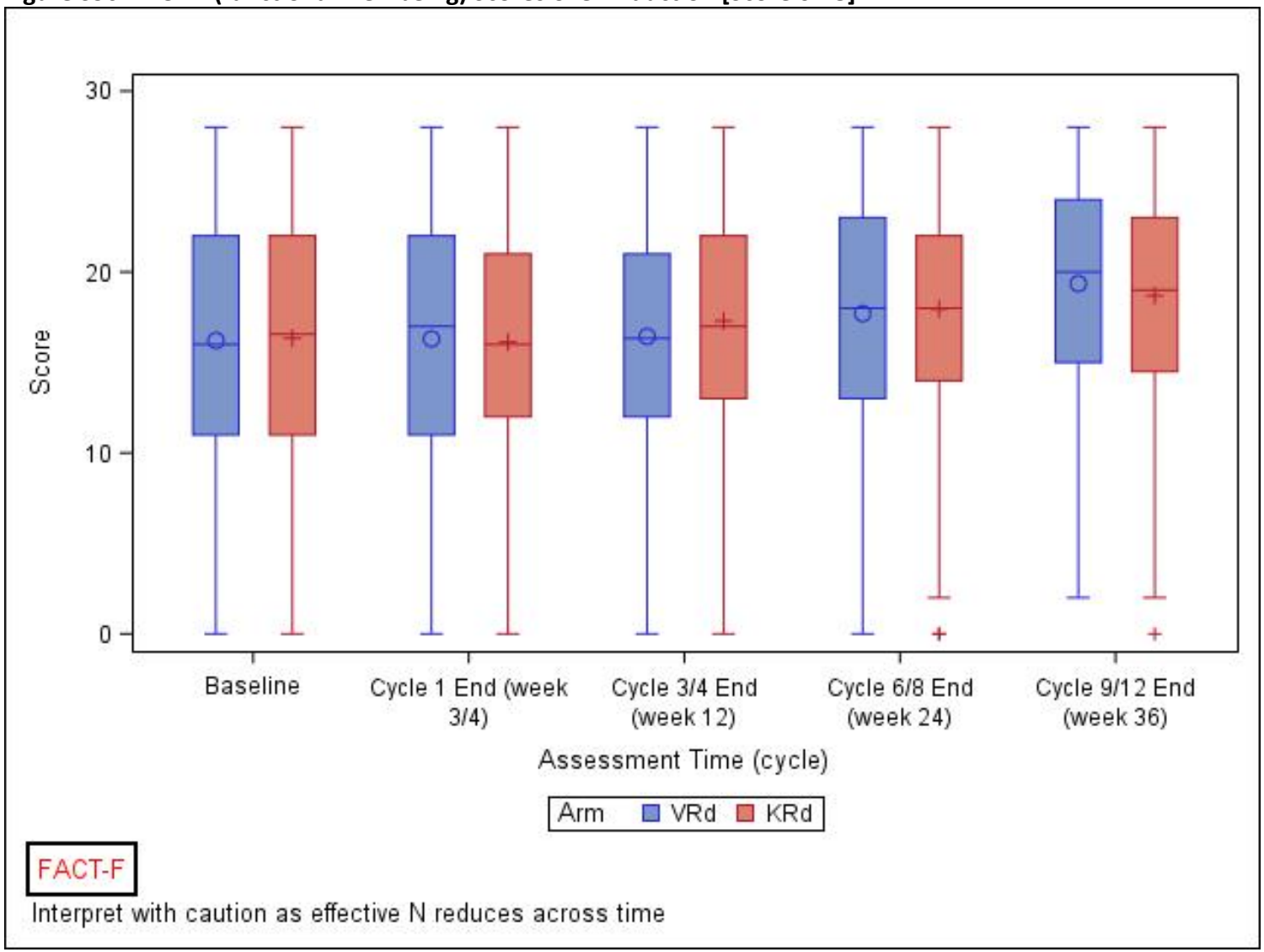


Figure S9d. FACT-P (physical well-being) Scores over Induction [Score 0-28]

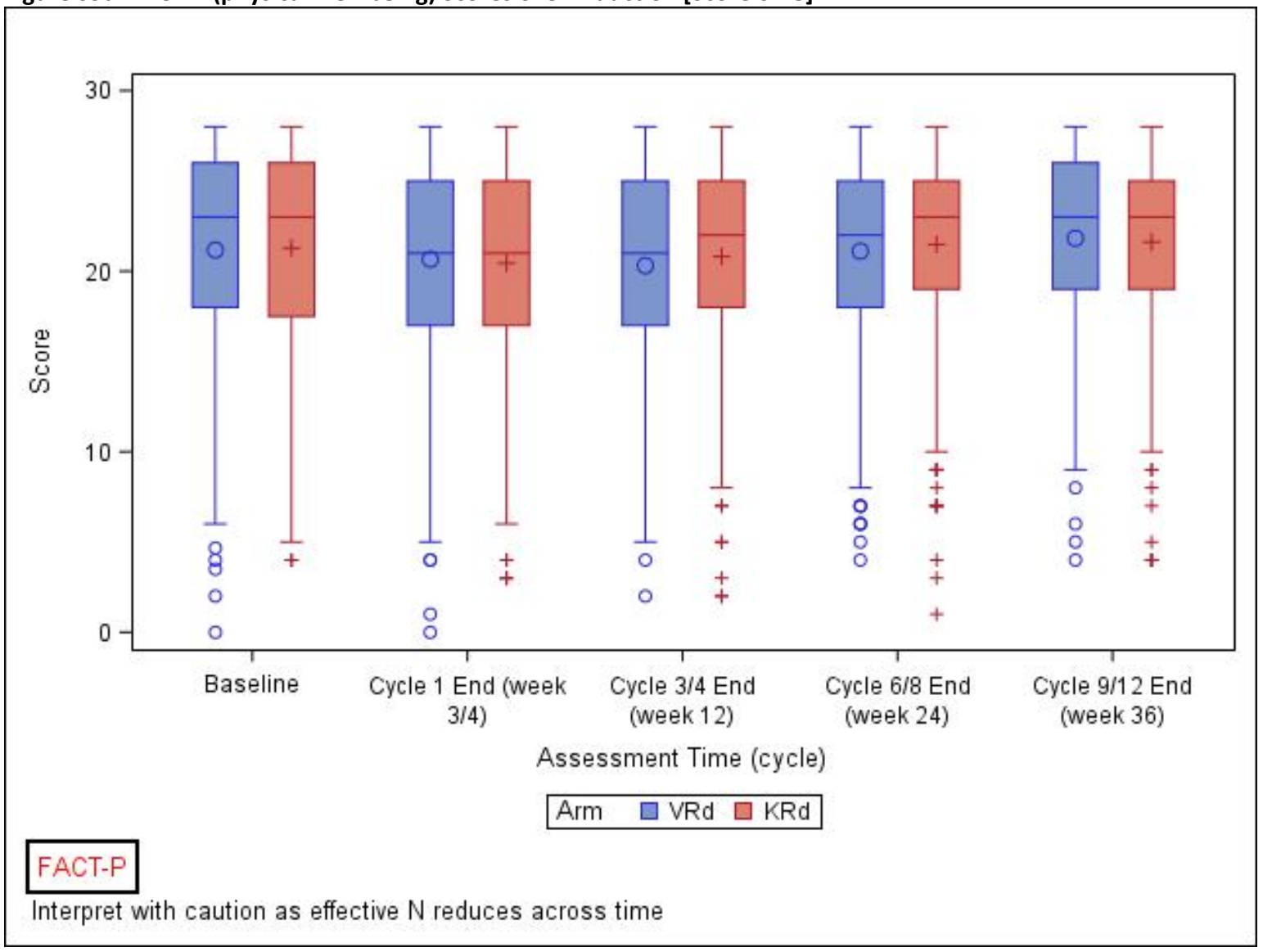
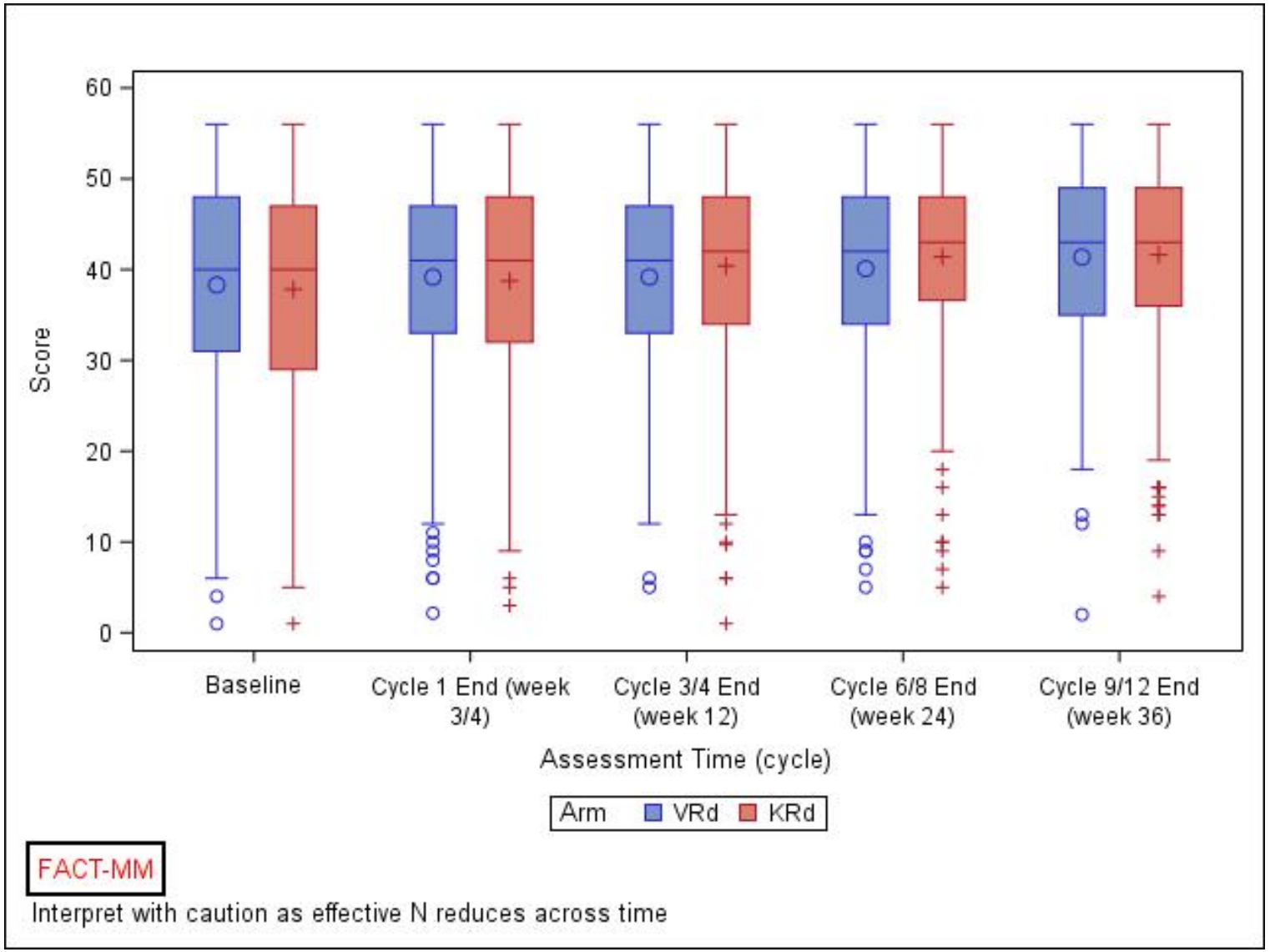


Figure S9e. FACT-MM (myeloma symptoms) Scores over Induction [Score 0-56]



12. Supplementary Table S1: Reason Off Treatment

	VRd (n=527)	KRd (n=526)	Total (n=1053)
Reason	N (%)	N (%)	N (%)
Treatment Completed	228 (43.3%)	324 (61.6%)	552 (52.4%)
Disease Progression	33 (6.3%)	19 (3.6%)	52 (4.9%)
Adverse Events/ Complications	91 (17.3%)	52 (9.9%)	143 (13.6%)
Death	6 (1.1%)	15 (2.9%)	21 (2.0%)
Patient Withdrawal/ Refusal	39 (7.4%)	22 (4.2%)	61 (5.8%)
Alternative Therapy	93 (17.7%)	72 (13.7%)	165 (15.7%)
Other Complicating Disease	13 (2.5%)	5 (1.0%)	18 (1.7%)
Non-Compliance	7 (1.3%)	3 (0.6%)	10 (1.0%)
MD Decision	8 (1.5%)	4 (0.8%)	12 (1.1%)
Other	9 (1.7%)	10 (1.9%)	19 (1.8%)

13. Supplementary Table S2: Reason Off Treatment by Age

	Age < 70			Age ≥ 70		
	VRd (n=369)	KRd (n=361)	Total (n=730)	VRd (n=158)	KRd (n=165)	Total (n=323)
Category	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Treatment Completed	161 (43.6%)	223 (61.8%)	384 (52.6%)	67 (42.4%)	101 (61.2%)	168 (52.0%)
Disease Progression	24 (6.5%)	15 (4.2%)	39 (5.3%)	9 (5.7%)	4 (2.4%)	13 (4.0%)
Adverse Events/ Complications	49 (13.3%)	29 (8.0%)	78 (10.7%)	42 (26.6%)	23 (13.9%)	65 (20.1%)
Death	3 (0.8%)	8 (2.2%)	11 (1.5%)	3 (1.9%)	7 (4.2%)	10 (3.1%)
Patient Withdrawal/ Refusal	26 (7.1%)	15 (4.2%)	41 (5.6%)	13 (8.2%)	7 (4.2%)	20 (6.2%)
Alternative Therapy	79 (21.4%)	63 (17.5%)	142 (19.5%)	14 (8.9%)	9 (5.5%)	23 (7.1%)
Other Complicating Disease	9 (2.4%)	0 (0.0%)	9 (1.2%)	4 (2.5%)	5 (3.0%)	9 (2.8%)
Non-Compliance	6 (1.6%)	2 (0.6%)	8 (1.1%)	1 (0.6%)	1 (0.6%)	2 (0.6%)
MD Decision	5 (1.4%)	1 (0.3%)	6 (0.8%)	3 (1.9%)	3 (1.8%)	6 (1.9%)
Other	7 (1.9%)	5 (1.4%)	12 (1.6%)	2 (1.3%)	5 (3.0%)	7 (2.2%)

14. Supplementary Table S3. Treatment Dose Modifications

	Bortezomib (n=527)	Carfilzomib (n=526)	Bortezomib (n=527)	Carfilzomib (n=526)
	Ever Dose Modification		Ever Dose Reduction	
	N (%)	N (%)	N (%)	N (%)
No	135 (26%)	132 (25%)	282 (54%)	352 (67%)
Yes	392 (74%)	394 (75%)	245 (46%)	174 (33%)
Dose Modification/Reduction Type				
Held	109 (28%)	151 (38%)	na	na
Delayed	82 (21%)	96 (24%)	na	na
Missed	48 (12%)	52 (13%)	na	na
Disc	3 (<1%)	16 (4%)	na	na
Reduced	123 (32%)	59 (15%)	210 (86%)	149 (86%)
Delayed & Reduced	25 (6%)	13 (3%)	35 (14%)	25 (14%)
Unknown	2 (<1%)	7 (2%)	0	0
Total	392 (100%)	394 (100%)	245 (100%)	174 (100%)
Dose Modification/Reduction Reason				
AE	269 (69%)	246 (63%)	231 (94%)	160 (92%)
Pt Ref/Non-Comp	10 (3%)	10 (3%)	0 (0.0)	0 (0.0)
Scheduling	36 (9%)	44 (11%)	0 (0.0)	0 (0.0)
Dosing Error	3 (<1%)	7 (2%)	3 (<1%)	4 (2%)
Alt Therapy	2 (<1%)	2 (<1%)	0	0
Other	72 (18%)	83 (21%)	11 (5%)	10 (6%)
Unknown	0	2 (<1%)	0	0
Total	392 (100%)	394 (100%)	245 (100%)	174 (100%)
Time to First Dose Modification/Reduction				
Cycle 1	72 (18%)	151 (38%)	10 (4%)	26 (15%)
Cycle 2	68 (17%)	76 (19%)	44 (18%)	54 (31%)
Cycle 3	56 (14%)	37 (9%)	30 (12%)	25 (14%)
Cycle 4	54 (14%)	30 (8%)	39 (16%)	16 (9%)
Cycle 5	63 (16%)	46 (12%)	52 (21%)	10 (6%)
Cycle 6	28 (7%)	22 (6%)	24 (10%)	19 (11%)
Cycle 7	15 (4%)	20 (5%)	20 (8%)	7 (4%)
Cycle 8	17 (4%)	5 (1%)	12 (5%)	10 (6%)
Cycle 9	7 (2%)	7 (2%)	4 (2%)	7 (4%)
Cycle 10	10 (3%)	---	6 (3%)	---
Cycle 11	1 (<1%)	---	11 (4%)	---
Cycle 12	1 (<1%)	---	---	---

15. Supplementary Table S4. Treatment Exposure Classification-bortezomib and carfilzomib

	Bortezomib*						Carfilzomib*					
			Percent Protocol Dose Received Class						% Protocol Dose Received Class			
			0-50%	50-75%	75-95%	95-110%			0-50%	50-75%	75-95%	95-110%
	n	n miss	N (%)	N (%)	N (%)	N (%)	n	n miss	N (%)	N (%)	N (%)	N (%)
Cycle 1	524	3	19 (4%)	24 (5%)	38 (7%)	443 (85%)	515	10	23 (5%)	71 (14%)	78 (15%)	343 (67%)
Cycle 2	506	2	12 (2%)	40 (71%)	71 (14%)	383 (76%)	495	5	18 (4%)	74 (15%)	88 (18%)	315 (64%)
Cycle 3	482	5	27 (6%)	44 (9%)	73 (15%)	338 (70%)	473	4	18 (4%)	76 (16%)	87 (18%)	292 (62%)
Cycle 4	457	3	34 (7%)	62 (14%)	81 (18%)	280 (61%)	452	3	19 (4%)	85 (19%)	81 (18%)	267 (59%)
Cycle 5	400	3	52 (13%)	59 (15%)	96 (24%)	193 (48%)	413	5	27 (7%)	98 (24%)	81 (20%)	207 (50%)
Cycle 6	353	1	52 (15%)	71 (20%)	83 (24%)	147 (42%)	385	3	26 (7%)	100 (26%)	70 (18%)	189 (49%)
Cycle 7	310	2	43 (14%)	80 (26%)	69 (22%)	118 (38%)	356	2	26 (7%)	91 (26%)	66 (18%)	173 (49%)
Cycle 8	281	2	38 (13%)	80 (29%)	70 (25%)	93 (33%)	337	4	20 (6%)	100 (30%)	66 (20%)	151 (45%)
Cycle 9	263	2	24 (9%)	80 (30%)	69 (26%)	90 (34%)	320	5	18 (6%)	98 (31%)	59 (18%)	145 (45%)
Cycle 10	252	0	17 (7%)	77 (31%)	73 (29%)	85 (34%)	---	---	---	---	---	---
Cycle 11	237	1	19 (8%)	77 (33%)	66 (28%)	75 (32%)	---	---	---	---	---	---
Cycle 12	229	3	22 (10%)	77 (34%)	58 (25%)	72 (31%)	---	---	---	---	---	---

*****Dataset includes patients with treatment and BSA data; Reported doses in excess of 110% PPD were excluded from the analyses (n miss count)

16. Supplementary Table 5: Treatment Exposure Classification-lenalidomide

	Len-VRd*						Len-KRd*					
			Percent Protocol Dose Received Class						% Protocol Dose Received Class			
			0-50%	50-75%	75-95%	95-110%			0-50%	50-75%	75-95%	95-110%
	n	n miss	N (%)	N (%)	N (%)	N (%)	n	n miss	N (%)	N (%)	N (%)	N (%)
Cycle 1	523	2	116 (22%)	28 (5%)	34 (7%)	345 (66%)	522	1	154 (30%)	46 (9%)	32 (6%)	290 (56%)
Cycle 2	504	0	110 (22%)	39 (8%)	34 (7%)	321 (64%)	495	1	117 (24%)	59 (12%)	14 (3%)	305 (62%)
Cycle 3	485	2	102 (21%)	54 (11%)	21 (4%)	308 (64%)	469	2	99 (21%)	64 (14%)	13 (3%)	293 (63%)
Cycle 4	466	0	100 (22%)	71 (15%)	17 (4%)	278 (60%)	448	1	95 (21%)	71 (16%)	10 (2%)	272 (61%)
Cycle 5	402	0	91 (23%)	65 (17%)	17 (4%)	229 (57%)	412	0	104 (25%)	76 (19%)	13 (3%)	219 (53%)
Cycle 6	353	1	79 (22%)	74 (21%)	14 (4%)	186 (53%)	382	1	107 (28%)	74 (19%)	4 (1%)	197 (52%)
Cycle 7	310	0	75 (24%)	58 (19%)	11 (4%)	166 (54%)	356	0	103 (29%)	73 (21%)	3 (<1%)	177 (50%)
Cycle 8	282	0	81 (29%)	51 (18%)	7 (3%)	143 (51%)	339	1	95 (28%)	75 (22%)	4 (1%)	165 (49%)
Cycle 9	270	0	67 (25%)	58 (22%)	8 (3%)	137 (51%)	324	2	100 (31%)	66 (20%)	4 (1%)	154 (48%)
Cycle 10	261	0	66 (25%)	56 (22%)	3 (1%)	136 (52%)	---	---	---	---	---	---
Cycle 11	249	1	61 (25%)	60 (24%)	2 (<1%)	126 (51%)	---	---	---	---	---	---
Cycle 12	240	0	63 (26%)	57 (24%)	5 (2%)	115 (48%)	---	---	---	---	---	---

*****Dataset includes patients with treatment data; Reported doses in excess of 110% PPD were excluded from the analyses (n miss count)

17. Supplementary Table 6: Treatment Exposure Classification-dexamethasone

	Dex-VRd*						Dex-KRd*					
			Percent Protocol Dose Received Class						% Protocol Dose Received Class			
			0-50%	50-75%	75-95%	95-110%			0-50%	50-75%	75-95%	95-110%
	n	n miss	N (%)	N (%)	N (%)	N (%)	n	n miss	N (%)	N (%)	N (%)	N (%)
Cycle 1	515	11	7 (1%)	18 (4%)	30 (6%)	460 (89%)	514	10	18 (4%)	40 (8%)	53 (10%)	403 (78%)
Cycle 2	499	5	12 (2%)	33 (7%)	28 (6%)	426 (85%)	497	4	23 (5%)	51 (10%)	36 (7%)	387 (78%)
Cycle 3	482	5	26 (5%)	48 (10%)	27 (6%)	381 (79%)	475	2	21 (4%)	59 (12%)	29 (6%)	366 (77%)
Cycle 4	460	4	23 (5%)	61 (13%)	20 (4%)	356 (77%)	454	3	31 (7%)	55 (12%)	33 (7%)	335 (74%)
Cycle 5	359	43	18 (5%)	14 (4%)	21 (6%)	306 (85%)	350	64	18 (5%)	16 (5%)	29 (8%)	287 (82%)
Cycle 6	335	20	18 (5%)	15 (5%)	21 (6%)	281 (84%)	351	31	14 (4%)	29 (8%)	11 (3%)	297 (85%)
Cycle 7	302	11	18 (6%)	17 (6%)	14 (5%)	253 (84%)	333	24	20 (6%)	20 (6%)	24 (7%)	269 (81%)
Cycle 8	281	6	20 (7%)	10 (4%)	11 (4%)	240 (85%)	314	25	12 (5%)	20 (6%)	17 (5%)	265 (84%)
Cycle 9	250	22	16 (6%)	9 (4%)	4 (2%)	221 (88%)	306	19	13 (4%)	26 (9%)	18 (6%)	249 (81%)
Cycle 10	248	14	17 (7%)	6 (2%)	2 (<1%)	223 (90%)	---	---	---	---	---	---
Cycle 11	238	12	16 (7%)	6 (3%)	2 (<1%)	214 (90%)	---	---	---	---	---	---
Cycle 12	233	8	20 (9%)	6 (3%)	3 (1%)	204 (88%)	---	---	---	---	---	---

*****Dataset includes patients with treatment data; Reported doses in excess of 110% PPD were excluded from the analyses (n miss count)

18. Supplementary Table S7: PFS by Treatment Results within Subgroups

Subgroup	VRd N pts/events	KRd N pts/events	VRd Median PFS (months) (95% CI)	KRd Median PFS (months) (95% CI)	Treatment HR (KRd/Vrd)^
Overall	542/141	545/157	34.4 (30.1-NE)	34.6 (28.8-37.8)	1.04 (0.83-1.31)
Age					
<65y	278/76	257/70	32.9 (27.6-NE)	36.1 (27.2-44.8)	0.92 (0.66-1.27)
>/=65y	264/65	288/87	36.8 (29.2-NE)	32.3 (27.9-37.8)	1.18 (0.85-1.63)
Age					
<70y	375/101	368/98	33.2 (29.5-NE)	36.3 (30.6-42.6)	0.93 (0.71-1.23)
>/=70y	167/40	177/59	36.8 (29.1-NE)	28.3 (24.0-36.3)	1.29 (0.86-1.94)
Sex					
Male	315/81	327/101	32.2 (27.3-NE)	31.1 (26.5-37.8)	1.04 (0.77-1.39)
Female	227/60	218/56	36.8 (29.1-NE)	36.3 (28.8-50.7)	1.01 (0.70-1.45)
Race					
White	443/120	448/134	34.4 (29.5-51.5)	33.0 (28.0-37.5)	1.02 (0.80-1.31)
Non-white	81/16	71/15	NE (29.2-NE)	42.6 (27.9-NE)	1.24 (0.60-2.56)
ISS Stage					
I-II	401/102	383/108	35.7 (30.5-NE)	34.6 (28.0-37.9)	1.05 (0.80-1.38)
III	138/39	159/48	29.5 (23.0-NE)	33.0 (24.4-49.0)	0.97 (0.63-1.48)
Cytogenetics*					
Normal	326/69	331/97	NE (34.9-NE)	34.6 (29.0-38.8)	1.35 (0.99-1.84)
Abnormal	128/50	127/43	28.9 (17.8-31.3)	28.3 (24.0-36.3)	0.75 (0.50-1.15)
13q Status					
Absent	272/69	262/77	32.2 (29.1-NE)	34.6 (26.6-42.8)	0.98 (0.71-1.36)
Present	151/36	165/49	35.7 (28.9-NE)	30.6 (23.9-37.5)	1.25 (0.81-1.94)
t(4;14) Status					
Absent	379/91	391/112	33.2 (30.1-NE)	34.6 (27.9-37.8)	1.07 (0.81-1.42)
Present	44/14	36/14	18.3 (14.9-NE)	19.3 (12.7-NE)	1.16 (0.54-2.47)
t(11;14) Status					
Absent	336/76	347/100	33.2 (29.2-NE)	33.0 (27.2-37.9)	1.14 (0.85-1.54)
Present	87/29	80/26	31.7 (18.3-NE)	34.6 (18.4-47.9)	0.84 (0.49-1.43)
ECOG PS					
0	212/50	241/68	41.3 (30.5-NE)	34.8 (27.9-42.6)	1.10 (0.77-1.59)
>0	330/91	304/89	32.2 (28.5-NE)	32.8 (27.2-37.9)	1.02 (0.76-1.36)
Creatinine					
<2 mg/dL	506/132	520/151	34.9 (30.1-NE)	34.6 (28.8-37.9)	1.04 (0.82-1.31)
>/=2 mg/dL	25/6	36/9	34.4 (15.3-41.3)	34.6 (9.8-36.3)	0.75 (0.23-2.42)
LDH					
<190 U/L	336/84	369/108	41.3 (28.5-NE)	33.0 (27.2-37.8)	1.05 (0.79-1.40)

>/=190 U/L	206/57	176/49	34.4 (29.5-NE)	36.3 (29.0-NE)	1.02 (0.69-1.49)
Disease Type					
Light Chain MM	58/18	51/17	34.4 (18.3-NE)	32.8 (25.9-NE)	0.93 (0.47-1.84)
Non-LC MM	484/123	494/140	34.9 (29.5-NE)	34.8 (28.3-38.8)	1.05 (0.83-1.34)

*****Interaction p-values (unadjusted for multiple testing) are not significant at p=0.05 except cytogenetics abnormal status (p=0.014)

19. Supplementary Table S8: PFS Sensitivity Analysis

PFS Sensitivity	Median Follow-Up (months) (95% CI)	N pts/events	VRd Median PFS (months) (95% CI)	KRd Median PFS (months) (95% CI)	Treatment HR (KRd/Vrd)
PFS Primary	15.3 (13.0-17.7)	1087/298	34.4 (30.1-NE)	34.6 (28.8-37.8)	1.04 (0.83-1.31)
PFS Sensitivity: All deaths counted as events	16.8 (14.6-18.8)	1087/330	32.9 (29.1-37.0)	32.8 (27.9-37.3)	1.02 (0.82-1.27)
PFS Sensitivity: Censor at time of SCT or alternative therapy	9.4 (8.9-9.8)	1087/256	31.7 (28.5-44.6)	32.8 (27.2-37.5)	0.98 (0.77-1.25)
PFS Sensitivity: Censor at time of last contact	25.8 (24.1-28.1)	1087/298	NR (NE)	49.1 (42.6-NE)	1.05 (0.84-1.32)
PFS Sensitivity: Eligible and Treated Pop	15.3 (12.7-18.0)	913/259	32.9 (29.1-51.5)	34.6 (28.3-37.8)	0.97 (0.76-1.24)

20. Supplementary Table S9: Response within 12 weeks of Induction

	VRd	KRd	
Category	(n=527)	(n=526)	
Category	N (%)	N (%)	
Stringent Complete Response	6 (1%)	7 (1%)	
Complete Response	11 (2%)	8 (2%)	
Very Good Partial Response	247 (47%)	257 (49%)	
Partial Response	158 (30%)	161 (31%)	
Stable Disease	57 (11%)	51 (10%)	
Progressive Disease	1 (<1%)	0	
Unevaluable/Insufficient	44 (10%)	39 (7%)	
Missing	3 (<1%)	3 (<1%)	
Rates	N (%)	N (%)	Chi sq p-value
CR	17 (3%)	15 (2.9)	p=0.72
(95% CI)	(2%-5%)	(2%-5%)	
VGPR	264 (50%)	272 (52%)	p=0.60
(95% CI)	(46%-55%)	(47%-56%)	
PR	422 (80%)	433 (82%)	p=0.35
(95% CI)	(76%-83%)	(79%-86%)	

21. Supplementary Table S10. Global Toxicity Rates

	VRd (n=527)	KRd (n=526)		
Non-Hematologic				
Rates	N (%)	N (%)	Difference KRd-VRd	Chi sq p-value
Treatment-Related				
Grades 3-5	218 (41.4%)	254 (48.3%)	6.9%	0.02
(95% CI)	(37.1%-45.7%)	(44.0%-52.6%)		
Grades 4-5	21 (4.0%)	43 (8.2%)	4.2%	<0.01
(95% CI)	(2.5%-6.1%)	(6.0%-10.9%)		
Treatment-Emergent				
Grades 3-5	310 (58.8%)	331 (62.9%)	4.1%	0.17
(95% CI)	(54.5%-63.0%)	(58.6%-67.1%)		
Grades 4-5	44 (8.3%)	67 (12.7%)	4.4%	0.02
(95% CI)	(6.1%-11.1%)	(10.0%-15.9%)		
Hematologic + Non-Hematologic^				
Rates	N (%)	N (%)	Difference KRd-VRd	Chi sq p-value
Treatment-Related				
Grades 4-5	61 (11.6%)	70 (13.3%)	1.7%	0.39
(95% CI)	(9.0%-14.6%)	(10.5-16.5%)		
Treatment-Emergent				
Grades 4-5	83 (15.7%)	96 (18.3%)	2.5%	0.28
(95% CI)	(12.7%-19.1%)	(15.1%-21.8%)		

^Grade 3 hematologic events not required reporting

21. Supplementary Table S11. Treatment-Related Non-Hematologic Toxicity by SOC

System Organ Class^	Treatment Arm					
	VRd (n=527)			KRd (n=526)		
	Grade			Grade		
	3	4	5	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Blood and lymphatic system disorders	2 (<1%)	2 (<1%)	-	7 (1%)	1 (<1%)	-
Cardiac disorders	10 (2%)	-	1 (<1%)	26 (5%)	4 (<1%)	3 (<1%)
Eye disorders	2 (<1%)	-	-	1 (<1%)	-	-
Gastrointestinal disorders	31 (6%)	2 (<1%)	-	32 (6%)	3 (<1%)	-
General disorders and administration site conditions	47 (9%)	-	-	52 (10%)	5 (1%)	1 (<1%)
Hepatobiliary disorders	-	-	-	2 (<1%)	-	1 (<1%)
Immune system disorders	1 (<1%)	-	-	2 (<1%)	-	-
Infections and infestations	25 (5%)	3 (<1%)	-	36 (7%)	9 (2%)	-
Injury, poisoning and procedural complications	2 (<1%)	-	-	-	-	-
Investigations*	12 (2%)	-	-	23 (4%)	4 (<1%)	-
Metabolism and nutrition disorders	43 (8%)	8 (2%)	-	45 (9%)	10 (2%)	-
Musculoskeletal and connective tissue disorders	29 (6%)	-	-	11 (2%)	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	1 (<1%)	-	-	-	-
Nervous system disorders	58 (11%)	-	-	12 (2%)	-	-
Psychiatric disorders	18 (3%)	-	-	16 (3%)	-	-
Renal and urinary disorders	6 (1%)	-	-	14 (3%)	4 (<1%)	1 (<1%)
Reproductive system and breast disorders	1 (<1%)	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	12 (2%)	-	-	40 (8%)	10 (2%)	1 (<1%)
Skin and subcutaneous tissue disorders	18 (3%)	-	-	32 (6%)	-	-
Surgical and medical procedures	-	-	-	1 (<1%)	-	-
Vascular disorders	25 (5%)	4 (<1%)	-	47 (9%)	4 (<1%)	-
Worst Degree (Non-Hematologic)	**197 (37%)**	**20 (4%)**	**1 (<1%)**	**211 (40%)**	**36 (7%)**	**7 (1%)**

^Non-hematologic includes Blood and lymphatic system disorders-Other, Febrile neutropenia and Thrombotic thrombocytopenic purpura

* Investigations SOC refers to standard terms based on CTCAE v4:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf

22. Supplementary Table S12. Treatment-Emergent Toxicity by Type

Adverse Event Type	Treatment Arm					
	VRd (n=527)			KRd (n=526)		
	Grade			Grade		
	3	4	5	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Non-Hematologic^						
Febrile neutropenia	2 (<1%)	1 (<1)	-	5 (1%)	1 (<1%)	-
Atrial fibrillation	7 (1%)	1 (<1)	-	10 (2%)	-	-
Cardiac disorders - Other	1 (<1%)	-	-	4 (<1%)	-	-
Chest pain - cardiac	1 (<1%)	-	-	3 (<1%)	-	-
Heart failure	10 (2%)	-	-	17 (3%)	5 (1%)	-
Myocardial infarction	1 (<1%)	-	1 (<1%)	3 (1%)	2 (<1%)	1 (<1%)
Sinus tachycardia	1 (<1%)	-	-	5 (1%)	-	-
Abdominal pain	2 (<1%)	-	-	6 (1%)	-	-
Diarrhea	33 (6%)	1 (<1%)	-	22 (4%)	-	-
Nausea	7 (1%)	-	-	5 (1%)	-	-
Vomiting	6 (1%)	-	-	8 (2%)	-	-
Fatigue	41 (8%)	-	-	31 (6%)	-	-
Fever	2 (<1%)	-	-	6 (1%)	1 (<1%)	-
Pain	8 (2%)	-	-	10 (2%)	-	-
Edema limbs	17 (3%)	-	-	12 (2%)	-	-
Infusion related reaction	-	-	-	4 (<1%)	3 (<1%)	-
Non-cardiac chest pain	1 (<1%)	-	-	5 (1%)	-	-
Infections and infestations - Other	10 (2%)	-	-	7 (1%)	1 (<1%)	-
Sepsis	-	4 (<1%)	2 (<1%)	-	17 (3%)	-
Skin infection	8 (2%)	-	-	8 (2%)	-	-
Upper respiratory infection	1 (<1%)	-	-	5 (1%)	-	-
Urinary tract infection	9 (2%)	-	-	8 (2%)	-	-
Lung infection	21 (4%)	-	-	43 (8%)	-	1 (<1%)

Adverse Event Type	Treatment Arm					
	VRd (n=527)			KRd (n=526)		
	Grade			Grade		
	3	4	5	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Fall	6 (1%)	-	-	-	-	-
Hip fracture	5 (1%)	-	-	1 (<1%)	-	-
Spinal fracture	5 (1%)	1 (<1%)	-	4 (<1%)	-	-
Creatinine increased	2 (<1%)	-	-	9 (2%)	1 (<1%)	-
Weight loss	7 (1%)	-	-	3 (<1%)	-	-
Ejection fraction decreased	-	-	-	9 (2%)	1 (<1%)	-
Anorexia	6 (1%)	-	-	2 (<1%)	-	-
Dehydration	18 (3%)	-	-	10 (2%)	-	-
Hyperglycemia	24 (5%)	5 (1%)	-	39 (7%)	5 (1%)	-
Hypoalbuminemia	2 (<1%)	-	-	5 (1%)	-	-
Hypocalcemia	4 (<1%)	3 (<1%)	-	10 (2%)	6 (1%)	-
Hypokalemia	11 (2%)	3 (1%)	-	15 (3%)	3 (1%)	-
Hyponatremia	11 (2%)	4 (1%)	-	11 (2%)	1 (<1%)	-
Back pain	18 (3%)	-	-	13 (2%)	-	-
Bone pain	9 (2%)	-	-	8 (2%)	-	-
Myalgia	4 (<1%)	-	-	5 (<1%)	-	-
Pain in extremity	9 (2%)	-	-	4 (<1%)	-	-
Generalized muscle weakness	13 (2%)	-	-	5 (1%)	-	-
Muscle weakness lower limb	7 (1%)	-	-	1 (<1%)	-	-
Dizziness	10 (2%)	-	-	1 (<1%)	-	-
Peripheral neuropathy	43 (8%)	-	-	5 (1%)	-	-
Syncope	20 (4%)	-	-	14 (3%)	-	-
Confusion	3 (<1%)	-	-	8 (2%)	1 (<1%)	-
Depression	5 (1%)	1 (<1%)	-	-	-	-
Insomnia	12 (2%)	-	-	11 (2%)	-	-
Chronic kidney disease	4 (<1%)	1 (<1%)	-	2 (<1%)	-	-
Acute kidney injury	5 (1%)	2 (<1%)	1 (<1%)	17 (3%)	4 (<1%)	1 (<1%)

Adverse Event Type	Treatment Arm					
	VRd (n=527)			KRd (n=526)		
	Grade			Grade		
	3	4	5	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dyspnea	17 (3%)	1 (<1%)	-	39 (7%)	9 (2%)	-
Hypoxia	7 (1%)	1 (<1%)	-	12 (2%)	1 (<1%)	1 (<1%)
Pneumonitis	5 (1%)	-	-	7 (1%)	-	-
Pulmonary edema	-	-	-	4 (<1%)	1 (<1%)	-
Respiratory failure	-	2 (<1%)	-	-	12 (2%)	2 (<1%)
Respiratory, thoracic and mediastinal disorders - Other	-	-	-	4 (<1%)	1 (<1%)	-
Rash acneiform	13 (2%)	-	-	12 (2%)	-	-
Rash maculo-papular	8 (2%)	-	-	21 (4%)	-	-
Hypertension	36 (7%)	-	-	64 (12%)	1 (<1%)	-
Hypotension	19 (<4%)	-	-	11 (2%)	2 (<1%)	-
Thromboembolic event	9 (2%)	4 (<1%)	-	25 (5%)	3 (<1%)	2 (<1%)
Worst Degree (Non-Hematologic)	**266 (50%)**	**38 (7%)**	**6 (1%)**	**264 (50%)**	**52 (10%)**	**15 (3%)**
Hematologic^*						
Lymphocyte count decreased	na	26 (5%)	-	na	22 (4%)	-
Neutrophil count decreased	na	14 (3%)	-	na	11 (2%)	-
Platelet count decreased	na	12 (2%)	-	na	7 (1%)	-
Worst Degree (Hematologic)	**na**	**47 (9%)**	**-**	**na**	**43 (8%)**	**-**

^Hematologic adverse events include Anemia, CD4 lymphocytes decreased, Lymphocyte count decreased, Neutrophil count decreased, Platelet count decreased, and White blood cell decreased and excludes Blood and lymphatic system disorders-Other, Febrile neutropenia and Thrombotic thrombocytopenic purpura
*Grade 3 hematologic adverse events were not required reporting

23. Supplementary Table S13. Treatment-Related CPR Toxicity by Type

Averse Event Type^	Treatment Arm					
	VRd (n=527)			KRd (n=526)		
	Grade			Grade		
	3	4	5	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Asystole	-	-	-	-	1 (<1%)	-
Atrial fibrillation	2 (<1%)	-	-	7 (1%)	-	-
Cardiac arrest	-	-	-	-	-	1 (<1%)
Cardiac disorders - Other	-	-	-	3 (<1%)	-	-
Chest pain – cardiac	1 (<1%)	-	-	2 (<1%)	-	-
Heart failure	6 (1%)	-	-	14 (3%)	5 (1%)	-
Myocardial infarction	1 (<1%)	-	1 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)
Sinus bradycardia	-	-	-	-	-	1 (<1%)
Sinus tachycardia	1 (<1%)	-	-	4 (<1%)	-	-
Supraventricular tachycardia	-	-	-	1 (<1%)	-	-
Ventricular tachycardia	-	-	-	1 (<1%)	-	-
Left ventricular systolic dysfunction	1 (<1%)	-	-	1 (<1%)	-	-
Renal colic	-	-	-	1 (<1%)	-	-
Proteinuria	2 (<1%)	-	-	2 (<1%)	-	-
Chronic kidney disease	1 (<1%)	-	-	2 (<1%)	-	-
Acute kidney injury	3 (<1%)	-	-	9 (2%)	4 (<1%)	1 (<1%)
Adult respiratory distress syndrome	-	-	-	1 (<1%)	-	-
Atelectasis	-	-	-	1 (<1%)	-	-
Dyspnea	9 (2%)	-	-	32 (6%)	6 (1%)	-
Hiccups	-	-	-	1 (<1%)	-	-
Hypoxia	2 (<1%)	-	-	6 (1%)	1 (<1%)	1 (<1%)
Pleural effusion	-	-	-	2 (<1%)	-	-
Pneumonitis	2 (<1%)	-	-	5 (1%)	-	-
Productive cough	-	-	-	1 (<1%)	-	-
Pulmonary edema	-	-	-	3 (<1%)	1 (<1%)	-
Pulmonary hypertension	-	-	-	3 (<1%)	1 (<1%)	-
Respiratory failure	-	-	-	-	5 (1%)	-

Averse Event Type^	Treatment Arm					
	VRd (n=527)			KRd (n=526)		
	Grade			Grade		
	3	4	5	3	4	5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Respiratory, thoracic and mediastinal disorders - Other	-	-	-	2 (<1%)	-	-
Wheezing	-	-	-	1 (<1%)	-	-
Worst Degree (CPR)*	**24 (5%)**	**0**	**1 (<1%)**	**66 (13%)**	**13 (2%)**	**5 (1%)**

^Composite rate of CTCAE system organ classes: Cardiac disorders; Respiratory, thoracic, mediastinal disorders; and Renal and urinary disorders

*Grade 3-5 rates: VRd 4.7% vs KRd 16%, chi-sq p=<0.001

24. Supplementary Table S14. Treatment-Related Toxicity Rates by Age

Treatment-Related Non-Hematologic			
Age<70y			
	VRd (n=369)	KRd (n=361)	
	N (%)	N (%)	Difference KRd-VRd
Grades 3-5 (95% CI)	218 (41.4%) (37.1%-45.7%)	254 (48.3%) (44.0%-52.6%)	6.9%
Grades 4-5 (95% CI)	21 (4.0%) (2.5%-6.1%)	43 (8.2%) (6.0%-10.9%)	4.2%
Age>/=70y			
	VRd (n=158)	KRd (n=165)	
Grades 3-5 (95% CI)	310 (58.8%) (54.5%-63.0%)	331 (62.9%) (58.6%-67.1%)	4.1%
Grades 4-5 (95% CI)	44 (8.3) (6.1%-11.1%)	67 (12.7%) (10.0%-15.9%)	4.4%
Treatment-Related Cardio-Pulmonary-Renal			
Age<70y			
	VRd (n=369)	KRd (n=361)	
	N (%)	N (%)	Difference KRd-VRd
Grades 3-5 (95% CI)	17 (4.6%) (2.7%-7.3%)	52 (14.4%) (11.0-18.5)	9.8%
Grades 4-5 (95% CI)	0 (0%-1.0%)	8 (2.2%) (0.9%-4.3%)	2.2%
Age>/=70y			
	VRd (n=158)	KRd (n=165)	
Grades 3-5 (95% CI)	8 (5.1) (2.2%-9.8%)	32 (19.4%) (13.7%-26.3%)	14.3%
Grades 4-5 (95% CI)	1 (0.6%) (0%-3.5%)	10 (6.1%) (2.9%-10.9%)	5.4%

25. Supplementary Table S15. Serious Adverse Event Rates

	VRd (n=527)	KRd (n=526)		
Serious Adverse Events				
Rates	N (%)	N (%)	Difference KRd-VRd	Chi sq p-value
Grades 3-5 (95% CI)	116 (22%) (19%-26%)	234 (45%) (40%-49%)	22.5%	<0.001
Grades 3-4 (95% CI)	108 (21%) (17%-24%)	220 (42%) (38%-46%)	21.3%	<0.001
Grades 4-5 (95% CI)	31 (6%) (4%-8%)	62 (12%) (9%-15%)	5.9%	<0.001
Lethal Adverse Events				
Rates	N (%)	N (%)	Difference KRd-VRd	Chi sq p-value
Grade 5 (95% CI)	9 (2%) (1%-3%)	16 (3%) (2%-5%)	1.3%	0.16

26. Supplementary Table S16. Causes of Death

Count*	Treatment Arm	Treatment-Related (No/Yes)^	Cause of Death
Step 1 Induction			
1	VRd	No	Disease progression
2	VRd	No	Sepsis
3	VRd	No	Sepsis
4	VRd	Yes	Myocardial infarction
5	VRd	No	Myelodysplastic syndrome
6	VRd	No	Acute kidney injury
7	VRd	Yes	Neoplasms - Other
8	VRd	No	Cardiac arrest
9	VRd	No	Sepsis
10	KRd	Yes	Myocardial infarction
11	KRd	Yes	Hepatic failure
12	KRd	Yes	Sinus bradycardia
13	KRd	Yes	Respiratory failure
14	KRd	No	Respiratory failure
15	KRd	Yes	Thromboembolic event
16	KRd	No	Thromboembolic event
17	KRd	Yes	Hypoxia
18	KRd	Yes	Acute kidney injury
19	KRd	No	Lung infection
20	KRd	Yes	Sudden death NOS
21	KRd	Yes	Sinus bradycardia
22	KRd	Yes	Cardiac arrest
23	KRd	No	Respiratory failure
24	KRd	Yes	Acute kidney injury
25	KRd	No	Stroke

*As reported through AERS

^As determined by safety principal investigators

27. Supplementary Table S17. Second Primary Cancers

	VRd (n=527)	KRd (n=526)
Category	N (%)	N (%)
Hematologic		
ALL	0	1
Leukemia	0	1
MDS	1	0
NHL	1	0
Subtotal Hematologic	2 (<1%)	2 (<1%)
Solid		
Bladder	0	2
Breast	2	2
Colon	0	1
Gastric	1	0
Liver	0	1
Lung	1	3
Melanoma	1	2
Pancreas	2	0
Prostate	4	2
Renal	1	1
Thyroid	0	2
Subtotal Solid Tumors	12 (2%)	16 (3%)
Total Invasive SPCs	14 (3%)	18 (3%)
Non-Melanoma Skin	1	6
Basal Cell	1	3
Breast In Situ (DCIS)	0	1
Total Non-Invasive SPCs	2 (<1%)	10 (2%)
Total SPCs#	16 (3%)	28 (5%)
Cumulative Incidence	**%**	**%**
3-Year		
Total Invasive SPCs	3.6	3.6
Total SPCs	4.1	5.7
5-Year		
Total Invasive SPCs	4.6	6.1
Total SPCs	5.1	9.1

#Only first SPC counted; 4 patients had 2 SPCs excl: case 10022 (prostate), 10312 (NMS), 10350 and 10413 (BCC)

28. Supplementary Table S18. Levels and Changes QoL Scores

FACT-Ntx (neurotoxicity) Trial Outcomes Index (TOI) over induction phase [Score 0-100]

	VRd						KRd							
	Scores			Change Score from Baseline			Scores			Change Score from Baseline			Difference Mean Change Score^*	
	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev		95% CI
Baseline	511	74.6	15.9	nm	nm	nm	510	74.8	15.9	nm	nm	nm	nm	nm
Cycle 1	490	73.3	15.2	480	-1.6	12.2	472	73.6	15.1	463	-1.7	11.3	0.1	(-1.4, 1.6)
Cycle 3/4	438	70.6	15.8	429	-4.7	15.8	455	74.6	14.8	449	-0.7	13.3	-4.0	(-5.9, -2.1)
Cycle 6/8	274	72.0	16.1	266	-3.1	16.7	353	76.0	14.5	346	1.1	12.9	-4.2	(-6.6, -1.8)
Cycle 9/12	229	74.7	15.3	220	-0.9	16.5	310	76.7	14.9	304	1.7	13.2	-2.6	(-5.2, -0.0)

^Wilcoxon p-value: (a) Diff Cyc1-base p=0.678 (b) Diff Cyc3/4-base p=<0.001 (c) Diff Cyc6/8-base p=0.003 (d) primary QOL comparison Diff Cyc9/12-base p=0.090

*Clinically meaningful difference per protocol ½ SD

FACT-Ntx (neurotoxicity) scores over induction phase [Score 0-44]

	VRd						KRd							
	Scores			Change Score from Baseline			Scores			Change Score from Baseline			Difference Mean Change Score	
	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev		95% CI
Baseline	514	37.2	6.4	nm	nm	nm	511	37.2	6.2	nm	nm	nm	nm	nm
Cycle 1	493	36.4	6.6	484	-0.9	5.2	472	36.9	6.1	463	-0.4	4.3	-0.5	(-1.1, 0.1)
Cycle ¾	440	33.9	7.5	432	-3.6	7.0	456	36.5	6.5	450	-1.0	5.2	-2.6	(-3.4, -1.8)
Cycle 6/8	276	33.1	7.6	269	-4.4	7.7	357	36.6	6.5	350	-0.7	5.1	-3.7	(-4.8, -2.6)
Cycle 9/12	233	33.4	7.3	225	-4.3	7.5	311	36.3	6.8	305	-1.1	5.1	-3.2	(-4.3, -2.1)

FACT-F (functional well-being) scores over induction phase [Score 0-28]

	VRd						KRd						Difference Mean Change Score	95% CI
	Scores			Change Score from Baseline			Scores			Change Score from Baseline				
	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev		
Baseline	510	16.2	7.2	nm	nm	nm	506	16.3	7.4	nm	nm	nm	nm	nm
Cycle 1	492	16.3	6.8	481	-0.1	6.1	474	16.1	6.6	462	-0.3	6.1	0.2	(-0.6, 1.0)
Cycle 3/4	437	16.4	6.3	427	-0.1	7.2	454	17.3	6.2	444	0.9	6.8	-1.0	(-1.9, -0.1)
Cycle 6/8	274	17.7	6.3	266	1.5	7.0	350	18.0	6.1	339	1.8	7.3	-0.3	(-1.4, 0.8)
Cycle 9/12	228	19.4	6.1	219	2.9	7.4	308	18.7	6.1	299	2.5	7.3	0.4	(-0.9, 1.7)

FACT-P (physical well-being) scores over induction phase [Score 0-28]

	VRd						KRd						Difference Mean Change Score	95% CI
	Scores			Change Score from Baseline			Scores			Change Score from Baseline				
	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev		
Baseline	513	21.2	5.6	nm	nm	nm	511	21.3	5.6	nm	nm	nm	nm	nm
Cycle 1	493	20.7	5.2	484	-0.6	4.8	474	20.4	5.7	465	-1.1	4.7	0.5	(-0.1, 1.1)
Cycle 3/4	441	20.3	5.4	432	-1.0	6.0	456	20.8	5.3	450	-0.7	5.1	-0.3	(-1.0, 0.4)
Cycle 6/8	275	21.1	5.3	267	-0.2	5.8	357	21.5	5.1	350	0.1	5.0	-0.3	(-1.2, 0.6)
Cycle 9/12	231	21.8	4.9	222	0.5	5.7	309	21.6	5.0	303	0.3	5.0	0.2	(-0.7, 1.1)

FACT-MM (myeloma symptoms) scores over induction phase [Score 0-56]

	VRd						KRd							
	Scores			Change Score from Baseline			Scores			Change Score from Baseline			Difference Mean Change Score	95% CI
	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev		
Baseline	511	38.3	11.7	nm	nm	nm	511	37.8	11.9	nm	nm	nm	nm	nm
Cycle 1	492	39.2	10.9	481	0.7	9.1	475	38.7	11.2	466	0.5	7.9	0.2	(-0.9, 1.3)
Cycle 3/4	437	39.2	10.4	426	0.6	10.1	453	40.4	10.2	447	2.0	8.8	-1.4	(-2.6, 0.2)
Cycle 6/8	273	40.1	10.5	266	2.1	11.1	357	41.4	9.8	350	3.4	8.8	-1.3	(-2.9, 0.3)
Cycle 9/12	232	41.4	10.0	224	2.9	11.0	309	41.6	9.8	303	3.7	9.1	-0.8	(-2.5, 0.9)

29. Supplementary Table S19 IMWG Response Review Criteria

International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma[4]

Category*	Multiple Myeloma Response Criteria
Minimum Residual Disease (MRD) Negative	• Serum Immunofixation = Negative • Urine Immunofixation = Negative • Flow MRD Negative Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Stringent complete response (sCR)	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow and • Normal serum free light-chain ratio and • Absence of clonal cells in bone marrow§
Complete response (CR)	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow
Very good partial response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-protein with urine M-protein <100 mg per 24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours • If present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting the criteria for either complete response, very good partial response, partial response, or progressive disease
Progressive disease (PD)¶	Any one or more of the following: • Increase of ≥25% from lowest response value in: ○ Serum M-component (absolute increase must be ≥0.5 g/dL) and/or

    - Urine M-component (absolute increase must be ≥200 mg per 24 hours) and/or
    - Bone marrow plasma cell percentages (absolute % must be ≥10%)
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) attributed solely to the plasma cell proliferative disorder

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*Response criteria for all categories except sCR, CR and VGPR are applicable only to patients that have "measurable" disease defined by at least one of serum (SPEP) ≥1 g/dL or urine (UPEP) ≥200 mg per 24 hours; except for assessment of sCR, CR, or VGPR, patients with measurable disease restricted to SPEP need to be followed only by SPEP. Correspondingly, patients with measurable disease restricted to UPEP need to be followed only by UPEP. Patients with measurable disease in both SPEP and UPEP at study entry are required to meet response criteria in both UPEP and SPEP.

Response categories (sCR, CR, VGPR, PR) require two consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.

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

¶The investigation that qualified as progression should be repeated and verified on a subsequent occasion only if treating physician deems it clinically necessary.

30. Supplementary Table S20: Accrual by Cooperative Group and Institution^

Group	Institution Name	Total	% Accrual
ECOG-ACRIN			
	University of Wisconsin Hospital and Clinics	32	2.9%
	Gundersen Lutheran Medical Center	23	2.1%
	Mayo Clinic	21	1.9%
	Indiana Univ/Melvin and Bren Simon Cancer Center	17	1.6%
	MetroHealth Medical Center	17	1.6%
	Northside Hospital	16	1.5%
	Cancer Care Specialists of Illinois	15	1.4%
	WellSpan Health-York Hospital	13	1.2%
	Virginia Commonwealth Univ/Massey Cancer Center	12	1.1%
	Regions Hospital	11	1.0%
	University of New Mexico Cancer Center	11	1.0%
	Helen F Graham Cancer Center	10	<1%
	Swedish American Regional Cancer Center	10	<1%
	University of Miami Miller Schl Med-Sylvester Cancer Center	10	<1%
	Cancer Center of Kansas - Wichita	9	<1%
	Smilow Cancer Hospital Care Ctr at Saint Francis	9	<1%
	The Mark H Zangmeister Center	9	<1%
	University of Virginia Cancer Center	9	<1%
	Illinois Cancer Care-Peoria	8	<1%
	CHI Health Saint Francis	7	<1%
	Cox Health South Hospital	7	<1%
	Fairview Ridges Hospital	7	<1%
	Illinois Cancer Care-Bloomington	7	<1%
	Siouxland Regional Cancer Center	7	<1%
	Tufts Medical Center	7	<1%
	Benefis Healthcare-Sletten Cancer Institute	6	<1%
	Carle Cancer Center	6	<1%
	Columbus Oncology and Hematology Associates Inc	6	<1%
	Essentia Health Cancer Center	6	<1%
	Great Lakes Ca Mgmt Spec-Van Elslander Cancer Ctr	6	<1%
	Hendrick Medical Center	6	<1%

LSU Health Sciences Center at Shreveport	6	<1%
Mercy Hospital	6	<1%
Park Nicollet Clinic-Saint Louis Park	6	<1%
Reading Hospital	6	<1%
Rutgers Cancer Institute of New Jersey	6	<1%
Saint John's Hospital-Healtheast	6	<1%
Sanford Roger Maris Cancer Center	6	<1%
Atlanta VA Medical Center	5	<1%
Aurora BayCare Medical Center	5	<1%
Baystate Medical Center	5	<1%
McFarland Clinic PC-Ames	5	<1%
Saint Joseph Hospital East	5	<1%
Saint Joseph Mercy Hospital	5	<1%
Saint Vincent Hospital Cancer Center Green Bay	5	<1%
William S Middleton VA Medical Center	5	<1%
Aspirus Regional Cancer Center	4	<1%
Fairview Southdale Hospital	4	<1%
Mayo Clinic in Arizona	4	<1%
Abbott-Northwestern Hospital	3	<1%
Aurora Cancer Care-Grafton	3	<1%
Aurora Medical Center in Summit	3	<1%
Chester County Hospital	3	<1%
Comprehensive Ca Ctrs of Nevada-Central Valley	3	<1%
Geisinger Wyoming Valley/Henry Cancer Center	3	<1%
IHA Hematology Oncology Consultants-Ann Arbor	3	<1%
Kalispell Regional Medical Center	3	<1%
Medical University of South Carolina	3	<1%
Minnesota Oncology Hematology PA-Woodbury	3	<1%
Morristown Medical Center	3	<1%
SCL Health Lutheran Medical Center	3	<1%
Unity Hospital	3	<1%
University of Pennsylvania/Abramson Cancer Center	3	<1%
UW Cancer Center at ProHealth Care	3	<1%
West Virginia University Charleston Division	3	<1%
Aultman Health Foundation	2	<1%
Aurora Cancer Care-Milwaukee	2	<1%

Aurora Cancer Care-Milwaukee West	2	<1%
Aurora Cancer Care-Southern Lakes VLCC	2	<1%
Bellin Memorial Hospital	2	<1%
Christiana Care Health System-Christiana Hospital	2	<1%
Crossroads Cancer Center	2	<1%
Delaware Clinical and Laboratory Physicians PA	2	<1%
Frederick Memorial Hospital	2	<1%
Hematology Oncology Assoc of Fredericksburg Inc	2	<1%
Hennepin County Medical Center	2	<1%
Loyola University Medical Center	2	<1%
Marshfield Clinic-Minocqua Center	2	<1%
Marshfield Clinic Stevens Point Center	2	<1%
Memorial Medical Center-Las Cruces	2	<1%
Mercy Hospital Springfield	2	<1%
Mercyhealth Hospital and Cancer Center-Janesville	2	<1%
Minnesota Oncology Hematology PA-Maplewood	2	<1%
Mountain Blue Cancer Care Center-Swedish	2	<1%
Nebraska Cancer Research Center	2	<1%
Nebraska Hematology and Oncology	2	<1%
Northwest Medical Specialties PLLC	2	<1%
Oncology Hematology Care Inc-Kenwood	2	<1%
Penn State Milton S Hershey Medical Center	2	<1%
Penrose-Saint Francis Healthcare	2	<1%
Rush-Copley Medical Center	2	<1%
Saint Alphonsus Cancer Care Center-Boise	2	<1%
Saint Francis Regional Medical Center	2	<1%
Sanford USD Medical Center - Sioux Falls	2	<1%
Sparrow Hospital	2	<1%
Vidant Oncology-Kinston	2	<1%
York Hospital	2	<1%
Alegent Health Bergan Mercy Medical Center	1	<1%
Alegent Health Immanuel Medical Center	1	<1%
Ann M Wierman MD LTD	1	<1%
Ascension Saint Michael's Hospital	1	<1%
Aurora Bay Area Medical Group-Marinette	1	<1%
Aurora Saint Luke's Medical Center	1	<1%

Beaumont Hospital–Dearborn	1	<1%
Blanchard Valley Hospital	1	<1%
Cancer and Blood Specialists-Henderson	1	<1%
Cancer Center of Kansas-Wichita Medical Arts Tower	1	<1%
Cancer Center of Kansas-Pratt	1	<1%
Cancer Center of Kansas-Salina	1	<1%
Capital Region Southwest Campus	1	<1%
CHI Health Good Samaritan	1	<1%
Dayton Physician LLC-Miami Valley Hospital North	1	<1%
Delaware Health Center-Grady Cancer Center	1	<1%
Freeman Health System	1	<1%
Geisinger Medical Center	1	<1%
Geisinger Medical Group	1	<1%
Great Falls Clinic	1	<1%
Harrison HlthPartners Hem and Oncology-Bremerton	1	<1%
Highline Medical Center-Main Campus	1	<1%
IHA Hematology Oncology Consultants-Brighton	1	<1%
Illinois CancerCare-Macomb	1	<1%
Illinois CancerCare-Peru	1	<1%
IU Health Bloomington	1	<1%
Lake Huron Medical Center	1	<1%
Lakeview Hospital	1	<1%
Lawrence Memorial Hospital	1	<1%
Lewis Ca & Res Pavilion at Saint Joseph's/Candler	1	<1%
Marietta Memorial Hospital	1	<1%
Marshfield Clinic-Weston Center	1	<1%
Marshfield Clinic Cancer Center at Sacred Heart	1	<1%
McFarland Clinic PC-Marshalltown	1	<1%
Medical Oncology and Hem Assoc-West Des Moines	1	<1%
Medical Oncology and Hematology Assoc-Des Moines	1	<1%
Medical Oncology and Hematology Associates-Laurel	1	<1%
Medical Oncology Hematology Consultants PA	1	<1%
Mercy Hospital Oklahoma City	1	<1%
Mount Sinai Hospital Medical Center	1	<1%
Ochsner LSU Health Monroe Medical Center	1	<1%
OptumCare Cancer Care at Oakey	1	<1%

	Our Lady of the Lake Physicians Group-Med Onc	1	<1%
	Parker Adventist Hospital	1	<1%
	PCR Oncology	1	<1%
	Penn State Health Saint Joseph Medical Center	1	<1%
	Ridgeview Medical Center	1	<1%
	Rocky Mountain Cancer Centers-Boulder	1	<1%
	Rush-Copley Healthcare Center	1	<1%
	Saint Louis Cancer and Breast Institute-South City	1	<1%
	Saint Mary Mercy Hospital	1	<1%
	Saint Vincent Hospital Cancer Ctr at Saint Mary's	1	<1%
	Saints Mary and Elizabeth Hospital	1	<1%
	Sanford Bismarck Medical Center	1	<1%
	Southeast Nebraska Cancer Ctr-68th Street Place	1	<1%
	United Hospital	1	<1%
	University of Michigan Comprehensive Cancer Center	1	<1%
	University of Nebraska Medical Center	1	<1%
	UW Cancer Center Johnson Creek	1	<1%
	Vince Lombardi Cancer Clinic	1	<1%
	Vince Lombardi Cancer Clinic-Sheboygan	1	<1%
	Vince Lombardi Cancer Clinic-Oshkosh	1	<1%
	West Michigan Cancer Center	1	<1%
	William Beaumont Hospital-Royal Oak	1	<1%
	William Beaumont Hospital-Troy	1	<1%
	Total ECOG-ACRIN	611	56.2%

Group	Institution Name	Total	% Accrual
SWOG			
	University of California Davis Comp Ca Center	23	2.1%
	Yale University	18	1.7%
	Henry Ford Hospital	15	1.4%
	Smilow Cancer Hospital Care Center-Trumbull	15	1.4%
	Loyola University Medical Center	13	1.2%
	Providence Hospital	11	1.0%
	Wayne State University/Karmanos Cancer Institute	11	1.0%
	Smilow Cancer Hospital Care Ctr at Saint Francis	9	<1%

University of Michigan Comprehensive Cancer Center	9	<1%
University of Texas Hlth Science Ctr @ San Antonio	9	<1%
Kansas City Veterans Affairs Medical Center	6	<1%
Mercy Hospital Saint Louis	6	<1%
William Beaumont Hospital-Royal Oak	6	<1%
Alta Bates Summit Medical Center-Herrick Campus	5	<1%
Kaiser Permanente-Oakland	5	<1%
Michael E DeBakey VA Medical Center	5	<1%
Smilow Cancer Hospital Care Center-Guiford	5	<1%
Ben Taub General Hospital	4	<1%
Cookeville Regional Medical Center	4	<1%
Kaiser Permanente-Franklin	4	<1%
Kaiser Permanente-Fresno	4	<1%
Kaiser Permanente-Lone Tree	4	<1%
Kaiser Permanente-Roseville	4	<1%
Kaiser Permanente-Santa Teresa-San Jose	4	<1%
Kaiser Permanente Medical Center-Santa Clara	4	<1%
Oregon Health and Science University	4	<1%
UC Irvine Health/Chao Family Comprehensive Ca Ctr	4	<1%
Cotton O'Neil Cancer Center / Stormont Vail Health	3	<1%
Margaret R Pardee Memorial Hospital	3	<1%
Central Care Cancer Center-Great Bend	2	<1%
Gene Upshaw Memorial Tahoe Forest Cancer Center	2	<1%
Kaiser Permanente-Modesto	2	<1%
Kaiser Permanente-South Sacramento	2	<1%
Park Ridge Health	2	<1%
Saint Jude Medical Center	2	<1%
Smilow Cancer Hospital-Waterbury Care Center	2	<1%
Veteran's Administration Medical Center	2	<1%
Ann M Wierman MD LTD	1	<1%
Asheville Hematology-Oncology Associates	1	<1%
Benefis Healthcare- Sletten Cancer Institute	1	<1%
CHI Health Saint Francis	1	<1%
Dayton Physicians LLC-Miami Valley South	1	<1%
Eisenhower Medical Center	1	<1%
Fremont - Rideout Cancer Center	1	<1%

	Kaiser Permanente-Fremont	1	<1%
	Kaiser Permanente-Richmond	1	<1%
	Kaiser Permanente-San Rafael	1	<1%
	Kaiser Permanente-Stockton	1	<1%
	Kaiser Permanente-Vallejo	1	<1%
	Kaiser Permanente-Walnut Creek	1	<1%
	Kaiser Permanente-Sacramento	1	<1%
	Kootenai Cancer Center	1	<1%
	McLaren Cancer Institute-Lapeer Campus	1	<1%
	Mid-Michigan Medical Center-Midland	1	<1%
	Oncology Hematology Care Inc-Crestview	1	<1%
	Palo Alto Medical Foundation-Santa Cruz	1	<1%
	Sacred Heart Hospital	1	<1%
	Saint Vincent Healthcare	1	<1%
	Singh and Arora Hematology Oncology PC	1	<1%
	Smilow Cancer Hospital-Orange Care Center	1	<1%
	Smilow Cancer Hospital Care Center-Fairfield	1	<1%
	Straub Clinic and Hospital	1	<1%
	Yale-New Haven Hospital North Haven Medical Center	1	<1%
	Total SWOG	259	23.8%

Group	Institution Name	Total	% Accrual
ALLIANCE			
	Saint Francis Cancer Center	16	1.5%
	Walter Reed National Military Medical Center	12	1.1%
	Wake Forest University Health Sciences	9	<1%
	Fort Wayne Med Oncology and Hem Inc-Parkview	8	<1%
	University of Nebraska Medical Center	8	<1%
	Eastern Maine Medical Center Cancer Care	4	<1%
	Oncare Hawaii Inc-POB II	4	<1%
	Sanford Roger Maris Cancer Center	4	<1%
	Spartanburg Medical Center	4	<1%
	Adams Cancer Center	3	<1%
	Good Samaritan Hospital - Dayton	3	<1%

Lowell General Hospital	3	<1%
Mission Hospital Inc-Memorial Campus	3	<1%
Oncology Hematology Care Inc-Crestview	3	<1%
ProHealth Oconomowoc Memorial Hospital	3	<1%
Essentia Health Cancer Center	2	<1%
MedStar Georgetown University Hospital	2	<1%
Saint Vincent Healthcare	2	<1%
State Univ of New York Upstate Medical Univ	2	<1%
WellSpan Health-York Hospital	2	<1%
Asheville Hematology-Oncology Associates	1	<1%
Central Care Cancer Center-Bolivar	1	<1%
Cone Health Cancer Center	1	<1%
Dayton Physician LLC-Miami Valley Hospital North	1	<1%
Essentia Health Virginia Clinic	1	<1%
Fort Wayne Med Onc and Hem Inc-Jefferson Blvd	1	<1%
Iredell Memorial Hospital	1	<1%
Kettering Medical Center	1	<1%
Legacy Good Samaritan Hospital and Medical Center	1	<1%
Mayo Clinic in Arizona	1	<1%
Mercy Hospital Springfield	1	<1%
Missouri Baptist Medical Center	1	<1%
Nebraska Hematology and Oncology	1	<1%
OnCare Hawaii-Liliha	1	<1%
Oncare Hawaii Inc-Kuakini	1	<1%
Oncare Hawaii Inc-Pali Momi	1	<1%
OptumCare Cancer Care at Fort Apache	1	<1%
ProHealth D N Greenwald Center	1	<1%
Randolph Hospital	1	<1%
Rapid City Regional Hospital	1	<1%
Saint Joseph Mercy Hospital	1	<1%
Univ of Iowa Healthcare Ca Services Quad Cities	1	<1%
University of New Mexico Cancer Center	1	<1%
UW Cancer Center at ProHealth Care	1	<1%
Total ALLIANCE	121	11.1%

Group	Institution Name	Total	% Accrual
NRG			
	University of Oklahoma Health Sciences Center	9	<1%
	Oklahoma Cancer Specialists & Res Institute-Tulsa	6	<1%
	Reading Hospital	6	<1%
	AMITA Health Alexian Brothers Medical Center	5	<1%
	Greenville Health System Cancer Institute-Eastside	5	<1%
	Sanford Roger Maris Cancer Center	4	<1%
	Southeastern Medical Oncology Center-Goldsboro	4	<1%
	AMITA Health Cancer Institute and Outpatient Ctr	3	<1%
	Greenville Health System Cancer Institute-Seneca	3	<1%
	Memorial Medical Center-Las Cruces	3	<1%
	Southeastern Medical Oncology Center-Jacksonville	3	<1%
	University of New Mexico Cancer Center	3	<1%
	West Virginia University Charleston Division	3	<1%
	Avera Saint Luke's Hospital and Cancer Center	2	<1%
	Greater Dayton Cancer Center	2	<1%
	Kaiser Permanente-Lone Tree	2	<1%
	MedStar Franklin Square Med Ctr/Weinberg Ca Inst	2	<1%
	Northwestern Medicine Cancer Center Warrenville	2	<1%
	The Community Hospital	2	<1%
	UW Cancer Center at ProHealth Care	2	<1%
	Alta Bates Summit Medical Center-Herrick Campus	1	<1%
	Ann M Wierman MD LTD	1	<1%
	Aurora BayCare Medical Center	1	<1%
	Aurora Saint Luke's Medical Center	1	<1%
	California Pacific Medical Center-Pacific Campus	1	<1%
	Columbus Oncology and Hematology Associates Inc	1	<1%
	Cotton O'Neil Cancer Center / Stormont Vail Health	1	<1%
	Ephrata Cancer Center	1	<1%
	Essentia Health Cancer Center	1	<1%
	Flaget Memorial Hospital	1	<1%
	Frederick Memorial Hospital	1	<1%
	Greenville Health System Cancer Inst-Spartanburg	1	<1%
	Greenville Health System Cancer Institute-Faris	1	<1%

Helen F Graham Cancer Center	1	<1%
Kaiser Permanente-Franklin	1	<1%
Marshfield Clinic-Weston Center	1	<1%
MedStar Union Memorial Hospital	1	<1%
Michigan State University Clinical Center	1	<1%
Mills-Peninsula Medical Center	1	<1%
Mountain Blue Cancer Care Center-Swedish	1	<1%
Palo Alto Medical Foundation Health Care	1	<1%
ProMedica Flower Hospital	1	<1%
Straub Clinic and Hospital	1	<1%
Sutter Solano Medical Center/Cancer Center	1	<1%
The Mark H Zangmeister Center	1	<1%
Total NRG	96	8.8%

^Some sites attribute accrual to different cooperative groups; 272 unique sites enrolled 1087 patients

31. REFERENCES

1. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35**: 549-56.
2. Freidlin B, Korn EL. Stopping clinical trials early for benefit: impact on estimation. *Clin Trials* 2009; **6**(2): 119-25.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958; **53**: 457-81.
4. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17**(8): e328-46.

ECOG-ACRIN cancer research group
Reshaping the future of patient care

E1A11

Randomized Phase III Trial of Bortezomib, L**EN**alidomide and Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide and Dexamethasone (CRd) Followed by Limited or Indefinite **DUR**ation Lenalidomide Mainten**ANCE** in Patients with Newly Diagnosed Symptomatic Multiple Myeloma (ENDURANCE)

Rev. Add11

STUDY CHAIR:	Shaji Kumar, M.D.
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Version Date: September 23, 2019
NCI Update Date: May 9, 2017

Rev. 5/14, 9/14

STUDY PARTICIPANTS

US Sites Only
ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG

Rev. Add11

NCTN STUDY CHAMPIONS

SWOG: Jeffrey Zonder, M.D.
CALGB: Edward A. Faber Jr., D.O., M.S.

ACTIVATION DATE

November 13, 2013
Addendum #1 – Incorporated Prior to Activation
Update #1 – Incorporated Prior to Activation
Update #2 – Incorporated Prior to Activation
Addendum #2 – 5/14
Addendum #3 – 9/14
Addendum #4 – 10/14
Addendum #5 – 2/15
Addendum #6 – 9/15
Addendum #7 – 11/15
Addendum #8 – 7/16
Update #3 – 5/17
Addendum #9 – 9/17
Addendum #10 - 9/17
Addendum #11
Addendum #12
Addendum #13
Addendum #14

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Agents	IND#	NSC#	Supplier
Carfilzomib	118503	756640	Amgen, Inc (formerly Onyx)
Lenalidomide		703813	Commercially available
Bortezomib		681239	Commercially available
Dexamethasone		34521	Commercially available

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Rev. 5/14
Rev. Add11

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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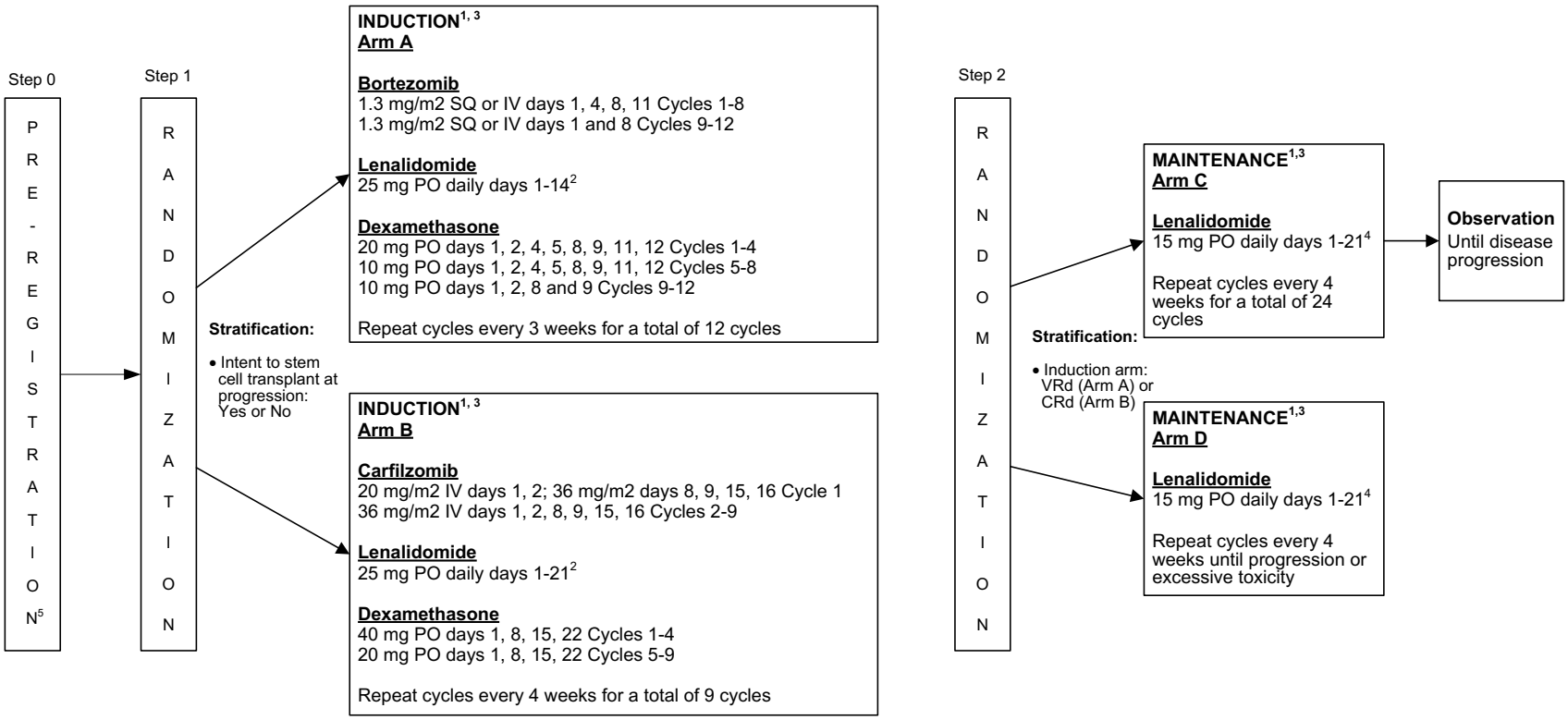
Schema



Rev. 7/17 Accrual Goal: 1,080 patients with newly diagnosed, standard risk myeloma (see section 3.1.2 for definition of standard risk)

1. Patients can mobilize stem cells any time following 4 cycles (Arm A) or 3 cycles (Arm B) of induction therapy. If stem cells are harvested, interruption of treatment cycles for up to 35 days is allowed for completion of stem cell collection. While stem cell collection is strongly encouraged for transplant eligible patients, it is not required for protocol participation.
2. In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥60 ml/min, the dose can be increased to 25 mg provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.
3. At discretion of enrolling MD if considered appropriate, patients randomized to Arm A (VRd) can receive bortezomib injections under care of a local oncologist, returning to the enrolling institution only at the beginning of each cycle. Patients randomized to Arm B (CRd) are required to receive Carfilzomib injections at the enrolling institution. During maintenance and observation (Arms C and D), patients will have to be seen at the enrolling institution once every three months.
4. In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 15 mg provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.

Rev. 5/14 5. Submission of pre-study specimens per patient consent.

1. Introduction

1.1 Initial therapy of multiple myeloma

The treatment paradigms for multiple myeloma have undergone a significant change in the past decade.[1-3] A decade ago, patients who were considered eligible for transplant underwent the procedure after a brief duration of therapy with a steroid based regimen with or without adriamycin. Patients ineligible for transplant went on to receive melphalan and prednisone. With these treatment approaches patients had a median survival of 3-4 years, with nearly 10-20% of patients dying in the first year after diagnosis. During the last decade several new drugs were introduced such as thalidomide and its analogue lenalidomide and the proteasome inhibitor bortezomib and these along with continued use of transplant has led to improved survival in myeloma.[4]In fact, in the recent clinical trials 3-year survival has approached 90% and 1-year mortality has dropped to under 2%.[5] This progress has come through a series of investigations examining the efficacy of the new drugs used in various combinations and sequences. Initial trials in the relapsed setting confirmed significant clinical activity for all these new drugs. This was followed by several clinical trials that examined the combination of novel agents with dexamethasone in the setting of newly diagnosed disease. The studies consistently demonstrated superior response rates, deeper responses, and improved progression-free survival for patients undergoing initial therapy with novel agents.[5-8] The trials examined the role of the new drugs in the context of transplant eligible and ineligible patients. This has been followed by three drug regimens that either combined the new drugs together or incorporated an alkylator drug to the novel agent-dexamethasone combination. These have included combinations of bortezomib and dexamethasone with thalidomide (VTD), lenalidomide (VRd) or cyclophosphamide (VCD).[6,7,9-11]

Of particular interest is the VRd regimen, which has shown high efficacy rates and is increasingly used for initial therapy in the community.[6,10,11] It is also the experimental arm in the S0777 trial, which has completed accrual. Based on phase II studies VRd is expected to be the winner of the S0777 trial, and is therefore already incorporated as the standard initial therapy in a large international phase III trial (IFM/DFCI). This regimen has been associated with high response rates approaching 100% and deep responses with very good partial response rates and complete response rates of over 70 and 40% respectively. It has proven to be a highly effective initial therapy for patients planning stem cell transplantation with no significant effect on the ability to successfully mobilize stem cells.

Richardson et al evaluated the VRd combination in a phase 1/2 trial in previously untreated myeloma. Patients (N = 66) received 3-week cycles (n = 8) of bortezomib 1.0 or 1.3 mg/m^2 (days 1, 4, 8, 11), lenalidomide 15 to 25 mg (days 1-14), and dexamethasone 40 or 20 mg (days 1, 2, 4, 5, 8, 9, 11, 12).[6] The recommended phase 2 dose was bortezomib 1.3 mg/m^2, lenalidomide 25 mg, and dexamethasone 20 mg. The common toxicities included sensory neuropathy seen in 80% and fatigue in 64%. In addition, 32% reported neuropathic pain. Grade 3/4 hematologic toxicities included lymphopenia (14%), neutropenia (9%), and thrombocytopenia (6%). Rate of partial response was 100% in both the phase 2 population and overall, with 74% and 67% each achieving very good

partial response or better. With median follow-up of 21 months, estimated 18-month progression-free and overall survival for the combination treatment with or without transplantation were 75% and 97%, respectively.

In the EVOLUTION trial, patients were randomized to receive bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 and dexamethasone 40 mg d 1, 8, 15, with either cyclophosphamide 500 mg/m^2 d 1, 8 and lenalidomide 15 mg d 1–14 (VDCR), lenalidomide 25 mg d1-14 (VRd), cyclophosphamide 500 mg/m^2 d 1, 8 (VCD) or cyclophosphamide 500 mg/m^2 d 1, 8, 15 (VCD-mod) in a 21 day cycle (maximum 8 cycles).[10,11] This was followed by bortezomib 1.3 mg/m^2 (d 1, 8, 15, 22) for four 42-day maintenance cycles in all arms. VGPR or better was seen in 58, 51, 41 and 53% (CR rate of 25, 24, 22 and 47%) of patients (VDCR, VRd, VCD and VCD-mod arms, respectively); the corresponding progression-free survival (PFS) at 1 year was 86, 83, 93 and 100%, respectively. Common adverse events included hematological toxicities, peripheral neuropathy, fatigue, and GI disturbances. Overall no substantial advantage was noted with the addition of cyclophosphamide to VRd, but the regimen did lead to more hematological toxicities.

Although the results with VRd appear better than other regimens studied in the past, they also indicate a need for significant improvement both in terms of safety and efficacy. In the EVOLUTION trial, companion studies evaluating the presence of minimal residual disease demonstrated MRD positivity in nearly half of the patients obtaining a CR.[11] This clearly suggests that the quality of response can be further improved and if done without significant increase in toxicity could potentially improve the outcomes in these patients. Secondly, the VRd regimen, while demonstrating high efficacy, has also been associated with significant toxicity.[6] While hematological toxicity is universal for the treatments employed for many of the hematological malignancies and easily managed, neurological toxicity has been of significant concern. Development of peripheral neuropathy, even if low grade, can have significant impact on the patient quality of life. The rates of grade 2 and higher PN was nearly 50% in these studies. Even with once weekly and subcutaneous dosing, grade-3 neuropathy occurs in 5-10% of patients and painful and debilitating grade-2 neuropathy remains a problem. Unfortunately these studies did not employ any quality of life (QoL) assessment and hence the real impact on patients remains unknown. In a recent phase 3 trial of three different combinations of bortezomib used as initial therapy in transplant ineligible patients with newly diagnosed myeloma a significant drop in the QoL parameters was observed early on in the trial.[12]

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The results of the phase 3 trial of VRd compared with Rd (S0777) was recently reported. 232 patients were randomized to Rd and 242 patients to VRd[13]. Rd patients received lenalidomide 25 mg/day on days 1-21 and dexamethasone 40 mg/day on days 1, 8, 15 and 22 of a 28-day cycle. VRd patients received lenalidomide 25 mg/day on days 1-14 and dexamethasone 20/mg/day on days 1, 2, 4, 5, 8, 9, 11 and 12 plus bortezomib 1.3 mg/m2 IV push on days 1, 4, 8 and 11 of a 21-day cycle. Addition of bortezomib improved the PFS (hazard ratio 0.742, P = 0.0066) and OS (HR = 0.666; p-value = 0.0114) compared with lenalidomide and dexamethasone. Median PFS was 43 months (VRd) versus 31 months (Rd). Median OS was not reached (VRd) versus 63 months (Rd). The most common hematologic adverse events (≥ Grade 3 and at least possibly attributable to therapy) were low hemoglobin (RVd=13%; Rd=16%), leukopenia

(RVd=14%; Rd=16%), lymphopenia (RVd=23%; Rd=18%), neutropenia (RVd=19%; Rd=21%), and thrombocytopenia (RVd=18%; Rd=14%). The most common non-hematologic adverse events (≥ Grade 3 and at least possibly attributable to therapy) were: fatigue (RVd=16%; Rd=14%), sensory neuropathy (RVd=23%; Rd=3%), hyperglycemia (RVd=7%; Rd=11%), thrombosis/embolism (RVd=8%; Rd=9%), hypokalemia (RVd=9%; Rd=6%), muscle weakness (RVd=7%; Rd=4%), diarrhea (RVd=8%; Rd=2%), and dehydration (RVd=8%; Rd=2%). As expected ≥ Grade 3 neuropathy was more frequent with VRd (24% vs. 5%: $P < 0.0001$).

1.2 Carfilzomib

More recently, development of a next generation proteasome inhibitor namely carfilzomib (Cfz), has introduced the possibility of enhancing the efficacy of a three drug combination with significantly reduced toxicity. Carfilzomib is also known as PR-171, which targets the chymotrypsin-like activity of the 20S proteasome.[14-18] Carfilzomib is a selective inhibitor and binds most specifically to the chymotrypsin-like protease, with less activity against the other subunits.[19] In addition, carfilzomib demonstrates less reactivity against non-proteasomal proteases when compared to bortezomib.

Carfilzomib has been shown to have significant anti-myeloma activity in the setting of relapsed myeloma both in bortezomib naïve as well as bortezomib refractory patients.[20-24] The toxicity pattern suggested that the drug is well tolerated, and in particular seemed to have very low rate of neuropathy. In the initial phase 1 study, Carfilzomib was administered intravenously on 2 consecutive days for 3 weeks of a 4-week cycle at doses ranging from 1.2 to 27 mg/m2.[20] The dose escalation phase enrolled 37 patients followed by a dose-expansion phase with 11 patients. During dose expansion, carfilzomib was administered starting with 20 mg/m2 during the first week (days 1, 2) and then escalated to 27 mg/m2 thereafter. A maximum tolerated dose (MTD) was not reached. The main hematologic grade 3 or higher adverse events were anemia and thrombocytopenia. Notably, there were no observations of grade III or more peripheral neuropathy. Carfilzomib was cleared rapidly with an elimination half-life of less than 30 minutes but still induced dose-dependent inhibition of the 20S chymotrypsin-like proteasome activity. At doses of 15 to 27 mg/m2, there was evidence of activity among patients with multiple myeloma and with non-Hodgkin lymphoma. In PX-171-003-A0 (20 mg/m2 carfilzomib throughout), 46 patients with relapsed and refractory multiple myeloma were enrolled.[21] All patients had progressive disease on study entry and 100% had received prior bortezomib alone or in combination with other agents; 70% were refractory to prior bortezomib, and 22% were removed from bortezomib therapy due to development of severe peripheral neuropathy. The response rate using IMWG criteria was 16.7% (7 PRs) and there were an additional 3 (7%) durable (> 6-week) MRs; the duration of response (DOR) was similar for MRs and PRs at ~7.2 months. Study PX-171-003-A1 enrolled 266 relapsed and refractory patients at 20 mg/m^2 for Cycle 1, and escalation to 27 mg/m^2 thereafter for patients who tolerate the drug.[22] In this trial, 82% of the patients had at least 4 prior therapies, 84% were refractory or intolerant to bortezomib and 95% were refractory to the last therapy. The responses included 6% patients with VGPR or better, 18% with a PR and 13% with an MR. In addition, stable disease was seen in 32% of patients. The median PFS was 3.7 months and the median OS was 15.6 months.

PX-171-004 was designed to assess the effect of carfilzomib on patients with MM who had 1–3 prior therapies, i.e., were less heavily pretreated than those in PX-171-003.[23,24] In the cohort of patients with at least one prior bortezomib based therapy, the overall response rate was 17.1% and the median duration of response was over 10.6 months with the median time to progression of 4.6 months. The most common adverse events were fatigue (62.9%), nausea (60.0%), and vomiting (42.9%). No exacerbation of baseline peripheral neuropathy was observed. In the cohort of patients with bortezomib naïve disease (n=129), patients received either 20 mg/m2 throughout (cohort 1) or only for cycle 1 followed by 27 mg/m2 for the remaining cycles (cohort 2). The overall response rate was 42.4% in Cohort 1 and 52.2% in Cohort 2. Median duration of response was 13.1 months and not reached, and median time to progression was 8.3 months and not reached, respectively.

Toxicities have generally been manageable. In relapsed or refractory MM patients treated at 20–27 mg/m^2, the most common adverse events (AEs) are anemia, fatigue, nausea, diarrhea, and cyclic thrombocytopenia. Peripheral neuropathy of any grade regardless of relationship to study drug is < 15% despite the majority of patients entering these studies with existing Grade 1 or 2 peripheral neuropathy. The most common Grade 3/4 AEs are anemia (14%), thrombocytopenia (12%), pneumonia (6%), and fatigue (5%). Importantly, Grade 3/4 neutropenia occurs in < 5% and Grade 3/4 peripheral neuropathy in < 3% (includes neuropathy, peripheral neuropathy, and neuropathic pain), despite the fact that nearly all of the patients have these conditions as a result of their prior drug therapies and disease. These results are consistent with the lack of myelosuppressive and neuropathic effects of carfilzomib in preclinical studies.

In the newly diagnosed setting, the combination of carfilzomib with lenalidomide and dexamethasone was evaluated in a recent phase 1/2 trial.[25] After 4 cycles of therapy all patients had a response including 59% with VGPR or better and 36% with a nCR or better. After a median of 12 cycles (range, 1-25), 62% (N = 53) achieved at least near-complete response (CR) and 42% stringent CR. Responses were rapid and improved during treatment. In 36 patients completing 8 or more cycles, 78% reached at least near CR and 61% stringent CR. The toxicities were mostly hematologic and no grade 3 or higher neuropathy was seen. Grade 1 or 2 neuropathy was seen in less than 10% of patients. Stem cell collection was successful in all patients in whom it was attempted. At 6-month median follow up, no disease progression was observed. To put these results in perspective we need to evaluate these in the context of the phase 2 VRd trials. In the DFCI study, responses to VRd after 4 cycles of treatment included CR + nCR in 6%, ≥ VGPR in 11%, and ≥ PR in 53%. In the Evolution trial, the CR, ≥VGPR and ≥ PR rates after 4 cycles were 9%, 32% and 73% respectively. In contrast the CR + nCR, ≥ VGPR and ≥ PR rates after 4 cycles in the phase 2 CRd trial were 36%, 59% and 100% respectively.

The overall CR rate with CRd is much higher than those seen with VRd. Higher CR rate have been shown to translate into better overall survival both in the non-transplant and transplant setting.[26-28]This is particularly true when more sensitive tests of minimal residual disease like flow cytometry or PCR have been used to demonstrate a more profound reduction of tumor burden.[29] The comparisons of CRd and VRd here are non-randomized data, but illustrate the need to test CRd against VRd in a phase III trial. Further grade 2 or higher neuropathy rates with

CRd are < 5% versus nearly 30% with VRd. These results clearly demonstrate the potential for CRd to further improve upon the results of the current three-drug regimen of VRd in myeloma, while simultaneously improving the toxicity profile and most likely QoL. The impact of prolonged therapy on the eventual depth of response is often underappreciated when the attention is focused solely on the response rates with initial cycles. In the initial lenalidomide-dexamethasone trials in newly diagnosed myeloma, patients who stayed on therapy beyond a year had VGPR rates comparable to that seen in the context of transplant with a deepening of responses seen for up to 18 months after initiating therapy.[30] In contrast, nearly half of the patients go off study when treated with VRd due to various toxicities including neuropathy. Ability to continue an effective regimen similar to VRd for longer duration will lead to deeper responses than would be anticipated from early results of the trials. It is possible that the significant anti-myeloma activity demonstrated by the combination along with the ability to continue therapy for longer term will result in deeper responses and higher percentage of MRD negative disease, in turn translating into improved overall survival.

1.3 Role of maintenance therapy in myeloma

The concept of maintenance therapy has been tested mostly in the setting of high dose therapy and autologous stem cell transplantation.[31] Patients invariably relapse after initial treatment strategies including SCT and various trials have attempted to maintain the SCT response through maintenance approaches. Initial trials prior to the availability of the new drugs have examined steroids or interferon, and a small randomized clinical trial of interferon (3×10^6 units/m^2) subcutaneously 3 times weekly, following initial ASCT, suggested a modest improvement in EFS.[32] The IFM99-02 trial randomized patients with standard-risk MM (Beta 2 microglobulin [B2M] < 3, no deletion 13 (del 13)) to receive no maintenance, pamidronate, or pamidronate plus thalidomide after tandem SCT.[33] Thalidomide was associated with higher response rates, improved EFS (52% vs. 36% with no maintenance) and improved overall survival (4-year estimated survival from diagnosis with thalidomide (87%) compared with no maintenance (77%)). At least 4 different randomized trials have examined the role of thalidomide as a maintenance therapy post-SCT.[33-36] A meta-analysis of these trials support the improved progression-free survival, but remains equivocal in terms of overall survival improvement.[37] In addition, high discontinuation rate has been noted in all these studies due to toxicity. In particular the Canadian study showed worsening of QoL parameters among patients getting thalidomide maintenance.

A phase 3 study from the IFM enrolled 614 patients < 65 years, with non-progressive disease, within 6 months after upfront ASCT.[38] Patients received 2 cycles of consolidation with lenalidomide 25 mg daily for 3 of 4 weeks followed by a randomization to lenalidomide 10-15 mg/d until relapse or to placebo (n=307 in each arm). Patients were stratified according to B2M, del13, and VGPR to initial therapy. There was an improvement in the PFS with maintenance therapy, with a median PFS of 42 months for lenalidomide vs. 24 months for the placebo. The improvement in the PFS was seen in all the subgroups based on stratification. With the current follow up, overall survival (OS) remains identical in the two groups. In a very similar trial, McCarthy and colleagues randomized patients 70 years or younger, who attained a stable disease or better with their induction

therapy and underwent ASCT within one year of diagnosis, to lenalidomide (5-15 mg/day) or placebo until relapse.[39] Patients were stratified based on B2M and use of thalidomide or lenalidomide therapy during induction. Patients were enrolled prior to the ASCT, with 19% of the 568 enrolled dropping out before randomization. As expected, grade 3 and 4 adverse events were significantly higher in the maintenance arm, with hematological toxicities being the common events. The median time to progression was 42 months with lenalidomide compared to 21.8 months with the placebo, results very similar to the French study. More recent updates suggest an improvement in the overall survival for the lenalidomide arm in this CALGB study. There are differences, however, between the two trials in terms of the design as well as duration of therapy. Patients in the IFM trial received uniform induction therapy unlike the CALGB trial. Patients in the IFM study received 2 cycles of consolidation with lenalidomide before starting maintenance. In addition, the IFM trial limited maintenance to approximately 24 months based on concerns regarding second malignancies and did not allow crossover. However, the CALGB trial allowed crossover from placebo arm to lenalidomide maintenance based on interim analysis and also allowed maintenance until progression.

Very few trials have explored the role of maintenance therapy outside the context of SCT prior to the advent of the new drugs. Three large recent trials have explored the role of maintenance therapy in the older patient population following a defined period of initial therapy with 3 or 4 drug combinations. In a recent multicenter phase 3 study (MM-015), Palumbo et al have evaluated the safety and efficacy of continuous lenalidomide treatment after MPR (MPR-R; n=152) versus MP (n=154) or MPR (n=153) in 459 newly diagnosed transplant ineligible MM patients who were ≥ 65 years of age.[40] The treatment schema consisted of melphalan 0.18 mg/kg on days 1-4, prednisone 2 mg/kg on days 1-4, with (MPR or MPR-R) or without (MP) lenalidomide 10 mg/day on days 1-21 for nine 28-day cycles. Following 9 cycles of MPR, patients received maintenance lenalidomide (10 mg/day on days 1-21) (MPR-R) or placebo (MPR) until progression; MP patients also received placebo until progression. After a median follow-up of 21 months, MPR-R compared with MP resulted in a higher overall RR (77% vs. 50%, $p < .001$) and higher rates of CR (16% vs. 4%, $p < .001$). In addition, MPR-R reduced the risk of disease progression by 58% compared with MP (HR =0.423, $p < .001$) and resulted in a higher 2-year PFS rate (55% vs. 16%). Adverse events associated with MPR-R and MP resulted in treatment discontinuation in 20% and 8% patients, respectively. In another trial, patients receiving initial therapy with bortezomib, thalidomide, melphalan and prednisone were continued on maintenance with bortezomib and thalidomide, resulting in superior PFS compared to the control group of patients receiving VMP.[41] Finally, a Spanish trial randomized patients to initial therapy with VMP or VTP and then randomized all patients at the end of therapy to maintenance with VT or VP and showed an improved PFS in patients getting VT maintenance. In all these trials patients assigned to receive maintenance therapy with an IMiD or bortezomib + IMiD combination appeared to have improvements in the depth of response and better progression-free survival.[42]

However, significant questions remain as to the duration of maintenance therapy with different trials sporting different designs in terms of duration of therapy. Given the data showing that the rate of second malignancies may be higher after 24 months of maintenance, and the cost and side effects of maintenance, it has

been suggested that two years of lenalidomide maintenance is sufficient, and the current IFM/DFCI trial has been amended to limit maintenance duration to two years. But the major improvement in OS seen with lenalidomide maintenance was with therapy until progression. Hence, the issue of optimal duration of maintenance is pressing.

1.4 Rationale for the current trial

We hypothesize that lenalidomide (R) maintenance following induction with a proteasome inhibitor–IMiD combination given until progression will result in significant overall survival (OS) improvement compared to lenalidomide maintenance therapy limited to 24 months. In addition, we hypothesize that the combination of carfilzomib, lenalidomide and dexamethasone (CRd) used as induction therapy will lead to deeper responses, longer progression-free survival (PFS), reduced toxicity and improved QoL compared with induction therapy using a combination of bortezomib, lenalidomide and dexamethasone (VRd).

This trial of VRd versus CRd for induction therapy will provide an excellent opportunity to address the maintenance question since very few patients are expected to progress in either arm during the induction therapy (approximately 8.3 months from enrollment), prior to the start of the maintenance phase. The duration of maintenance is not expected to have any differential effect between the two induction arms, and conversely, the induction arm assignment is not expected to have any differential benefit between the two maintenance durations.

The results of this proposed trial would form a stepping-stone for future investigations and has the potential to alter current clinical practice. If the trial demonstrates better overall survival with indefinite maintenance, then a clinically relevant and informed decision for adoption of that strategy can be made in conjunction with the QoL data and long-term toxicity. If no overall survival improvement is seen with indefinite maintenance, then limited maintenance will become the default approach and this will result in immense cost savings. Examination of the two induction approaches will lead to adoption of CRd as standard induction therapy, if it indeed demonstrates improved PFS in the context of reduced toxicity and better preserved QoL parameters. In contrast, if no improvement is seen, then the less expensive regimen can be used as the standard induction regimen.

1.5 Quality of Life

Patient reported outcomes (PRO) that measure the impact of disease and treatment on well-being from a physical, functional, emotional and social perspective are an important part of the benefit equation. Quality of Life assessments have been incorporated into prior phase 3 multiple myeloma clinical trials. In fact, one of the earliest studies to address this was the phase 3 trial comparing an early SCT to a delayed SCT.[43] It was concluded that an early SCT was preferable based on the QoL estimates analyzed, which was defined as the time without symptoms and toxicity (Q-TWiST). More recently there has been increased interest in assessing QoL among patients with MM given significant improvement of survival observed as well as the availability of different treatment options. QoL studies have been very useful in putting the results of these phase 3 trials in perspective. A recent phase 3 trial of thalidomide maintenance reported improvement in PFS with maintenance therapy, but significant worsening of all

the QoL parameters studied.[35] Patients' health-related quality of life was assessed using EORTC QLQ-C30 instrument in combination with a disease specific module. Assessments were performed every 2 months to 6 months then Q3 monthly to 5 years. A change score of 10 points from baseline was defined as clinically relevant. In a more recent phase 3 trial comparing three different bortezomib combinations in non-transplant eligible patients (bortezomib-dexamethasone, bortezomib-thalidomide-dexamethasone, bortezomib-melphalan-prednisone, followed by bortezomib maintenance therapy), patient-reported QoL was recorded using the EORTC QLQ-C30 questionnaire.[44] Decline in QoL parameters were observed in the early phases of therapy in all groups with recovery over time. These results demonstrate the feasibility of conducting health-related QoL assessments in the context of multicenter clinical trials as well as its value in reaching the eventual conclusions.

Regarding induction therapy, health-related QoL has neither been reported for patients with newly diagnosed MM treated with CRd nor a comparison been made to VRd. Therefore, QoL will need to be assessed comprehensively during induction utilizing PRO measures to elucidate potential advantages and expand understanding of QoL at key clinical decision points during and at the end of induction therapy. We hypothesize that CRd will be associated with better QoL than VRd due to a more rapid reduction in disease specific symptom burden and fewer treatment specific side-effects. We will specifically evaluate the relationship between early induction response status (at 2.8 months) and change in QoL over this period with the hypothesis that responders have comparatively better QoL than non-responders, a favorable outcome for the CRd arm presuming patients treated with CRd have quicker and deeper responses. This assessment will have clinical translational value, as this is often the decision node from stem cell transplantation standpoint. Patients and physicians often make a decision to proceed to stem cell transplant or to continue therapy based on a variety of factors including patient age, patient and physician preference, response status, and toxicity from induction therapy. Differences seen at this time point in the QoL parameters may be informative with respect to this decision making process. Cumulative treatment specific side-effects i.e. anticipated greater neurotoxicity with VRd will also be assessed formally by comparing changes in QoL from baseline to the end of induction therapy between arms. Further, it is believed that QoL metrics along with response status will influence decision-making regarding initiation of non-protocol therapy including stem cell transplant, completion of induction and continuation to maintenance. With additional assessments at the intermediate time points of 5.5 months and/or early discontinuation of therapy incorporated, we will be able to identify patterns of QoL associated with such decisions. The QoL parameters at the end of the induction therapy will also provide valuable information regarding patients' decisions and preference for maintenance therapy. Finally, we have limited information regarding the toxicities associated with Carfilzomib, as there is limited long-term experience with this drug. Whether any of the other described toxicities with carfilzomib, such as the cardiac and pulmonary symptoms, will have any impact on the QoL parameters is critical to decision making regarding choice of therapy in future.

Maintenance therapy following induction therapy with VRd or CRd for patients with newly diagnosed standard risk MM may or may not improve overall survival. Assessing QoL during maintenance utilizing PRO measures will, therefore, be of critical importance to the evaluation of the overall benefit of this therapeutic

strategy and its clinical utility. We hypothesize that during the early maintenance phase (first 6 cycles), QoL will improve with less intense therapy provided and recovery from induction side effects. We will evaluate whether the degree and rate of improvement is dependent on type of previous induction therapy. QoL assessments at 1 year (cycle 12) and 2 years (cycle 24) post maintenance randomization will provide valuable longitudinal data to quantify the impact of maintenance therapy generally on patient QoL. Finally, the QoL impact associated with 2 opposite maintenance strategies will be examined. It is hypothesized that transitioning off maintenance after 24 cycles (~2 years post maintenance randomization) and onto observation confers improved QoL with cessation of treatment but that eventually QoL diminishes in these patients due to symptoms of recurrent disease compared to those patients continuing on indefinite maintenance therapy. QoL analyses include formal comparisons of the change in QoL from 2 years (cycle 24) to 3 years (cycle 36 of maintenance/ observation month 33) and 5 years (cycle 60 of maintenance/observation month 55) post maintenance randomization parallel to 1- and 3-years since departure to either observation or indefinite maintenance. To interpret maintenance analyses, it will be essential to know patient adherence to treatment. Frequent QoL assessments during maintenance will be matched with careful recording of actual treatment received over the given period such that the impact of symptom burden and treatment-related side effects on observed adherence to therapy can be evaluated.

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1.6 Laboratory Research Studies

1.6.1 Minimal Residual Disease and Plasma Cell Phenotyping

Currently 30-40% of patients achieve a CR with initial therapy. In most cases, patients classified as CR in reality have minimal residual disease (MRD) since (i) many such patients relapse, and (ii) residual clonal disease is detectable in most by more sensitive techniques such as multiparameter flow cytometry and PCR based techniques.

Several studies have demonstrated the clinical significance of obtaining MRD status following different therapies.The two most commonly used modalities are multiparameter flow cytometry and RT-PCR based methods. In a recent study from the novel agent era, Ladetto et al demonstrated that achievement of MRD negative status using ASO-PCR translates to improved PFS as well as overall survival in patients with myeloma undergoing bortezomib, thalidomide and dexamethasone induction followed by stem cell transplant and additional consolidation.[45] While it affords significant sensitivity, attempts to use RT-PCR have been compromised by the significant somatic hypermutation seen in the immunoglobulin gene regions, precluding development of universal probes. As a result, the majority of studies so far has used allele specific oligonucleotide (ASO)-PCR for MRD detection.[45-49] This requires development of patient specific probes at baseline and thus precludes application in all patients as the process may be unsuccessful in many. This can be a particular problem in multicenter clinical trials where baseline samples may not always be of sufficient quality for development of patient specific probes. In contrast, flow cytometry has grown increasingly more powerful in terms of the number of markers that can be analyzed

simultaneously as well as the speed of acquisition, allowing analysis of a large number of events in a short time frame.[29,50-53] Use of surface phenotype stabilizing agents has also allowed use of this methodology in multicenter setting. Various surface markers in addition to cytoplasmic kappa and lambda expression have been used in different studies to characterize the clonal/ myeloma plasma cell. These include in addition to the traditional CD138/38/45, markers such as 56, 19, 20, 27, 28 and 117. We have previously used this approach in a multicenter, randomized, phase 2 trial of various bortezomib combinations and successfully analyzed all samples at baseline and in a majority of patients at the time of the clinically suspected CR.[10,11]

We will determine minimal residual disease positivity at various stages of treatment, among all patients. Bone marrow aspirates will be evaluated at baseline for determination of baseline phenotype and at predetermined time points during therapy for presence of clonal plasma cells as well as the ratio of clonal to non-clonal plasma cells. These time points are after 3 and 9 cycles (Arm B) or 4 and 12 cycles (Arm A) of induction therapy associated with 2.8 months and 8.3 months from induction randomization, as well as two and three years after starting maintenance therapy. In addition, the tests will be performed on any sample obtained for confirmation of CR in between these time points.

We hypothesize that MRD negativity will be significantly higher with CRd compared with VRd at the end of the induction. The time to MRD negativity in the subset of patients that achieve MRD negativity is expected to be more rapid in the CRd group as demonstrated by higher proportions of MRD negative disease at 2.8 months after start of induction therapy. Additionally, we hypothesize that the MRD negative status at the end of three years after start of maintenance will be significantly higher in the group of patients receiving continuous lenalidomide.

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1.6.2 Integrated Study of Genomic Sequencing (collaboration with Multiple Myeloma Research Foundation (MMRF) through the CoMMpass Study)

Application of modern genomic analyses to myeloma cells has given us a better understanding of the genetic complexity in this disease. Previously FISH based-approaches demonstrated presence of translocations, trisomies or deletions and amplifications in nearly all patients with myeloma. While some changes such as trisomies and translocations were present in nearly all cells, other abnormalities such as deletions were progressively acquired during disease evolution. Subsequently, the use of gene expression profiling demonstrated critical changes in the expression of a variety of genes, which then led to development of several GEP-based risk stratification systems. In one study, use of array CGH, RNA sequencing and FISH studies was utilized to demonstrate alternating dominance of different clones and eventual dominance of a minor clone leading to refractory disease. Several studies in the recent past have examined the

myeloma genome for mutations in patients with relapsed disease as well as in newly diagnosed patients. These have demonstrated recurrent mutations involving a limited set of genes and less common mutations involving a large number of genes. In terms of genetic heterogeneity, myeloma appears to be in the middle of the spectrum. In particular, mutations involving the N-Ras and K-Ras appear to be present in nearly half of the patients. Limited results from clinical trials suggest that identification of the mutations can have a therapeutic value, with MEK inhibitors demonstrating clinical benefit in patients with Raf mutation. The implications of these mutations in the newly diagnosed patients and their prognostic value is less well understood, especially how they influence the response to primary therapy and the natural history of the disease. Walker et al recently performed whole-exome sequencing in 463 patients with newly diagnosed myeloma, enrolled onto the Myeloma XI trial. The study identified 15 significantly mutated genes: IRF4, KRAS, NRAS, MAX, HIST1H1E, RB1, EGR1, TP53, TRAF3, FAM46C, DIS3, BRAF, LTB, CYLD, and FGFR3. Mutations in the RAS (43%) and nuclear factor-κB (17%) pathways predominated, but though they did not have any prognostic effect, they could be targeted therapeutically. In contrast, mutations in CCND1 and DNA repair pathway alterations (TP53, ATM, ATR, and ZNFHX4 mutations) were associated with inferior survival. However, those in IRF4 and EGR1 are associated with a favorable overall survival. This study is significantly limited by the treatment regimens used, which consisted predominantly on cyclophosphamide and thalidomide, neither of which constitute the current generation of triplets being used for initial therapy of myeloma. A recent phase 3 trial in SWOG demonstrated improved overall survival with the VRD regimen compared with Rd, making VRd (the control arm of this trial) the standard induction regimen. Understanding the clonal evolution of the myeloma cells, especially on therapy, will give us more insights into the mechanisms of resistance to the commonly used drugs and also provide us with potential therapeutic targets in these patients. It is important that we build on our knowledge in the context of current generation therapies such as VRd and even the next generation of therapy which is likely represented by the experimental arm of this trial, namely CRd. Given this, genomic dissection of samples from this trial will provide us with information that cannot only help us understand the molecular basis of any difference seen between the two arms of ENDURANCE, but also inform us to intelligently design the next trial.

CoMMpass Study: The MMRF CoMMpass Study was designed to expand our understanding of the genomic basis of myeloma and the response to treatment as well as the relationship with the longitudinal evolution of the disease. The study opened in July of 2011 and now includes 1,000 patients from more than 100 sites in the United States, Canada and European Union. Data from the MMRF CoMMpass Study is made available to researchers via the MMRF's Researcher Gateway (https://research.themmrf.org), an online, open-access portal designed to make key genomic and clinical data available for

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additional study. The MMRF CoMMpass Study is being supported through a public-private partnership of patient donors and industry partners.

Rev. Add11

1.7 Rationale for Tobacco Use Assessment

NOTE: Please refer to Appendix XIII for EAQ16T references

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited.

Tobacco use following a cancer diagnosis compromises treatment outcomes but is not well understood. About 10% to 30% of cancer patients are smoking at the time of diagnosis,[1–4,14,15] and the majority of cancer patients who smoke at diagnosis continue to smoke following diagnosis.[3,16] Quitting smoking upon cancer diagnosis may improve cancer treatment effectiveness, reduce risk of recurrence and of developing new primary tumors,[9–11,17–21] and improve chances of survival.[1,22–24] Conversely, continuing to smoke may result in diminished QOL,[1,25,26] treatment delays and increased treatment complications.[2,6–8,22,27–34]

Tobacco use following a cancer diagnosis may compromise patient reported outcomes. It is hypothesized that smoking may be used as a means of reducing symptom burden among cancer patients, which may be a barrier to smoking cessation. Relatedly, research has shown that cancer patients who are smoking experience more difficulty with physical and psychological symptom control, compared to nonsmokers. [35–38] Research is needed to examine how symptom levels differ, by tobacco use and exposure and how tobacco use changes may affect reported symptom burden.

National initiatives emphasize the importance of identifying tobacco use in cancer care settings. Smoking status was designated as a core objective in the 2010 federal government “Meaningful Use” electronic health record documentation.[39,40] In 2013, the American Association for Cancer Research (AACR) released guidelines emphasizing the provision of tobacco cessation services to cancer patients.[41] The American Society of Clinical Oncology (ASCO) recommends cessation counseling to all smokers by their second oncology visit as a core quality indicator.[42] The National Comprehensive Cancer Network (NCCN) published Smoking Cessation guidelines to formalize these initiatives.[43]

Integrated, evidence-based services are needed during cancer care. The USPHS Practice Guidelines recommend that evidence-based tobacco treatment be delivered to all smokers in health care settings, yet little progress has been made to integrate these guidelines into cancer care.[44] This is unfortunate, as cessation closer to the time of diagnosis results in a higher likelihood for continued

abstinence,[1,45–48] effective interventions exist,[1,45–48] and many cancer patients who smoke want to quit smoking.[45,46,49,50] Little work has been done to explore the delivery and effectiveness of tobacco treatment among racial/ethnic minority cancer patients who are at elevated risk of continued smoking.[51–53]

Tobacco use is often not being assessed or intervened upon during cancer care. Recent surveys of oncologists and of clinical practices at comprehensive cancer centers and community oncology settings demonstrate that assessment of tobacco dependence is lacking.[54–57] During treatment, most cancer patients do not get assistance with smoking cessation support.[58–60] Tobacco use assessments and cessation support have not been incorporated in most cooperative group clinical trials.[61] No one has assessed cancer patients' reports of their oncology providers' assistance behaviors.

The NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). We propose that administering selected C-TUQ items to participants enrolling in 8 Phase II and Phase III ECOG ACRIN (EA) therapeutic trials will add value to parent trial research questions by advancing the field. Specifically, among patients with varied cancers (tobacco-related and non tobacco-related) and cancer treatments, we will administer C-TUQ questions at EA trial enrollment and 3 and 6 month follow-up.

We have the following aims:

1. **Treatment toxicity:** To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).
2. **Symptom burden:** To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.
3. **Cessation patterns and treatment:** To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.
4. **Trial outcomes:** To explore the effect of tobacco use and exposure on treatment duration and relative dose intensity, and on therapeutic benefit, of 8 selected EA trials.

The findings will advance the nascent field of tobacco use in the context of cancer care by: 1) longitudinal assessment of cigarette smoking, other forms of tobacco use and secondhand smoke exposure at trial enrollment and at 3 and 6 month follow-up; 2) increase knowledge about the effects of tobacco use and exposure on treatment toxicity, physical and psychological symptoms and 3) oncology provider delivery, and 4) patient's perceptions of stigma and utilization of behavioral and pharmacological treatment of tobacco dependence. Finally, the use of this assessment would provide a unique additional value to the hypothesis of this trial, by allowing investigation of previously unanswered questions about the effects of tobacco use and exposure on trial adherence and outcomes among patients with smoking-related and non-smoking related cancers.

2. Objectives

Rev. Add11

2.1 Primary Objective

2.1.1 To compare the overall survival between two strategies of lenalidomide maintenance following induction with a proteasome inhibitor–IMiD combination: limited duration of maintenance (24 months) versus indefinite maintenance therapy until disease progression.

2.1.2 To compare the progression-free survival between VRd and CRd induction followed by lenalidomide maintenance in patients with newly diagnosed symptomatic multiple myeloma.

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2.2 Secondary Objectives

2.2.1 To compare the progression-free survival between two strategies of lenalidomide maintenance following induction with a proteasome inhibitor–IMiD combination: limited duration of maintenance (24 months) or indefinite maintenance therapy until disease progression.

2.2.2 To compare induction rates of response between VRd and CRd arms.

2.2.3 To evaluate the time to progression, duration of response and overall survival between VRd and CRd induction therapy.

2.2.4 To compare induction rates of toxicity between VRd and CRd arms.

2.2.5 To evaluate toxicity during lenalidomide maintenance.

2.2.6 To compare minimal residual disease (MRD) negative rates between VRd and CRd arms at end of induction therapy.

2.3 Quality of Life Objectives

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2.3.1 To compare the short and long-term health-related quality of life impact between the two strategies of lenalidomide maintenance .

2.3.2 To compare the impact on health-related quality of life between VRd and CRd induction therapy.

2.3.3 To evaluate the association between early induction response and change in health-related quality of life.

2.3.4 To describe changes in health-related quality of life during the induction, active maintenance and observation phases.

2.3.5 To evaluate correlation between treatment adherence during maintenance and health-related quality of life.

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2.4 Laboratory Research Study Objectives

2.4.1 To compare MRD negative rates between the two strategies of lenalidomide maintenance.

2.4.2 To compare MRD negative rates between VRd and CRd arms during induction therapy.

2.4.3 To examine patterns of change in MRD levels over time and examine conversion from detectable to MRD negative status.

2.4.4 To evaluate agreement and association between IMWG and MRD based disease-free status.

2.4.5 To describe the mutational profile of newly diagnosed multiple myeloma.

2.4.6 To identify mutations associated with resistance to VRd and CRd induction therapy.

2.4.7 To identify expression profiles associated with MRD negative status with each induction therapy.

2.4.8 To determine the ability of MRD status at induction end to predict short-term and long-term overall and progression-free survival.

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2.5 Exploratory Tobacco Use Objectives

2.5.1 To determine the effects of tobacco, operationalized as combustible tobacco (1a), other forms of tobacco (1b), and environmental tobacco exposure (ETS) (1c) on provider-reported cancer-treatment toxicity (adverse events (both clinical and hematologic) and dose modifications).

2.5.2 To determine the effects of tobacco on patient-reported physical symptoms and psychological symptoms.

2.5.3 To examine quitting behaviors and behavioral counseling/support and cessation medication utilization.

2.5.4 To explore the effect of tobacco use and exposure on treatment duration, relative dose intensity, and therapeutic benefit.

NOTE: Tobacco Use objectives described above are ancillary for the Tobacco Use Assessment project approved by NCI. A combined analysis of the data from the selected ECOG-ACRIN studies is planned. Data collected from the tobacco use assessment in each parent study will not be analyzed and reported in the clinical study report.

3. Selection of Patients

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Each of the criteria in the checklist that follows must be met for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

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NOTE: This study involves pre-registration (see Section 4). Bone marrow and peripheral blood specimens are to be submitted for defined laboratory research studies and future undefined research studies as outlined in Section 10 per patient consent.

3.1 Step 1 Randomization

_____ 3.1.1 Age ≥ 18 years.

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_____ 3.1.2 Patients must be diagnosed with symptomatic standard-risk multiple myeloma (SR-MM) as defined by all of the following (except GEP70 status if unknown):

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- No evidence of t(14;16) by FISH testing on bone marrow or not available:

  please circle: yes or no or NA date of test_____

  No evidence of t(14:20) by FISH testing on bone marrow or not available:

  please circle: yes or no or NA date of test_____

  No evidence of deletion 17p by FISH testing on bone marrow; please circle yes or no date of test_____

  FISH should be from within 90 days of registration.

  NOTE: If the FISH result states that no IgH abnormality is present, both t(14;16) and t(14;20) can be considered negative. In addition, if the patient has a t(11;14) or t(4;14) translocation present, they can be considered negative for t(14;16) and t(14;20). If testing for t(14;16) or t(14;20) could not be performed for lack of sufficient material or non-availability of the probe in the test panel, patients can be enrolled on the study.

- Standard Risk GEP70 signature within the past 90 days (only if GEP has been done and results are available).
  NOTE: GEP testing is NOT a requirement for the study.
  If the test has been done, patients found to have a GEP70 status of High-Risk will not be eligible.
  GEP70 Test Done? Yes _____ No_____ (skip remainder)
  Date of Test: _____
  GEP70 Status Standard-Risk? Yes _____ No_____
- Serum LDH ≤ 2 x ULN within the past 28 days
  Serum LDH: _____ (IU/L) ULN_____ (IU/L)
  Date of Test: _____

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- No more than 20% circulating plasma cells on peripheral blood smear differential or 2,000 plasma cells/microliter on WBC differential of peripheral blood within the past 90 days

  NOTE: This is NOT the plasma cell % from the marrow aspirate.

  NOTE: If peripheral blood flow cytometry was done and no plasma cells reported, the following can be marked "0".

  Plasma cell %:_____
  Plasma cells: _____ (/microL)
  Date of Test: _____

Rev. Add11 _____ 3.1.3 Patients must have measurable or evaluable disease as defined by having one or more of the following, obtained within 28 days prior to randomization:

- ≥ 1g/dL monoclonal protein (M-protein) on serum protein electrophoresis
- ≥ 200 mg/24 hrs of monoclonal protein on a 24 hour urine protein electrophoresis
- Involved free light chain ≥ 10 mg/dL or ≥ 100 mg/L AND abnormal serum immunoglobulin kappa to lambda free light chain ratio (< 0.26 or > 1.65)
- Monoclonal bone marrow plasmacytosis ≥ 30% (evaluable disease)

Rev. 9/17 _____ 3.1.4 SPEP, UPEP, and serum FLC assay are required to be performed within 28 days prior to randomization. A bone marrow biopsy and/or aspirate is required within 28 days if bone marrow is being followed for response.

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Serum M-protein by SPEP _____ (g/dL)

Date of Test: _____

Urine M-protein measurement by 24 hr UPEP_____ (mg/24hr)

Date of Test: _____

NOTE: UPEP (on a 24-hour collection) is required, no substitute method is acceptable. Urine must be followed monthly if the

baseline urine M-spike is ≥ 200 mg/24 hr. Please note that if both serum and urine M-components are present, both must be followed in order to evaluate response.

Serum Free Light Chain Assay

Kappa FLC_____ (mg/dL) or _____ (mg/L);

Lambda FLC_____ (mg/dL) or _____ (mg/L);

kappa/lambda ratio_____

Date of Test: _____

NOTE: The serum free light chain test is required to be done if the patient does not have measurable disease in the serum or urine. Measurable disease in the serum is defined as having a serum M-spike ≥ 1 g/dL. Measurable disease in the urine is defined as having a urine M-spike ≥ 200mg/24 hr.

Plasma cell % on Bone Marrow _____%

Date of Test: _____

_____ 3.1.5 The following laboratory levels must be obtained within 28 days prior to randomization:

_____ 3.1.5.1 Hemoglobin ≥ 8 g/dL.

Hemoglobin: _____ Date of Test: _____

_____ 3.1.5.2 Untransfused platelet count ≥ 75,000 cells/mm^3.

Platelet: _____ Date of Test: _____

_____ 3.1.5.3 Absolute neutrophil count ≥ 1000 cells/mm^3.

ANC: _____ Date of Test: _____

_____ 3.1.5.4 Calculated creatinine clearance ≥ 30 mL/min

Creatinine clearance: _____ Date of Test: _____

_____ 3.1.5.5 Bilirubin ≤ 1.5 mg/dL.

Bilirubin: _____ Date of Test: _____

_____ 3.1.5.6 SGPT (ALT) and SGOT (AST) < 2.5 times the upper limit of normal.

SGPT (ALT): _____ Institutional ULN: _____

Date of Test: _____

SGOT (AST): _____Institutional ULN: _____

Date of Test: _____

_____ 3.1.6 Patients must have received no more than one cycle (4 weeks or less) of prior chemotherapy and no more than 160mg of prior dexamethasone (or equivalent dose of prednisone) for treatment of symptomatic myeloma. They should not have been exposed to lenalidomide, bortezomib or carfilzomib for treatment of symptomatic myeloma. Prior radiation therapy to symptomatic lesions is allowed provided there are no residual toxicity related to radiation and blood counts that meet the study requirements.

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_____ 3.1.7 Prior systemic glucocorticoid use for the treatment of non-malignant disorders is permitted. Prior or concurrent topical or localized glucocorticoid therapy to treat non-malignant comorbid disorders is permitted.

_____3.1.8 Patients must not have active, uncontrolled seizure disorder. Patients must have had no seizures in the last 6 months.

_____3.1.9 Patients must not have uncontrolled intercurrent illness including uncontrolled hypertension, symptomatic congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, uncontrolled psychiatric illness or social situation that would limit compliance with the study, or a prior history of Stevens Johnson Syndrome.

_____3.1.10 ECOG performance status 0, 1, or 2. (PS 3 allowed if secondary to pain)

_____3.1.11 Patients with monoclonal gammopathy of undetermined significance or asymptomatic multiple myeloma are not eligible.

_____3.1.12 Patients must not have Grade 2 or higher peripheral neuropathy by CTCAE 4.0.

_____ 3.1.13 Patients must not have active, uncontrolled infection.

_____ 3.1.14 Patients may have a history of current or previous deep vein thrombosis or pulmonary embolism but must be willing to take some form of anti-coagulation as prophylaxis if they are not currently on full-dose anticoagulation.

_____3.1.15 Patients should not have New York Heart Association classification III or IV heart failure or myocardial infarction within the previous 6 months.

_____ 3.1.16 Patients with a history of prior malignancy are eligible provided they were treated with curative intent and do not require active therapy (currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast are not excluded).

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_____3.1.17 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 of starting lenalidomide 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, throughout the entire duration of study treatment, and for 28 days after the last dose of lenalidomide. FCBP must also agree to ongoing pregnancy testing. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. If randomized to Arm B, FCBP must agree to use contraception or abstinence for 30 days after last dose of carfilzomib.

Female of childbearing potential (Y/N)? _____

Date of Test: _____

† A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.

Rev. Add11 Rev. Add13 _____ 3.1.18 Sexually active males must be willing to use a condom (even if they have undergone a prior vasectomy) while having intercourse, while taking lenalidomide and for 28 days after stopping lenalidomide. Male subjects must also agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from lenalidomide. If randomized to Arm B, male subjects must be willing to use condoms while having intercourse, while taking carfilzomib and for 90 days after discontinuation of carfilzomib.

_____ 3.1.19 The following patients will be excluded as this study involves an agent that may have genotoxic, mutagenic and teratogenic effects.

3.1.19.1 Pregnant women

3.1.19.2 Nursing women

_____ 3.1.20 HIV infection is not excluded. Known HIV positive patients must meet the following criteria:

- CD4 cell count ≥ 350/mm^3
- No history of AIDS-related illness
- Not currently prescribed zidovudine or stavudine

_____ 3.1.21 Patient enrolling to this study must agree to register to the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

3.2 Step 2 Randomization

Rev. Add11 _____ 3.2.1 Patients must have completed induction without experiencing progression or patients must have received at least 6 cycles on Arm A and 4 cycles on Arm B but stopped induction therapy due to adverse events.

_____ 3.2.2 Step 2 registration must be within 6 weeks of completing Step 1 therapy.

Date Step 1 Therapy Completed: _____

Rev. Add11 _____ 3.2.3 Patients must not have received any non-protocol therapy outside of the assigned induction therapy including stem cell transplant.

_____ 3.2.4 ECOG performance status 0, 1, or 2. (PS 3 allowed if secondary to pain).

_____ 3.2.5 Any adverse event related to Step 1 therapy must have resolved to grade 2 or less.

_____ 3.2.6 Patient must have adequate laboratory levels as follows (within 28 days prior to randomization to Step 2)

_____ 3.2.6.1 Hemoglobin ≥ 8 g/dL.

Hemoglobin: _____Date of Test:_____

_____ 3.2.6.2 Platelet count ≥ 75,000 cells/mm^3.

Platelet:_____ Date of Test:_____

_____ 3.2.6.3 Absolute neutrophil count ≥ 1000 cells/mm^3.

ANC:_____ Date of Test:_____

_____3.2.6.4 Calculated creatinine clearance ≥ 30 mL/min.

Creatinine clearance:_____ Date of Test:_____

_____3.2.6.5 Bilirubin ≤ 1.5 mg/dL.

Bilirubin:_____ Date of Test:_____

_____3.2.6.6 SGPT (ALT) and SGOT (AST) < 2.5 times the upper limit of normal.

SGPT (ALT):_____ Institutional ULN:_____

Date of Test:_____

SGOT (AST):_____Institutional ULN:_____

Date of Test:_____

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_____ 3.2.7 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 of starting lenalidomide 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, throughout the entire duration of study treatment, and for 28 days after the last dose of lenalidomide. FCBP must also agree to ongoing pregnancy testing. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. If previously randomized to Arm B, FCBPs must also continue to use contraception or abstinence for 30 days after the last dose of carfilzomib.

Female of childbearing potential (Y/N)? _____ Date of Test: _____

† A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal

(amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.

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_____ 3.2.8 Sexually active males must be willing to use a condom (even if they have undergone a prior vasectomy) while having intercourse, while taking lenalidomide and for 28 days after stopping lenalidomide. Male subjects must also agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from lenalidomide. If previously randomized to Arm B, males must agree to continue use of contraception and agree to not donate sperm for at least 90 days after the last dose of carfilzomib.

_____ 3.2.9 The following patients will be excluded as this study involves an agent that may have genotoxic, mutagenic and teratogenic effects.

3.2.9.1 Pregnant women

3.2.9.2 Nursing women

_____3.2.10 Patient enrolling to this study must agree to register to the mandatory RevAssist® program and be willing and able to comply with the requirements of RevAssist®.

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration Procedures

CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at <TBD>.For questions, please contact the RCR Help Desk by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization

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- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following critiera:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a partiipating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study

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Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E1A11** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand

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- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E1A11**
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided

Requirements for E1A11 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review
   - Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

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Treatment should start within fourteen working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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4.1 Step 0 Pre-Registration

NOTE: Patients who are only pre-registered must not begin treatment.

The following information will be requested at time of randomization:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- 4.1.2.1 Institution and affiliate name (Institution CTEP ID)
- 4.1.2.2 Investigator's name (NCI number)
- 4.1.2.3 Cooperative Group Credit
- 4.1.2.4 Credit Investigator
- 4.1.2.5 Protocol specific contact information

4.1.3 Patient Identification

- 4.1.3.1 Patient's initials (first and last)
- 4.1.3.2 Patient's Hospital ID and/or Social Security number
- 4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

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4.1.3.3.7 Country of residence

4.1.3.4 Additional Requirements

4.1.3.4.1 Patients must provide a signed and dated written informed consent form.

4.1.3.4.2 Patients must be considered potential candidates for participation in E1A11.

4.1.3.4.3 Bone marrow and peripheral blood specimens are to be submitted at pre-registration for defined laboratory research studies described in Section 11 and future undefined research studies as outlined in Section 10 per patient consent.

NOTE: ECOG- ACRIN requires that biological samples submitted from patients participating in E1A11 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.4.

4.2 Step 1 Registration

Patients must not start protocol treatment prior to randomization.

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Treatment should start within 14 working days after registration. The following information will be requested at time of randomization:

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

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4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1. Provided with signature, the eligibility checklist can be used as source documentation.

4.2.5 Stratification Factors

Intent to stem cell transplant at progression: Yes or No

4.2.6 Additional Requirements

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4.2.6.1 Patients must provide a signed and dated written informed consent form.

4.2.6.2 Quality of Life forms are to be submitted as indicated in Section 6.

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4.2.6.3 Follow-up peripheral blood and bone marrow specimens are to be submitted for defined laboratory research studies described in Section 11 and future undefined research studies as outlined in Section 10 per patient consent.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E1A11 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.4.

4.2.6.4 RevAssist Program

Lenalidomide will be dispensed in accordance with the RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all enrolled research subjects must be registered to and comply with all requirements of the RevAssist® program. Refer to Section 8.3.10 of the protocol for complete information on the RevAssist® Program.

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4.2.6.5 Data Collection

Data collection for this study will be done through Medidata Rave and the EASEE-PRO system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS after IRB approval is obtained. To access iMedidata/Rave the site

user must have an active CTEP IAM account (https://ctepcore.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA, Read-Only, CRA, Lab Admin, SLA or Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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4.2.6.6 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System:

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the

patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

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4.2.7 Instructions for Patients who do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted to Medidata Rave and EASEE-PRO according to the schedule in the E1A11 Forms Completion Guidelines. Document the reason for not starting protocol treatment on the Off Treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

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4.3 Step 2 Registration

Patients should not start protocol treatment prior to Step 2 registration.

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Treatment should start within 14 working days after registration and within 6 weeks of completing Step 1 treatment (last day of the induction cycle).

The following information will be requested at time of registration

4.3.1 Protocol Number

4.3.2 Investigator Identification

4.3.2.1 Institution and affiliate name (Institution CTEP ID)

4.3.2.2 Investigator's name (NCI number)

4.3.2.3 Cooperative Group Credit

4.3.2.4 Credit Investigator

4.3.2.5 Protocol specific contact information

4.3.3 Patient Identification

4.3.3.1 Patient's initials (first and last)

4.3.3.2 Patient's Hospital ID and/or Social Security number

4.3.3.3 Patient demographics

4.3.3.3.1 Gender

4.3.3.3.2 Birth date

4.3.3.3.3 Race

4.3.3.3.4 Ethnicity

4.3.3.3.5 Nine-digit ZIP code

4.3.3.3.6 Method of payment

4.3.3.3.7 Country of residence

4.3.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2. Provided with signature, the eligibility checklist can be used as source documentation.

4.3.5 Stratification Factors

Induction Arm: VRd (Arm A) or CRd (Arm B)

4.3.6 Additional Requirements

4.3.6.1 Patients must provide a signed and dated written informed consent form

4.3.6.2 Quality of Life forms are to be submitted as indicated in Section 6.3

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4.3.6.3 Follow-up peripheral blood and bone marrow specimens are to be submitted for defined laboratory research studies described in Section 11 and future undefined research studies as outlined in Section 10 per patient consent.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E1A11 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.4.

4.3.6.4 RevAssist Program

Lenalidomide will be dispensed in accordance with the RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects randomized to Arms C or D, must be registered in and comply with all requirements of the RevAssist® program. Refer to Section 8.3.10 of the protocol for complete information on the RevAssist® Program.

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4.3.6.5 Data Collection

Data collection for this study will be done in Medidata Rave and the EASEE-PRO system. Prior to beginning data entry in Rave, study staff must be registered in Medidata and complete the required training modules. Study staff will receive an invitation to join the study in Rave after evidence of IRB approval is submitted to RSS.

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4.3.7 Instructions for Patients who do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave and EASEE-PRO according to the schedule in the E1A11 Forms Completion Guidelines. Document the reason for not starting protocol treatment on the Off Treatment form. Also report

the date and type of the first non-protocol treatment that the patient receives.

4.4 Investigator's Drug Brochure and Safety Alerts

The Investigator Drug Brochures (IDB) for carfilzomib (IND# 118503) is available for download from the ECOG webpage. The IDB provides relevant and current scientific information about the investigational product. The IDB should be submitted to your IRB/EC according to GCP regulations. The IDB and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E1A11 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the respective pharmaceutical company to regulatory authorities globally (including the FDA) and ECOG-ACRIN. If applicable, ECOG-ACRIN will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E1A11 study files.

5. Treatment Plan

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5.1 Administration Schedule

NOTE: *All doses are based on actual body weight.*

NOTE: *If a dose of carfilzomib or bortezomib cannot be administered on a planned day due to a holiday, the dose should be given the next possible day. The subsequent doses within the cycle should be delayed by the same duration, but the subsequent cycle can start on time as planned.*

5.1.1 ARM A-VRd *

*VRd = combination of Bortezomib (Velcade), Lenalidomide (Revlimid) and dexamethasone

Induction

Bortezomib

1.3 mg/m2 SQ or IV days 1, 4, 8 and 11 Cycles 1-8

1.3 mg/m2 SQ or IV days 1 and 8 Cycles 9-12

Lenalidomide **

25 mg PO daily days 1-14

Dexamethasone

20 mg PO days 1, 2, 4, 5, 8, 9, 11, 12 Cycles 1-4

10 mg PO days 1, 2, 4, 5, 8, 9, 11, 12 Cycles 5-8

10 mg PO days 1, 2, 8 and 9 Cycles 9-12

Repeat cycles every 3 weeks for a total of 12 cycles.

** In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 25 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would have required a dose reduction for lenalidomide.

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5.1.2 ARM B-CRd *

* CRd = combination of Carfilzomib, Lenalidomide (Revlimid) and dexamethasone

Induction

*Carfilzomib***

20 mg/m^2 IV days 1 and 2; 36 mg/m^2 IV days 8, 9, 15, 16 Cycle 1

36 mg/m^2 IV days 1, 2, 8, 9, 15, 16 Cycles 2-9

(Carfilzomib is given as a 30-minute infusion)

Lenalidomide ***

25 mg PO daily days 1-21

Dexamethasone ****

40 mg PO days 1, 8, 15, 22 Cycles 1-4

20 mg PO days 1, 8, 15, 22 Cycles 5-9

Repeat cycles every 4 weeks for a total of 9 cycles.

** The dose is calculated using patient's actual body surface area. Patients with a body surface area more than 2.2 mg/m^2 should receive a dose based on 2.2 mg/m^2

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** In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 25 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would have required a dose reduction for lenalidomide.

****Up to 4 mg of dexamethasone can be given per institutional practice with the subsequent days (days 2, 9, 16) of carfilzomib prior to infusion.

5.1.3 ARM C–Limited Lenalidomide Maintenance

Maintenance

Lenalidomide

15 mg PO daily days 1-21*

Repeat cycles every 4 weeks for 24 cycles

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** In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 15 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would have required a dose reduction for lenalidomide.

Observation

Observation until disease progression

5.1.4 ARM D- Indefinite Lenalidomide Maintenance

Lenalidomide

15 mg PO daily days 1-21*

Repeat cycles every 4 weeks until progression or excessive toxicity

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** In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 15 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would have required a dose reduction for lenalidomide.

5.1.5 Site of Drug Administration

At discretion of enrolling MD, if considered appropriate, patients randomized to Arm A (VRd) can receive induction therapy under care of a local oncologist, returning to the enrolling institution only at the beginning of each cycle. Patients randomized to Arm B (CRd) are required to receive carfilzomib injections at the enrolling institution. During maintenance and observation (Arms C and D), patients will have to be seen at the enrolling institution at least once every three months.

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5.1.6 Lenalidomide Fertility Instructions

NOTE: Please also see Appendix V "Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods."

Before starting study drug:

All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®. 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 of prescribing lenalidomide (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 to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

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5.2 Adverse Event Reporting Requirements

NOTE: Effective April 1, 2018 all expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines for this study will continue to be based on CTCAE version 4.0 terminology and grading.

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The

following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
  - 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 a 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.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The CTEP guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) for Arm A, B, C and D
- The FDA (1-800-332-1088) for Arms A, C and D

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (1-800-332-0178) for Arms A, C and D in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E1A11 and outline the specific expedited adverse event reporting requirements for study E1A11.

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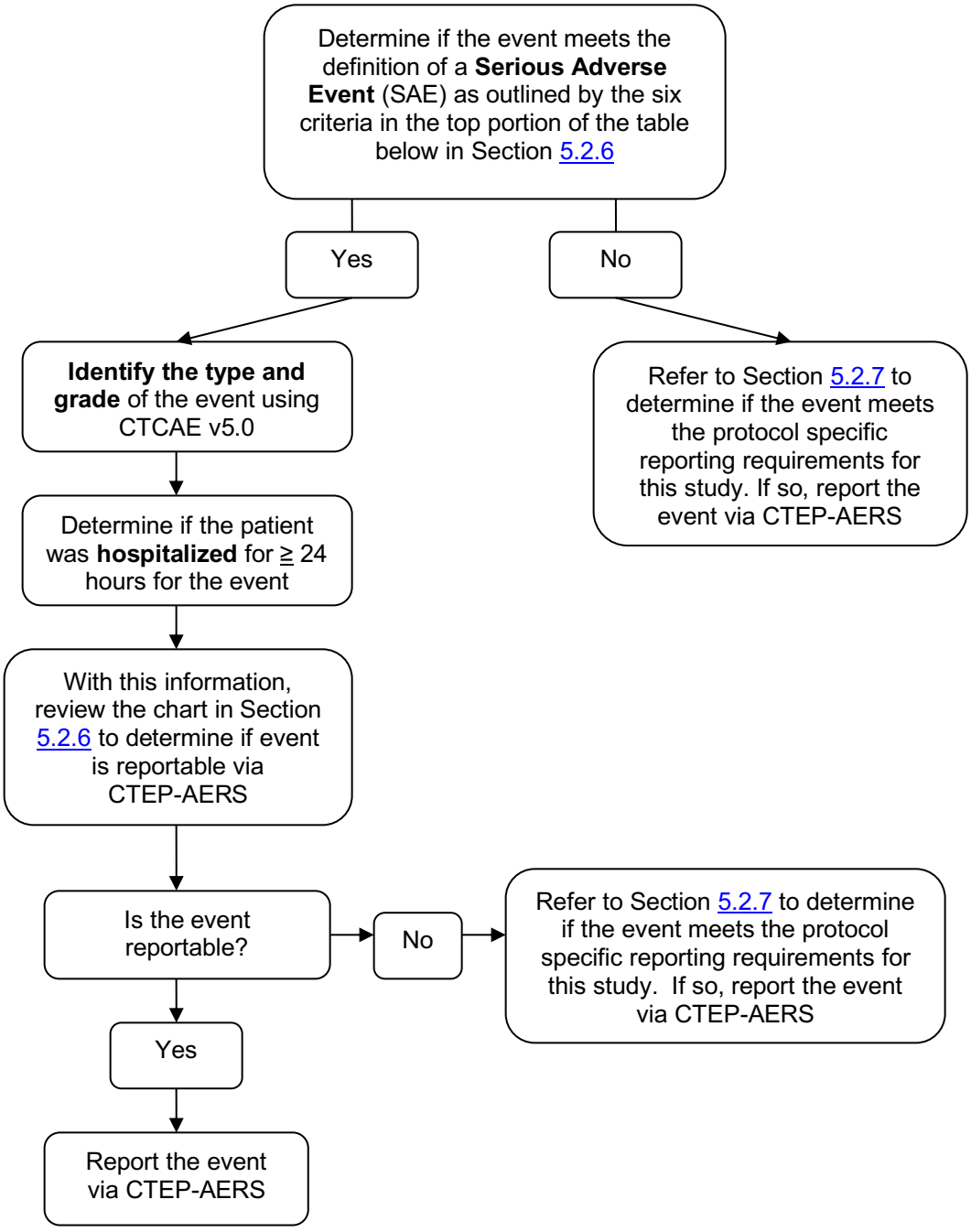
5.2.5 **Arm B:** Steps to determine if an adverse event is to be reported in an expedited manner

5.2.5.1 Guidelines for adverse events **OCCURRING ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.6 Expedited Reporting Requirements for Arm B on protocol E1A11

Investigational Agents: ***Carfilzomib***

Commercial Agents: ***Lenalidomide and Dexamethasone***

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention* [1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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5.2.7 Additional instructions, requirements and exceptions for Arm B on protocol E1A11

Additional Instructions:

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomalies, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study**: A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

E1A11 specific expedited reporting requirements:

- **Pregnancy**

Pregnancies and suspected pregnancies (including a positive/ inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Carfilzomib or Lenalidomide, or within 28 days of the subject's last dose of Carfilzomib or Lenalidomide, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix VIII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

E1A11 specific expedited reporting exceptions:

There are no protocol specific exceptions

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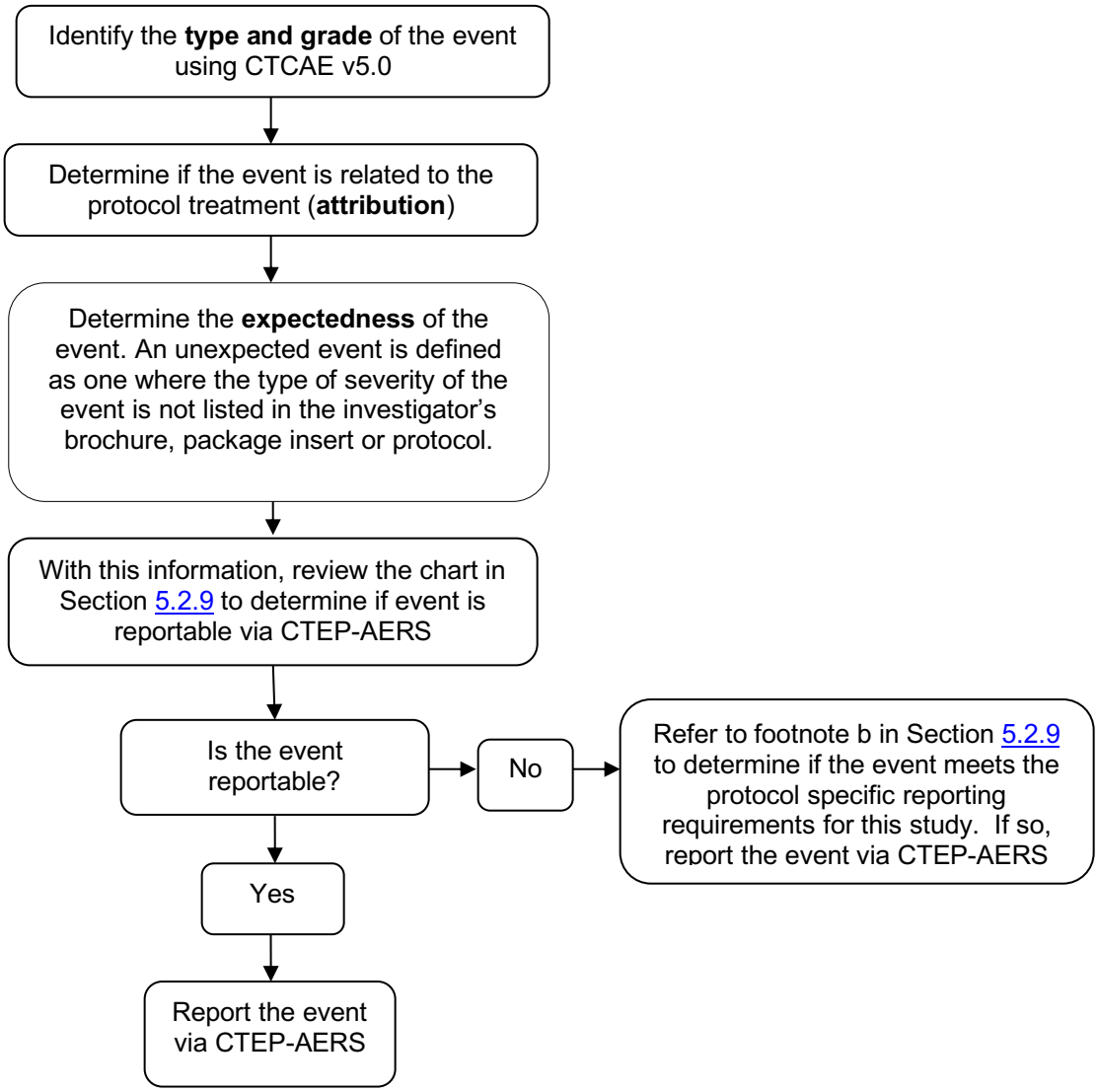
5.2.8 **Arm A, C and D** - Steps to determine if an adverse event is to be reported in an expedited manner



5.2.9 Expedited Reporting Requirements for Arm A, C and D on protocol E1A11

Commercial Agents: Bortezomib, Lenalidomide, Dexamethasone

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm A, C and D

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

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a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: **Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event**

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Pregnancy

Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Lenalidomide, or within 28 days of the subject's last dose of Lenalidomide, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix VIII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

5.2.10 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

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Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.11 Second Primary Cancer Reporting Requirements

All cases of second and secondary malignancies including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), regardless of attribution, that occur following treatment on NCI-sponsored trials must be reported as follows:

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis via CTEP-AERS, regardless of attribution, at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, c.) treatment related secondary malignancy, or d.) Neoplasm Other, malignant (grade 3 or 4)
3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and in situ tumors.

Whenever possible, the CTEP-AERS report should include the following:

- Tumor pathology
- History of prior tumors
- Prior treatment/current treatment including duration
- Any associated risk factors or evidence regarding how long the tumor may have been present
- When and how the tumor was detected
- Molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor
- Tumor treatment and outcome (if available).

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated

pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.3 Comprehensive Adverse Events and Potential Risks List

5.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bortezomib, Velcade (PS-341)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). *Frequency is provided based on 2084 patients.* Below is the CAEPR for bortezomib (PS-341).

NOTE: Arm A - The information listed in the CAEPR below, as well as the package insert or protocol can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS.

Rev. 9/14

Version 2.7, March 25, 2019[1]

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 5.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
CARDIAC DISORDERS		
		Heart failure
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dyspepsia	
	Gastrointestinal hemorrhage[2]	
		Gastrointestinal perforation[3]
	Ileus	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
Fever		
HEPATOBILIARY DISORDERS		
		Hepatic failure[4]
		Hepatobiliary disorders - Other (hepatitis)[4]
INFECTIONS AND INFESTATIONS		
Infection[5]		
INVESTIGATIONS		
		Alanine aminotransferase increased[4]

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 5.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Alkaline phosphatase increased[4]
		Aspartate aminotransferase increased[4]
		Blood bilirubin increased[4]
		GGT increased[4]
		INR increased[4]
		Investigations - Other (albumin)[4]
	Neutrophil count decreased	
Platelet count decreased		
	Weight loss	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Dehydration	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Leukoencephalopathy
	Neuralgia	
	Paresthesia	
Peripheral motor neuropathy		
Peripheral sensory neuropathy		
		Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS		
	Anxiety	
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Cough	
	Dyspnea	
	Pharyngeal mucositis	
		Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash maculo-papular	
VASCULAR DISORDERS		
	Hypotension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on bortezomib (Velcade) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bortezomib (Velcade) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hematocrit low, hematocrit); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome; Leukocytosis

CARDIAC DISORDERS - Asystole; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac amyloidosis); Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Left ventricular systolic dysfunction; Mobitz type I; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Blurred vision; Dry eye; Extraocular muscle paresis; Eye disorders - Other (chalazion); Eye disorders - Other (choroidal effusion); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (retinal hemorrhage with bilateral vision impairment); Keratitis; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Belching; Bloating; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (colonic wall thickening); Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (ileitis); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (mouth/tongue ulceration); Gastrointestinal disorders - Other (retching); Gastrointestinal pain; Gingival pain; Hemorrhoids; Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter related complication); General disorders and administration site conditions - Other

(hepato-renal syndrome); Hypothermia; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Portal vein thrombosis; Sinusoidal obstruction syndrome

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Investigations - Other (BUN); Investigations - Other (low chloride); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Buttock pain; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Osteonecrosis of jaw

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Akathisia; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Hypersomnia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (autonomic neuropathy, autonomic dysfunction); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Nervous system disorders - Other (L sided facial droop); Nervous system disorders - Other (paralysis); Nervous system disorders - Other (polyneuropathy); Nervous system disorders - Other (tongue paralysis); Presyncope; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Depression; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (glomerular nephritis proliferative); Renal calculi; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Mediastinal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Tracheal mucositis; Tracheal stenosis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Erythema multiforme; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous

tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other (leukoclastic vasculitis); Skin and subcutaneous tissue disorders - Other (skin lesion NOS); Urticaria

VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hematoma; Hypertension; Thromboembolic event; Vascular disorders - Other (trach site); Vasculitis

NOTE: Bortezomib (Velcade) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Rev. 10/14
Rev. 7/16
Rev. Add12

5.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). Frequency is provided based on 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

NOTE: Arms A, C and D – These three arms **ONLY** use expectedness as a factor in determining the reportability of an event per Section 5.2.8 and 5.2.9. Therefore, the information listed in the CAEPR below, as well as package insert or protocol can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS.

Rev. Add14

Version 2.8, June 27, 2019[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
	Blood and lymphatic system disorders - Other (pancytopenia)	
	Febrile neutropenia	
	Hemolysis	
CARDIAC DISORDERS		
		Atrial fibrillation
		Heart failure
		Myocardial infarction[2]
EAR AND LABYRINTH DISORDERS		
	Vertigo	
ENDOCRINE DISORDERS		
		Hyperthyroidism
	Hypothyroidism	
EYE DISORDERS		
	Blurred vision	
	Cataract	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Nausea	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
	Generalized edema	
	Non-cardiac chest pain	
	Pain	
HEPATOBILIARY DISORDERS		
		Hepatic failure
		Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Anaphylaxis
		Immune system disorders - Other (angioedema)
		Immune system disorders - Other (graft vs. host disease)[3]
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
	Fall	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	GGT increased	
	Investigations - Other (C-Reactive protein increased)	
		Lipase increased
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hyperuricemia	
	Hypocalcemia	
	Hypokalemia	
	Hypomagnesemia	
	Hyponatremia	
	Hypophosphatemia	
	Iron overload	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Generalized muscle weakness	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
		Rhabdomyolysis[5]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy[6]
		Myelodysplastic syndrome[6]
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)
		Treatment related secondary malignancy[6]
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Depressed level of consciousness	
	Dysesthesia	
	Dysgeusia	
	Headache	
	Paresthesia	
	Peripheral motor neuropathy	
	Peripheral sensory neuropathy	
		Stroke[2]
	Syncope	
	Tremor	
PSYCHIATRIC DISORDERS		
	Depression	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Insomnia	
	Psychiatric disorders - Other (mood altered)	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Epistaxis	
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])
	Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
SURGICAL AND MEDICAL PROCEDURES		
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]
VASCULAR DISORDERS		
	Hematoma	
	Hypertension	
	Hypotension	
	Peripheral ischemia	
	Thromboembolic event[9]	
	Vasculitis	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3] Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5] The rare adverse event of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome. Statins, infections, trauma, and serotonin syndrome are known risk factors for rhabdomyolysis.

[6] There has been an increased frequency of secondary malignancies (SPM) including ALL, AML, and MDS, and certain other types of cancers of the skin and other organs in multiple myeloma (MM) patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant. The use of lenalidomide in cancers other than MM, shows that invasive SPMs occurred in a small number of patients. Patients treated with lenalidomide should be closely followed for the occurance of SPMs.

[7] Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[8] A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[9] Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[10] Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[11] Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[12] Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

NOTE: In a trial of first line treatment of patients with chronic lymphocytic leukemia (CLL), single agent lenalidomide (CC-5013) increased the risk of death as compared to control arm (chlorambucil).

NOTE: In two randomized trials of patients with multiple myeloma (MM), the addition of MK-3475 (pembrolizumab) to a thalidomide analog plus dexamethasone, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody, such as MK-3475 (pembrolizumab), in combination with a thalidomide analog, such as lenalidomide, is not recommended outside of controlled clinical trials.

NOTE: In a clinical trial in patients with Mantle cell lymphoma (MCL), there was an increase in early deaths (within 20 weeks); 12.9% in the lenalidomide (CC-5013) arm vs. 7.1% in the control arm.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia

CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Cushingoid

EYE DISORDERS - Dry eye; Flashing lights; Retinopathy

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure

HEPATOBILIARY DISORDERS - Cholecystitis

INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis

RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet’s Syndrome); Urticaria

VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

NOTE: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Rev. 2/15, 9/15, 9/17 5.4 Dose Modifications

Rev. Add11

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

NOTE: Dose modifications are based on adverse events, which are possibly, probably or definitely related to drug. More than one dose reduction per cycle may occur.

Subjects experiencing grade 3 or 4 AE's that are possibly, probably or definitely related to a particular agent(s) requiring dose modifications as per the tables below will have that particular agent(s) held until resolution of the AE. If AE improves to baseline or <=grade 1 prior to next scheduled dose, treatment should be restarted with a one dose level reduction for the causative drug for the remainder of the cycle. The next cycle will then continue with this reduced dose level. For grade 3 or 4 AEs that are possibly, probably or definitely related to a particular agent(s) which occur on or after the last treatment day of a cycle, will have that particular agent(s) reduced by one dose level beginning with the next cycle.

NOTE: If the AE is attributed to a specific drug, only that drug needs dose reduction. If the AE is possibly attributed to more than one agent, the more likely agent can be first reduced, and then the other drug if the toxicity recurs.

Once a subject's dose has been reduced, no dose-re-escalation is permitted.

A delay of up to 14 days is allowed between cycles. Any delay beyond 14 days should be discussed with the study chair.

If there is a delay in obtaining lenalidomide for start of a new cycle, the cycle can be delayed until it is available in order to allow all drugs to be started at the same time. However, if the cycle has already started, treatment may continue and lenalidomide should be started when it becomes available and continue for the remaining days of lenalidomide as per cycle.

5.4.1 Lenalidomide Treatment Adjustment

See Table below for Lenalidomide Treatment Adjustment Steps

Lenalidomide (CC-5013) Treatment Adjustment Steps (Induction phase)		
	Baseline Creatinine Clearance ≥ 60 ml/min	**Baseline Creatinine Clearance < 60 ml/min***
Starting Dose	**25 mg daily for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)**	**10 mg daily for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)**
Dose Level -1	15 mg daily for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)	5 mg daily for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)
Dose Level -2	10 mg daily for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)	5 mg every other day for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)
Dose Level -3	5 mg daily for 21 days every 28 days (Arm B) or 14 days every 21 days (Arm A)	

*In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 25 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.

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Lenalidomide (CC-5013) Treatment Adjustment Steps (Maintenance phase)		
	Creatinine Clearance ≥ 60 ml/min	**Creatinine Clearance < 60 ml/min****
Starting Dose	**15 mg daily for 21 days every 28 days**	**10 mg daily for 21 days every 28 days**
Dose Level -1	10 mg daily for 21 days every 28 days	5 mg daily for 21 days every 28 days
Dose Level -2	5 mg daily for 21 days every 28 days	5 mg every other day for 21 days every 28 days
Dose Level -3	5 mg every other day for 21 days every 28 days	

** In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 15 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would require a dose reduction for lenalidomide.

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5.4.2 Bortezomib Treatment Adjustment

See Table below for Bortezomib Treatment Adjustment Steps

Bortezomib Treatment Adjustment Steps (Arm A)	
Starting Dose	**1.3 mg/m^2 days 1, 4, 8, 11 (Cycle 1-8), days 1, 8 (Cycles 9-12) every 21 days**
Dose Level -1	1 mg/m^2 days 1, 4, 8, 11 (Cycle 1-8), days 1, 8 (Cycles 9-12) **every 21 days**
Dose Level -2	0.7 mg/m^2 days 1, 4, 8, 11 (Cycle 1-8), days 1, 8 (Cycles 9-12) **every 21 days**
Dose Level -3	0.7 mg/m^2 days 1, 8 (Cycle 1-8), days 1, 8 (Cycles 9-12) **every 21 days**

5.4.3 Carfilzomib Treatment Adjustment

See Table below for Carfilzomib Treatment Adjustment Steps

Carfilzomib Treatment Adjustment Steps (Arm B)	
Starting Dose	**20 mg/m^2 IV days 1 and 2; 36 mg/m^2 IV days 8, 9, 15, 16 Cycle 1 (cycle = 28 days)** **36 mg/m^2 IV days 1, 2, 8, 9, 15, 16 Cycles 2-9 (cycle = 28 days)**
Dose Level -1	27 mg/m^2 days 1, 2, 8, 9, 15,16 every 28 days
Dose Level -2	20 mg/m^2 days 1, 2, 8, 9, 15,16 every 28 days
Dose Level -3	10 mg/m^2 days 1, 2, 8, 9, 15,16 every 28 days

5.4.4 Dexamethasone Treatment Adjustment

See Table below for Dexamethasone Treatment Adjustment Steps

Dexamethasone Treatment Adjustment Steps			
Schedule as originally intended and described above			
Starting Dose	**40 mg**	**20 mg**	**10 mg**
Dose Level -1	20 mg	10 mg	4 mg
Dose Level -2	10 mg	4 mg	
Dose Level -3	4 mg		

5.4.5 Dose modifications for lenalidomide and bortezomib based on toxicity (Arm A)

NOTE: Lenalidomide can be introduced after resolution of certain toxicities, midway through the cycle, provided the toxicity resolves prior to day 14. If all drugs need to be held at the time of retreatment for adverse events, then the date of when treatment is resumed is considered day 1 of new treatment cycle. If only one drug needs to be held, then the cycle can start as planned with the other drugs given per schedule and the remaining drug restarted once they meet criteria for restarting. Patients requiring a treatment delay beyond 6 weeks due to non-resolution of treatment related toxicity will end all protocol treatment.

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	At retreatment and Day 2-14 of Cycle	
NCI CTC AE Grade	**If attributed to Lenalidomide**	**If attributed to Bortezomib**
Sustained (≥ 7 days) Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	Hold (interrupt dose) and follow CBC on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.	Hold (interrupt dose) and follow CBC on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Thrombocytopenia ≥ Grade 3 (platelets < 50,000/mm³)	Hold (interrupt dose) and follow CBC on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow CBC on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Infection ≥ grade 2 (with normal neutrophil count)	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow CBC on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Non-blistering rash Grade 2-3 Grade 4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. Discontinue lenalidomide and do not resume.	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide.	Start next cycle at the reduced dose level.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.	Start next cycle at the reduced dose level.
Sinus bradycardia/ other cardiac Arrhythmia Grade 2 Grade 3-4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. Discontinue lenalidomide.	No dose modifications required

Allergic reaction or Hypersensitivity Grade 2-3	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Grade 4	Discontinue lenalidomide.	Discontinue bortezomib and do not resume.
Constipation Grade 1-2	Initiate bowel regimen and maintain dose level.	Initiate bowel regimen and maintain dose level.
≥ Grade 3	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	
Renal Function CrCl < 30 mL/min	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	No dose modifications required
Venous Thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion after adequate anticoagulation (maintain dose level).	No dose modifications required.
Nervous system toxicity Peripheral neuropathy Grade 1 or 2 without pain		Reduce dose of bortezomib to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.
Grade >2 or grade 2 with pain	Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.	Discontinue bortezomib until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate bortezomib at the next lower dose level.
Grade 4	Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.	If a patient is already at the lowest drug level, go to event monitoring. Discontinue bortezomib
Hyperthyroidism or Hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).	No dose modifications required

Any other ≥ grade 3 non-hematologic toxicity assessed as at least possibly related to the drugs (nausea, emesis and diarrhea included only if the grade persists despite maximal supportive care)	Hold (interrupt dose) and observe if toxicity is thought to be at least possible related to lenalidomide. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14 restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level.	Hold (interrupt dose) if toxicity is thought to be at least possible related to bortezomib. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.

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5.4.6 Dose modifications for lenalidomide and carfilzomib based on toxicity (Arm B)

NOTE: Lenalidomide can be introduced after resolution of certain toxicities, midway through the cycle, provided the toxicity resolves prior to day 21. If all drugs need to be held at the time of retreatment for adverse events, then the date of when treatment is resumed is considered day 1 of new treatment cycle. If only one drug needs to be held, then the cycle can start as planned with the other drugs given per schedule and the remaining drug restarted once they meet criteria for restarting. Patients requiring a treatment delay beyond 6 weeks due to non-resolution of treatment related toxicity will end all protocol treatment.

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	At retreatment and Day 2-21 of Cycle	
NCI CTC AE Grade	**If attributed to Lenalidomide**	**If attributed to Carfilzomib**
Sustained (≥ 7 days) Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	Hold (interrupt dose) and follow CBC on days of scheduled carfilzomib doses. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21. If toxicity is noted at day ≥ 17, omit lenalidomide for the remainder of the cycle. Start next cycle at the reduced dose level. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the lenalidomide dose maintained	Hold (interrupt dose) and follow CBC on days of scheduled carfilzomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart carfilzomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Thrombocytopenia ≥ Grade 3 (platelets < 50,000/mm³)	Hold (interrupt dose) and follow CBC on days of scheduled carfilzomib doses. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21. If toxicity is noted at day ≥ 17, omit lenalidomide for the remainder of the cycle. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow CBC on days of scheduled carfilzomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart carfilzomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Infection ≥ grade 2 (with normal neutrophil count)	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.	Hold (interrupt dose) and follow CBC on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart carfilzomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.

Non-blistering rash Grade 2-3 Grade 4	Hold (interrupt) dose and follow. If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. Discontinue lenalidomide and do not resume.	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or < grade 1, restart carfilzomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide.	Start next cycle at the reduced dose level.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.	Start next cycle at the reduced dose level.
Sinus bradycardia/ other cardiac Arrhythmia Grade 2 Grade 3-4	Hold (interrupt) dose and follow. If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. Discontinue lenalidomide.	No dose modifications required
Allergic reaction or Hypersensitivity Grade 2-3 Grade 4	Hold (interrupt) dose and follow. If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. Discontinue lenalidomide.	Hold (interrupt dose) and follow on days of scheduled carfilzomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart carfilzomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level. Discontinue carfilzomib and do not resume.
Nervous system toxicity Peripheral neuropathy Grade 1 or 2 without pain Grade >2 or grade 2 with pain Grade 4	 Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring. Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.	 Reduce dose of carfilzomib to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring. Discontinue carfilzomib until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate carfilzomib at the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring. Discontinue carfilzomib
Constipation Grade 1-2 ≥ Grade 3	 Initiate bowel regimen and maintain dose level. Hold (interrupt) dose and follow. If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	 Initiate bowel regimen and maintain dose level. Omit carfilzomib for the remainder of the cycle. If toxicity resolves, restart carfilzomib next cycle with a decrease in dose by one dose level.

Renal Function CrCl < 30mL/min	Hold (interrupt) dose and follow. If the toxicity resolves to < grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	No dose modifications required
Venous Thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion after adequate anticoagulation (maintain dose level).	No dose modifications required
Any other ≥ grade 3 non-hematologic toxicity assessed as at least possibly related to the drugs (nausea, emesis and diarrhea included only if the grade persists despite maximal supportive care)	Hold (interrupt dose) and observe if toxicity is thought to be at least possible related to lenalidomide. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.	Hold (interrupt dose) if toxicity is thought to be at least possible related to carfilzomib. If the toxicity resolves to baseline or ≤ grade 1, restart carfilzomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.
Hyperthyroidism or Hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).	No dose modifications
PRES	No dose modifications	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate. If condition recurs, permanently discontinue carfilzomib
Thrombotic Microangiopathy	No dose modifications	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed and related to carfilzomib, permanently discontinue carfilzomib. If the diagnosis is excluded or TMA is not related to carfilzomib, carfilzomib can be restarted

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5.4.7 Dose modifications for dexamethasone (Arms A and B)

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	At retreatment and Day 2 to end of Cycle
NCI CTC AE Grade	**If attributed to Dexamethasone**
Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3	Omit dexamethasone until symptoms adequately controlled. Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume. Other drugs should be continued
Pancreatitis ≥ Grade 3	Discontinue dexamethasone and do not resume. Other drugs should be continued
Edema ≥ Grade 3	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction. Other drugs should be continued.
Confusion or Mood alteration ≥ Grade 2	Omit dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume. Other drugs should be continued
Muscle weakness > Grade 2	Decrease dexamethasone dose by one dose level; if weakness persists despite above measures decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms continue to persist. Other drugs should be continued.
Hyperglycemia Grade 3 or higher	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory.
Infection ≥ grade 2 (with normal neutrophil count)	Hold (interrupt dose) and observe until the toxicity resolves to baseline or ≤ grade 1, and then resume dexamethasone dose decreased by 1 dose level.
Any other ≥ grade 3 non-hematologic toxicity assessed as at least possibly related to dexamethasone	Hold (interrupt dose) and observe until the toxicity resolves to baseline or ≤ grade 1, and then resume dexamethasone dose decreased by 1 dose level.

5.4.8 Dose Modifications for lenalidomide (Arms C and D)

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	At retreatment and Day 2-21 of Cycle
NCI CTC AE Grade	**If attributed to Lenalidomide**
Sustained (≥ 7 days) Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	Hold (interrupt dose) and follow CBC weekly. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.
Thrombocytopenia ≥ Grade 3 (platelets < 50,000/mm³)	Hold (interrupt dose) and follow CBC weekly. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.
Infection ≥ grade 2 (with normal neutrophil count)	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.
Non-blistering rash Grade 2-3 Grade 4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Discontinue lenalidomide and do not resume.
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.
Sinus bradycardia/ other cardiac Arrhythmia Grade 2 Grade 3-4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Discontinue lenalidomide.
Allergic reaction or Hypersensitivity Grade 2-3 Grade 4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Discontinue lenalidomide.
Constipation Grade 1-2 ≥ Grade 3	 Initiate bowel regimen and maintain dose level. Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.
Renal Function CrCl < 30 mL/min	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.
Venous Thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion after adequate anticoagulation (maintain dose level).

Nervous system toxicity Peripheral neuropathy Grade 1 or 2 without pain Grade >2 or grade 2 with pain Grade 4	 Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring. Reduce dose of lenalidomide to the next lower dose level. If a patient is already at the lowest drug level, go to event monitoring.
Hyperthyroidism or Hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).
Any other ≥ grade 3 non-hematologic toxicity assessed as at least possibly related to the drugs (nausea, emesis and diarrhea included only if the grade persists despite maximal supportive care)	Hold (interrupt dose) and observe if toxicity is thought to be at least possible related to lenalidomide. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Palliative radiation for the treatment of bone pain or fracture is permitted. Kyphoplasty or vertebroplasty can be considered for patients with compression fracture related pain, based on local guidelines and standards of practice.

5.5.3 Routine concomitant bisphosphonate therapy is recommended for all patients and can be done in accordance with standard local practice. Therapy can be initiated with pamidronate or zoledronic acid. Monthly administration for 18-24 months is recommended based on clinical course and tolerability. Careful follow up should focus on early identification of complications such as osteonecrosis of jaw.

5.5.4 All patients should receive herpes zoster prophylaxis with acyclovir 400 mg BID or similar drug as per standard institutional practice (dosage to be adjusted for renal function where required).

5.5.5 Routine antibiotic prophylaxis is not mandated and can follow standard practice for individual sites.

5.5.6 Prophylactic H2 blockers or other similar agents may be used for patients receiving dexamethasone.

5.5.7 Prophylactic full dose aspirin (325 mg) is mandatory to protect against thrombosis. If patients are intolerant to aspirin or if patient is at higher risk for DVT due to prior thrombosis, immobility, planned surgery during trial, hereditary predisposition or use of birth control pill or estrogen replacement therapy, full dose anticoagulation with warfarin

or LMWH is recommended. If warfarin is used, INR should be followed carefully with a target INR of 2-3. Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis.

5.5.8 For patients at increased risk of tumor lysis, laboratory evaluations should be performed more frequently to identify occurrence of this complication early. Patients at risk should also be started on allopurinol prior to initiating therapy.

5.5.9 Granulocyte Growth Factors

Granulocyte colony- stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) allowed. The use of growth factors should be considered in the following circumstances:

- Prolonged febrile neutropenia (lasting > 10 days) or febrile neutropenia complicated by pneumonia, cellulitis, abscess, sinusitis, hypotension, multi-organ dysfunction, or invasive fungal infection.
- For patients with an ANC less than 100/uL, especially if patient is elderly or immunosuppressed.
- For patients who experience recurrence of Grade 3-4 neutropenia despite dose reduction.
- For patients who are experiencing treatment delays greater than 2 weeks.

If determined to be necessary, commercially available growth factors are to be administered according to the manufacturer's prescribing information, as follows:

- G-CSF 5 mcg/kg/day
- Pegfilgrastim 6 mg subcutaneously

5.5.10 Guidelines for Hematopoietic Recombinant Erythropoietin Products

Hematopoietic recombinant erythropoietin products are associated with higher rates of DVT and are strongly discouraged but are allowed in the following circumstances:

- If the patient is receiving recombinant erythropoietin products prior to study entry, the treatment may continue while participating in the study.
- If the patient has a hemoglobin value < 9 g/dL.
- If a recombinant erythropoietin product is used, it should be used according to the manufacturer's recommendations.

Thrombocytopenia and anemia can occur as a consequence of bone marrow infiltration by myeloma cells or may be related to study drug administration. The clinical significance of the thrombocytopenia or anemia experienced by a patient should be assessed in light of its etiology (disease), the state of the underlying myeloma (stable versus worsening disease), and whether the patient is symptomatic

5.5.11 Guidelines for Platelet Transfusions

Consider transfusion prior to surgery, in the setting of active bleeding, in the setting of Grade 4 thrombocytopenia.

5.5.12 Guidelines for Red Cell Transfusions

Consider transfusion if hemoglobin < 7 g/dL, if the patient is actively bleeding, or has symptomatic cardiac or pulmonary disease.

5.6 Duration of Therapy

5.6.1 Step 1

Patients will receive either 12 cycles (Arm A) or 9 cycles (Arm B) of induction therapy unless:

5.6.1.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the schedule in the E1A11 Forms Completion Guidelines.

5.6.1.2 Patient withdraws consent.

5.6.1.3 Patient experiences progression of disease.

5.6.1.4 Patient experiences unacceptable toxicity.

5.6.1.5 Non-protocol therapies are administered.

5.6.1.6 Patient proceeds to stem cell transplant.

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5.6.2 Step 2

Patients who have completed induction without experiencing progression or patients who have received at least 6 cycles on Arm A and 4 cycles on Arm B but stopped early due to adverse events will be randomized to a maintenance strategy of either limited duration (24 months-Arm C) or indefinite maintenance therapy (Arm D) unless:

5.6.2.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E1A11 Forms Completion Guidelines.

5.6.2.2 Patient withdraws consent.

5.6.2.3 Patient experiences progression of disease.

5.6.2.4 Patient experiences unacceptable toxicity.

5.6.2.5 Non-protocol therapies are administered.

5.6.2.6 Patient proceeds to stem cell transplant.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression and for survival for 15 years from the date of registration to Step 1.

5.8 Patient Medication Calendar

Patient medication calendar: An accurate assessment of patient compliance is an important objective of this protocol as it can potentially impact the assessment of response as well as the QoL parameters. Patients should be provided the medication calendar at the time of initiating each treatment cycle (See Appendix III). They should be carefully instructed that entries should be made at the time of taking the medications; carefully noting the time the drug was taken. The calendar should be turned in at the end of each cycle, when a new calendar should be provided. Each participating center should develop a standard procedure that will allow collection of completed medication calendars prior to each cycle.

6. Measurement of Effect

Definitions of Stringent complete response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Stable Disease (SD), and Progression (PD) are based on International Uniform Response Criteria for Multiple Myeloma.[93]

6.1 Response Considerations

6.1.1 Terms and Definitions

6.1.1.1 M-Protein

Synonyms include M-spike, monoclonal protein and myeloma protein, monoclonal paraprotein, M-component.

6.1.1.2 Response Terms:

The following response terms will be used: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progression (PD).

See Section 6.2 for definitions.

6.1.1.3 Measurable Disease

Defined by at least one of the following three measurements

- Serum M protein ≥ 1 g/dL (≥ 10gm/L)(10 g/L)
- Urine M protein ≥ 200 mg/24 hours
- Serum free light chain (FLC) assay: Involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal (< 0.26 or > 1.65)

6.1.1.4 Evaluable Disease

Patients who do not have a “measurable” serum or urine M-spike should have monoclonal bone marrow plasmacytosis ≥ 30%.

6.1.1.5 Oligosecretory Myeloma:

Patient with multiple myeloma who has NEVER had “measurable” disease, but has had a detectable monoclonal protein in his/her serum and/or urine.

6.1.1.6 Non-Secretory Myeloma

Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

6.1.2 Response Evaluation and Confirmation

6.1.2.1 Measurable Disease

Except for assessment of CR and sCR, patients with measurable disease restricted to the SPEP will need to be followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP.

Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine.

To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine.

In order to be classified as a sCR, CR, PR, or VGPR, confirmation of serum and urine monoclonal protein results is required and must be made at any time before the institution of any new therapy. Confirmation is mandatory for CR, PR and VGPR documentation.

Bone marrow biopsy is required for CR; however, a repeat bone marrow biopsy is not needed for confirmation.

Bone radiographs are not required to document response. If bone radiographs are obtained, their findings must be consistent with the bone response criteria.

6.1.2.2 Monoclonal Protein Considerations

Serum M protein level is quantitated using densitometry on serum protein electrophoresis (SPEP) except in cases where the SPEP is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. IF SPEP is not available or felt to be unreliable for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidometry can be accepted. However, this must be explicitly reported; and only nephelometry can be used for that patient to assess response and SPEP and nephelometric values cannot be used interchangeably.

Urine M protein measurement is estimated using 24-hour urine protein electrophoresis (UPEP) only. Random or 24 hour urine tests measuring kappa and lambda light chain levels are not reliable and are not allowed.

6.1.2.3 Bone Progression

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression.

When progression is based on skeletal disease alone, it should be discussed with the study chair before removing the patient from the study.

6.1.2.4 Oligosecretory and Non-Secretory myeloma (Evaluable Disease)

Patients with oligosecretory myeloma, who have measurable levels on the serum FLC assay, are assessed for response using the FLC assay instead of serum and urine M protein levels. All other requirements as outlined in each response category must be met. Patients with oligosecretory myeloma who do not have measurable levels on the serum FLC assay and patients with non-secretory myeloma may be assessed for response using bone marrow plasma cell involvement provided baseline bone marrow plasma cell percentage was ≥30%.

6.2 Response Categories

6.2.1 Stringent Complete Response (sCR)

CR as defined below plus all of the following:

- Normal serum FLC ratio
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence. Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of > 4:1 or < 1:2

6.2.2 Complete Response (CR)

Patients who have complete disappearance of an M-protein and no evidence of myeloma in the bone marrow are considered to have complete response. To be considered CR, patients must meet all of the following criteria:

- Negative immunofixation on the serum and urine *and*
- Disappearance of any soft tissue plasmacytomas *and*
- < 5% plasma cells in bone marrow
- If serum and urine are unmeasurable and the immunoglobulin free light chain parameter is being used patients must additionally have a normal ratio of 0.26-1.65 at two consecutive times

6.2.3 Very Good Partial Response (VGPR)

- Serum and urine M-component detectable by immunofixation but not on electrophoresis *or*
- 90% or greater reduction in serum M-component plus urine M-component < 100 mg per 24 hours (by SPEP and UPEP)
- If the serum and urine M protein are unmeasurable and the immunoglobulin free light chain parameter is being used to measure response, a ≥ 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels is required in place of the M protein criteria.

6.2.4 Partial Response (PR)

Requires all of the following:

- Patients who have measurable disease in the serum at baseline require ≥ 50% reduction in the level of serum M-protein (by SPEP)
- Patients who have measurable disease in the urine at baseline require ≥ 90% reduction in the level of urine M-protein or the urine M-protein must be < 200mg/24hr (by 24 hour UPEP)
- If the serum and urine M protein are unmeasurable and the immunoglobulin free light chain parameter is being used to measure response, a ≥ 50% decrease in the difference between involved and uninvolved free light chain (FLC) levels is required in place of the M protein criteria
- If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M protein, provided baseline bone marrow plasma cell percentage was ≥ 30%
- In addition to above listed criteria, if present at baseline, a ≥ 50% reduction in size of soft tissue plasmacytomas is also required

6.2.5 Stable Disease (SD)

Failure to meet response criteria outlined above on two consecutive disease assessments.

6.2.6 Progression (PD)

Patients will be considered to have progression if one of the following criteria is met. The investigation that qualified as progression should be repeated and verified on a subsequent occasion only if treating physician deems it clinically necessary.

Increase of ≥ 25% from lowest value reported in

- Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)
- Urine M-component and/or (the absolute increase must be ≥ 200 mg/ 24 hours

- Only in patients without measurable serum and urine M protein levels: the increase in difference between involved and uninvolved FLC levels by ≥ 25% above the lowest response level. The absolute increase must be > 10 mg/dL.
- Bone marrow plasma cell percentage: Increase in bone marrow plasma cell percentage by ≥ 25% above the lowest response level: the absolute % must be ≥ 10%
- Definite development of new bone lesions or soft tissue plasmacytomas OR increase in size of existing bone lesions or soft tissue plasmacytomas by ≥ 25% from lowest reported value.
- 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

6.3 Quality of Life Measurement

6.3.1 QoL Instruments

Quality of life (QoL) will be assessed to capture disease and treatment-related patient reported outcomes. The following instruments will be utilized:

- FACT-Physical (Physical): 7 questions score 0-28
- FACT-Functional (Functional): 7 questions score 0-28
- FACT-Neurotoxicity (Ntx): 11 questions score 0-44
- FACT-Multiple Myeloma Subscale (MM): 14 questions score 0-56

These instruments will be scored according to established practice. The primary QoL instrument will be the FACT-Neurotoxicity Trial Outcome Index (FACT-Ntx TOI), which is the sum of the physical, functional and neurotoxicity instruments (25 questions, score 0-100). We will also assess patient reported outcomes using the disease-specific FACT-MM. This instrument has been validated extensively and has been incorporated into our prior E1A05 and E1A06 phase III MM treatment trials as well as the ongoing Phase III trial in patients with smoldering MM (E3A06). More recently, data from E1A05 showed the FACT-MM was feasible for use in clinical trials to measure myeloma-related functions and demonstrated acceptable psychometric properties.[75]

6.3.2 Timing of QoL Assessments

Timing of QoL assessments are either related to a cycle on treatment (Step 1 or Step 2) or observation month (post Step 2 randomization). QoL assessments at baseline and on treatment have a window of +/- 7 days. QoL assessments will first be administered at induction registration (baseline) prior to initiation of treatment. During the induction phase, there will be 4 assessments for each arm as follows: for the VRd arm (Arm A), QoL will be measured at the end of cycles 1, 4 (month 2.8), 8 (month 5.5) and 12 (month 8.3 induction end) and for the CRd arm (Arm B), at the end of cycles 1, 3 (month 2.8), 6 (month 5.5) and 9 (month 8.3 induction end). QoL will also be assessed at early discontinuation of induction therapy for any reason. During the maintenance therapy phase, there will be 7 assessments as follows: for the limited lenalidomide maintenance arm (Arm C), QoL will be assessed at the end of cycles 6, 12 and 24 of therapy and at observation months 28, 33, 44 and 55 and for the indefinite lenalidomide maintenance arm (Arm D) at the end of cycles 6, 12, 24, 30, 36, 48 and 60 of therapy. Again, there will be an assessment at time of early therapy discontinuation for any reason. It should be noted, ECOG-ACRIN has an established strategy of notifying participating sites when PRO assessments are due for specific enrolled subjects to enhance data completeness.

7. Study Parameters

7.1 Therapeutic Parameters

The following pre-study tests and procedures should be done **≤ 4 weeks** before randomization/registration:

1. Pre-study scans and x-rays used to assess all measurable or non-measurable sites of disease.
2. Pre-study CBC (with differential and platelet count).
3. All required pre-study chemistries and hematology tests, as outlined in Section 3.

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7.2 Schedule of events [Arm A (followed by Arm C or Arm D)]

Rev. Add11

Rev. 10/14

Tests and procedures	≤ 28 days prior to registration	Days of bortezomib administration[14]	At the end of each cycle (induction) [5,8]	At the end of every third cycle of maintenance [8]	At end of cycle 4 and 12 of induction, and end of cycle 24 of maintenance[8] or at PD (whichever comes first)	Observation quarterly post treatment to PD or NPT	Post PD or NPT to a maximum of 15 years from study entry[15]
History and physical exam, Weight, Performance Status[16]	X		X	X		X	X
Height	X						
Hematology group (WBC, ANC, Hgb, PLT)	X	X[11]	X	X[6]		X[6]	X
Chemistry group (Calcium, creatinine, creatinine clearance, ALT, AST, Alk Phos, Total Bilirubin, LDH, glucose and TSH)[7]	X		X	X		X	X
EKG	X						
Beta-2 microglobulin	X						
C-reactive protein	X						
SPEP (Serum M-spike and albumin)	X		X[3]	X[3]		X[3]	X[3]
UPEP (Urine M-spike, 24 hour collection)	X		X[3]	X[3]		X[3]	X[3]
Serum free light chain assay[3]	X		X	X		X	X
Rev. 2/15 Immunofixation of serum and urine[4]	X[2]		X[4]	X[4]		X[4]	X[4]
Involved immunoglobulin[12]	X		X[3]	X[3]		X[3]	X[3]
Rev. 2/15 Bone marrow biopsy, aspirate, FISH[4,10,17]	X		X[4,17]		X	X[4,17]	
Metastatic bone survey	X[2]				X[2]	X[2]	
Serum or urine pregnancy test[1]	X[1]		X[1]	X[1,6]			
Register patient into RevAssist® program	See Sections 4 and 8						

	Tests and procedures	≤ 28 days prior to registration	Days of bortezomib administration[14]	At the end of each cycle (induction) [5,8]	At the end of every third cycle of maintenance [8]	At end of cycle 4 and 12 of induction, and end of cycle 24 of maintenance[8] or at PD (whichever comes first)	Observation quarterly post treatment to PD or NPT	Post PD or NPT to a maximum of 15 years from study entry[15]
Rev. 10/14	Prescribe lenalidomide via RevAssist®			X[5, 9]				
	Adverse Event assessment	X		X	X		X	X
	Quality of Life assessment	See Section 7.5						
	Tobacco Use Assessment (optional)	See Section 7.6 and Appendix XIII						
	Patient Medication Calendar			X[18]				
Rev. 9/17	Age appropriate cancer screening (see Appendix VI)[13]	X						
Rev. 9/14	Biological Sample Submissions	See Sections 7.4 and 10						

1. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks 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 4 weeks 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 V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
2. ≤ 90 days prior to registration. Metastatic bone survey should be done at the end of induction and then repeated every 12 cycles during maintenance and observation.
3. Required only if used to assess disease response.
4. Rev. 2/15 Serum and urine immunofixation and bone marrow examination are required to document complete response; serum free light chain is required in addition for documenting CR in patients with light chain as the only measurable disease at baseline. Serum free light chain is always required to document stringent complete response. All these measurements should be repeated (mail-in acceptable) to confirm complete response or stringent complete response, as applicable. Bone marrow biopsy does not need confirmation. Bone marrow should be scheduled for the end of the subsequent cycle after a negative immunofixation in serum and urine has been observed.
5. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.
6. These tests need to be done at the beginning of every cycle during maintenance phase.
7. TSH to be repeated every three months, for patients on active treatment.
8. Rev. 9/14 +/- 7 days but before starting each cycle of treatment. Screening labs can be used for cycle 1 day 1 labs. Only CBC and creatinine needs to be available from within 7 days of starting therapy.
9. Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions must be filled within 7 days.

Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the RevAssist® program.

10. FISH only required at baseline, and must be done ≤ 90 days prior to registration.
11. Hematology group to be done first day of bortezomib administration each week.
12. Involved immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient is "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma.
13. If age appropriate cancer screening is not up-to-date, it should be completed within 3 months after registration.
14. Bortezomib administered days 1, 4, 8 and 11 during cycles 1-8 and days 1 and 8 during cycles 9-12.
15. Follow up will occur every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, and then yearly until patient is 15 years from study entry. No further assessments are required after progression; however, patients must continue to be followed for survival.

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16. If plasmacytoma is detected on physical examination at baseline, follow-up should be performed during therapy and documented. The same approach used at baseline should be used at follow-up.
17. A bone marrow biopsy/aspirate is not required to be performed within 28 days prior to registration unless measureable disease is only present in bone marrow. If measurable disease is only present in bone marrow, biopsies will be done after the first 2 cycles of therapy and then every 3-4 cycles per investigator discretion. Please note, a bone marrow biopsy/aspirate should be performed at end of cycle 4 and 12 of induction, and end of cycle 24 of maintenance or at PD (whichever comes first)
18. The Patient Medication Calendar must be completed for each cycle of treatment to record lenalidomide capsules and dexamethasone tablets taken. Please see Section 5.8 and Appendix III: Patient Medication Calendar.

Rev. 9/15, 9/17

7.3 Schedule of events [Arm B (followed by Arm C or Arm D)]

Rev. Add11

Tests and procedures	≤ 28 days prior to registration	Days of carfilzomib administration[14]	At the end of each cycle (induction)[5, 8]	At the end of every third cycle of maintenance[8]	At End of Cycle 3 and 9 of induction, and end of cycle 24 of maintenance[8] or at PD (whichever comes first)	Observation quarterly post treatment to PD or NPT	Post PD or NPT to a maximum of 15 years from study entry[15]
History and physical exam, Weight, Performance Status[16]	X		X	X		X	X
Height	X						
Hematology group (WBC, ANC, Hgb, PLT)	X	X[11]	X	X[6]		X[6]	X
Chemistry group (Calcium, creatinine, creatinine clearance, ALT, AST, Alk Phos, Total Bilirubin, LDH, glucose and TSH)[7]	X		X	X		X	X
EKG	X						
Beta-2 microglobulin	X						
C-reactive protein	X						
SPEP (Serum M-Spike and albumin)	X		X[3]	X[3]		X[3]	X[3]
UPEP (Urine M-spike, 24 hour collection)	X		X[3]	X[3]		X[3]	X[3]
Serum free light chain assay[3]	X		X	X		X	X
Rev. 2/15 Immunofixation of serum and urine[4]	X[2]		X[4]	X[4]		X[4]	X[4]
Involved immunoglobulin[12]	X		X[3]	X[3]		X[3]	X[3]
Rev. 2/15 Bone marrow biopsy, aspirate, FISH[4,10, 17]	X		X[4,17]		X	X[4,17]	
Metastatic bone survey	X[2]				X[2]	X[2]	
Serum or urine pregnancy test[1]	X[1]		X[1]	X[1,6]			

	Tests and procedures	≤ 28 days prior to registration	Days of carfilzomib administration[14]	At the end of each cycle (induction)[5, 8]	At the end of every third cycle of maintenance[8]	At End of Cycle 3 and 9 of induction, and end of cycle 24 of maintenance[8] or at PD (whichever comes first)	Observation quarterly post treatment to PD or NPT	Post PD or NPT to a maximum of 15 years from study entry[15]
	Register patient into RevAssist® program	See Sections 4 and 8						
	Prescribe lenalidomide via RevAssist®			X[5,9]				
Rev. 9/17	Adverse Event assessment	X		X	X		X	X
	Quality of life assessment	See Section 7.5						
	Tobacco Use Assessment (optional)	See Section 7.6 and Appendix XIII						
Rev. Add13	Patient Medication Calendar			X[18]				
	Age appropriate cancer screening (see Appendix VI)[13]	X						
Rev. 9/14	Biological Sample Submission	See Sections 7.4 and 10						

1. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks 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 4 weeks 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 V: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). If previously randomized to Arm B, FCBPs must also continue to use contraception or abstinence for 30 days after the last dose of carfilzomib and males must continue to use condoms for 90 days after the last dose of carfilzomib.
2. ≤ 90 days prior to registration. Metastatic bone survey should be done at the end of induction and then repeated every 12 cycles during maintenance and observation.
3. Required only if used to assess disease response.

Rev. 2/15

4. Serum and urine immunofixation and bone marrow examination are required to document complete response; serum free light chain is required in addition for documenting CR in patients with light chain as the only measurable disease at baseline. Serum free light chain is always required to document stringent complete response. All these measurements should be repeated (mail-in acceptable) to confirm complete response or stringent complete response, as applicable. Bone marrow biopsy does not need confirmation. Bone marrow should be scheduled for the end of the subsequent cycle after a negative immunofixation in serum and urine has been observed.
5. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

6. These tests need to be done at the beginning of every cycle during maintenance phase.
7. TSH to be repeated every three months, for patients on active treatment.

Rev. 9/14

8. +/- 7 days but before starting each cycle of treatment. Screening labs can be used for cycle 1 day 1 labs. Only CBC and creatinine needs to be available from within 7 days of starting therapy.
9. Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions must be filled within 7 days. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the RevAssist® program.
10. FISH only required at baseline and must be done ≤ 90 days prior to registration.

Rev. Add14

11. Hematology group to be done +/- 1 day from the first day of carfilzomib administration each week.
12. Involved immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient is "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma.

Rev. 9/17

13. If age appropriate cancer screening is not up-to-date, it should be completed within 3 months after registration.
14. Carfilzomib administered 20 mg/m2 IV days 1, 2 and the 36 mg/m2 IV days 8, 9, 15, 16 during cycle 1 and 36 mg/m2 days 1, 2, 8, 9, 15, 16 during cycles 2-9.
15. Follow up will occur every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry, and then yearly until patient is 15 years from study entry. No further assessments are required after progression; however, patients must continue to be followed for survival.
16. If plasmacytoma is detected on physical examination at baseline, follow-up should be performed during therapy and documented. The same approach used at baseline should be used at follow-up.

Rev. Add11

17. A bone marrow biopsy/aspirate is not required to be performed within 28 days prior to registration unless measurable disease is only present in bone marrow. If measurable disease is only present in bone marrow, biopsies will be done after the first 2 cycles of therapy and then every 3-4 cycles per investigator discretion. Please note, a bone marrow biopsy/aspirate should be performed at end of Cycle 3 and 9 of induction, and end of cycle 24 of maintenance or at PD (whichever comes first).
18. The Patient Medication Calendar must be completed for each cycle of treatment to record lenalidomide capsules and dexamethasone tablets taken. Please see Section 5.8 and Appendix III: Patient Medication Calendar.

Rev. 9/17

7.4 Biological Sample Submissions

1. Peripheral blood and bone marrow should be submitted as outlined in Section 10 of E1A11 for the laboratory research studies and/or banking per patient consent. Follow-up bone marrow aspirates are required to be submitted for the MRD analysis outlined in Section 11.2.
2. Kits are being provided for the collection and shipment of the bone marrow and peripheral blood submissions, please refer to Section 10 for instructions.

Rev. 5/14

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) (see Section 10) for purposes of monitoring compliance.

NOTE: Biological samples for the optional laboratory research studies and/or banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

Rev. 5/14, 9/14, Add11

Biological Materials	Pre-Registration[1]	After Induction Cycle Three [Arm B]	After Induction Cycle Four [Arm A]	After Induction Cycle Nine [Arm B]	After Induction Cycle Twelve [Arm A]	After Maintenance Cycles 24 and 36	Confirmation of CR[2]	Disease Progression
MANDATORY *for Defined Laboratory Research Studies*								
Bone Marrow Aspirate (1) 1mL Streck Cell Preservative® vial		X		X		X	X	
From Patients Who Answer *"YES"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*								
Bone Marrow Aspirate (1) 1mL Streck Cell Preservative® vial	X							
Peripheral Blood (1) 8.5mL ACD (yellow top) tube	X	X		X		X	X	X
From Patients Who Answer *"YES"* to *"I agree to provide additional specimens for research."*								
Bone Marrow Aspirate (2) 6mL ACD (yellow top) tubes	X	X		X		X	X	X[5]
Peripheral Blood (1) 10mL Red Top tube	X	X		X		X		X
Bone Marrow Core Biopsy Slides (5)	X	X		X		X	X	X
From Patients Who Answer *"YES"* to *"I agree to participate in the genomic sequencing laboratory research study." [through the CoMMpass Study]*								
Bone Marrow Aspirate (1) 5mL Green Top Sodium Heparin Vacutainer Tube[6]	X						X[3,4]	X[3,4]
Peripheral Blood (2) 5mL Purple Top EDTA Vacutainer Tubes[6]	X						X[3,4]	X[3,4]

Rev. 5/14, 9/17

1. Prior to treatment. The blood and bone marrow collections are to occur at the time of those performed for clinical assessments. Additional procedures to collect the research specimens should not be required.
2. Any subsequent marrow performed for CR confirmation.
3. At relapse/progression and suspected CR. For any given patient, specimens at relapse/progression are not required beyond the second episode (first and subsequent relapse) during the follow-up period.
4. Bone marrow specimens at relapse/progression must be obtained before a new therapeutic regimen is begun.

Rev. Add11

5. Or excessive toxicity for Arm D patients.
6. If participating in this substudy, both bone marrow and peripheral blood must be submitted together on the day of collection. The sequencing cannot be performed without both specimen types.

7.5 Quality of Life Assessments

1. The questionnaires must be administered at the time points listed below. Timing of QoL assessments are either related to a cycle on treatment (Step 1 or Step 2) or observation month (post Step 2 randomization). QoL assessments at baseline and on treatment have a window of +/- 7 days. The patient should be instructed to respond to the questionnaires in terms of his or her experience during the timeframe specified on each questionnaire.
2. The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the questionnaires as long as the staff person does not influence the patient's responses.
3. The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how he or she is feeling. If a question was not answered, the patient should be asked if he or she would like to answer it. The patient should always have the option to refuse.
4. If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted according to the instructions in the E1A11 Forms Completion Guidelines.

Rev. 9/15

Step 1 Induction[2]			
Assessment Number[1]	Calendar Time (months) From Step 1 Randomization	Arm A	Arm B
Baseline	0	Prior to Treatment	Prior to Treatment
1	~ 1	Cycle 1 End	Cycle 1 End
2	2.8	Cycle 4 End	Cycle 3 End
3	5.5	Cycle 8 End	Cycle 6 End
4	8.3	Cycle 12 End	Cycle 9 End
Step 2 Maintenance[2] and Observation			
Assessment Number[1]	Calendar Time (months) From Step 2 Randomization	Arm C	Arm D
1	5.5	Cycle 6 End	Cycle 6 End
2	11	Cycle 12 End	Cycle 12 End
3	22	Cycle 24 End	Cycle 24 End
4	28	28	Cycle 30 End
5	33	33	Cycle 36 End
6	44	44	Cycle 48 End
7	55	55	Cycle 60 End

1. QoL will also be assessed at early discontinuation of induction or maintenance therapy for any reason.
2. +/- 7 days at cycle end.

Rev. Add11

7.6 Patient Reported Outcome Measures: Tobacco Use Assessment

7.6.1 Assessments

Assessments will be captured directly from the participants using the EASEE-PRO portal. When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to EASEE-PRO, and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

The Core and Extension C-TUQ items will be assessed, together with patient-reported physical and psychological symptoms (See Table below). Specifically, these items will be administered using the EASEE-PRO system described in the companion EA NCORP application. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, sleep difficulties, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU). Detailed information on various measures is outlined in Appendix XIII.

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1-Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4-Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15-Q16	Q11-Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17-Q18	Q13-Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20-21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending specific cancer type and treatment.

7.6.2 Assessment Schedule

Survey of Tobacco Use will be administered at the following time points:

- at baseline (trial enrollment)
- at 3 month follow-up from study registration
- at 6 month follow-up from study registration

8. Drug Formulation and Procurement

8.1 Carfilzomib

Complete instructions for storage and use of Lyophilized Carfilzomib for Injection are available in Appendix XI.

8.1.1 Other Names

Kyprolis®, PR171

8.1.2 Classification:

Proteasome inhibitor

8.1.3 Mode of Action

Carfilzomib is an analog of epoxomicin and eponemycin; a tetrapeptide keto-epoxide-based irreversible inhibitor of the chymotrypsin-like activity of the 26S proteasome. Proteasome inhibition leads to the accumulation of polyubiquitinated protein substrates within cells and to the selective induction of apoptosis in malignant cells while sparing most normal cells.

8.1.4 Storage and Stability

Lyophilized Carfilzomib for Injection is an investigational therapeutic agent provided in a single-dose vial as a sterile, lyophilized powder in the following dosage:

- 60 mg single-use glass vial / 4 pk carton

Each single-dose vial provides 60 mg of carfilzomib in a 50 cc labeled glass vial with an elastomeric stopper and a flip-off lid. Flip-off lid colors may vary.

The product is supplied in labeled carton(s) containing four (4) single-use vials per carton and is shipped and stored between 2°C–8°C (36°F–46°F).

Prior to administration, the lyophilized product is aseptically reconstituted with Water for Injection.

Lyophilized drug product is stored in a refrigerator at 2°C–8°C (36°F–46°F). After reconstitution, Carfilzomib for Injection must be used on the day of preparation. The clear solution can be stored until use in a refrigerator (recommended) controlled at 2°C–8°C (36°F–46°F) or at room temperature at 15°C–30°C (59°F–86°F) until use. Do not freeze lyophilized or reconstituted drug.

Rev. Add11

The storage temperature must be monitored and a temperature log maintained and recorded daily at minimum. The refrigerator should also be on a backup generator and alarmed for temperature deviations if available. Any temperature excursions during storage must be reported to Amgen (formerly Onyx) for evaluation and disposition. Please utilize the Temperature Excursion Disposition Form. Amgen (formerly Onyx) contact information is provided on the form. This form can be downloaded from the E1A11 Study Specific

Tools section on the ECOG website (www.ecog.org) in WORD format. A copy of this form is also located in Appendix X.

8.1.5 Dose Specifics

For Arm B patients only, Carfilzomib will be administered at doses of 36 mg/m^2 or less on days 1, 2, 8, 9, 15, and 16 of the induction cycles. On days 1 and 2 of cycle 1 only, the dose will be 20 mg/m^2.

8.1.6 Preparation

Aseptically reconstitute each vial by slowly injecting 29 mL Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming. Do not use alternative diluents. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product

8.1.7 Route of Administration

Carfilzomib is administered intravenously. It should be given as a slow infusion over 30 minutes. Patients should receive 250 ml Normal Saline hydration prior to Carfilzomib infusion. Post carfilzomib infusion can be used as clinically indicated.

8.1.8 Pharmacokinetics

a) Absorption – carfilzomib doses of 15 to 36 mg/m2 lead to an average of 77% to 86% proteasome inhibition in whole blood and PBMCs 1 hour after dosing.

b) Distribution – Vss = 10-228L. Due to metabolism in a variety of tissues and the irreversible, covalent binding of carfilzomib to the 20S proteasome, the Vss values may underestimate the extent of tissue distribution of carfilzomib, which has rapid and wide distribution of carfilzomib to tissues except brain. An in vitro protein-binding study using equilibrium dialysis demonstrated that approximately 94% of carfilzomib is bound to human plasma proteins, however this binding has not been observed to affect the disposition of any concomitant medication in the clinic

c) Metabolism – Peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism; none of these metabolites inhibit the activity of the 20S proteasome. Cytochrome P450-mediated pathways are not significant in the overall metabolism of carfilzomib.

d) Excretion – Carfilzomib is cleared rapidly, with a mean terminal half-life of ≤ 60 minutes in humans. Despite the rapid clearance of carfilzomib from the blood compartment, prolonged potent proteasome inhibition is observed. The pharmacodynamic half-life of carfilzomib is approximately 24 hours. Renal excretion accounts

for 20-30% of dose. There is no systemic accumulation of drug after repeat doses.

8.1.9 Incompatibilities

To date, the administration of carfilzomib in the clinic has not required modification of doses of any concomitant medications, although studies are ongoing to determine if there is a significant clinical inhibitory effect of carfilzomib on human cytochrome CYP3A4/5. Caution should be exercised in administration of concomitant medications, which are substrates of human CYP3A4.

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8.1.10 Availability

Carfilzomib is an investigational agent (IND# 118503) available free of charge from Amgen, Inc and distributed by Amgen Thousand Oaks (CA). Carfilzomib for injection is supplied as cartons of 4 single-use 60 mg vials. **Carfilzomib should only be ordered for patients randomized to Arm B.**

Initial Drug Orders for Each Patient

Following randomization to Arm B a supply of Carfilzomib may be ordered. Investigators must email a completed E1A11 Carfilzomib Study Drug Request Form (Appendix IX) to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu who will then forward the drug request to Amgen NASCR (US) for site shipment set-up; upon completion of site set up, Amgen NASCR will forward to Amgen Clinical Customer Service for order fulfillment. If email is not available, the completed form may be faxed to ATTN: ECOG-ACRIN Drug Team at 617-589-0919. **No starter supplies are available for this protocol.**

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Carfilzomib will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution. Sites should order enough vials to complete 2 cycles of treatment (maximum of 6 cartons totaling 24 vials).

Institutions should allow 8-9 business days for INITIAL shipment of drug from Amgen Thousand Oaks from receipt of the E1A11 Carfilzomib Drug Request Form by the ECOG-ACRIN Drug Team. Shipments will be made from Amgen Thousand Oaks on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Any order that would fall on a Friday under the lead time criteria below is scheduled for Monday. Any order that has a ship date that falls on a holiday will default to the next available shipping day according to the lead time criteria below.

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Date Request Received By ECOG-ACRIN Drug Team	Site Set Up Complete	Ship Date	Receipt of Drug at Institution
Orders received on day 1 before 12pm ET	Day 5	Day 7	Day 8

Date Request Received By ECOG-ACRIN Drug Team	Site Set Up Complete	Ship Date	Receipt of Drug at Institution
Orders received on day 1 after 12pm ET	Day 6	Day 8	Day 9

Amgen Thousand Oaks (ATO) offices will be closed each year during the week of 04 July and prior to 25 December. During this time, there will be no shipments to clinical sites. Shipments to clinical sites will not occur from the Monday of the beginning of each shutdown, resuming the following Monday for 04 July, and the first business weekday of the New Year for 25 December. It is recommended that drug supply is assessed at each site and orders for (re)-supply are submitted prior to each shutdown.

The E1A11 Carfilzomib Drug Request Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format and is also located in Appendix IX.

Lyophilized Carfilzomib for Injection is using 2°C-8°C Credo shippers via UPS or FedEx. Credo is a re-usable shipping system and all shippers need to be returned to Amgen. See the return process details in the attachment. The returns costs are covered by Amgen.. Please refer to the complete instructions for storage and use of Lyophilized Carfilzomib for Injection which may be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org).

As part of Amgen's shipper performance monitoring system, temperature of the shipments will be monitored on an ad hoc basis. In case that a temperature logger is included in the shipment, the receiving site is asked to follow instructions included.

Each site will need to complete and return the POR to the email on the form.

If needed, the Temperature Excursion Disposition Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format and can also be found in Appendix X.

IMPORTANT REORDER INSTRUCTIONS

Once it is determined that the patient will continue treatment, please reorder **2 cycles** of study drug immediately. Institutions should keep in mind the number of vials used per cycle, and that Carfilzomib is provided in cartons of 4 single-use 60 mg vials.

Institutions should allow 3-4 business days for shipment of drug from Amgen Thousand Oaks (CA) from receipt of the E1A11 Carfilzomib Drug Request Form by the ECOG-ACRIN Drug Team. Shipments will be made from Amgen Thousand Oaks on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Any order that would fall on a Friday under the lead time criteria below is scheduled for Monday. Any order

that has a ship date that falls on a holiday will default to the next available shipping day according to the lead time criteria below.

Rev. 5/14

Date Request Received By ECOG-ACRIN Drug Team	Ship Date	Receipt of Drug at Institution
Orders received on day 1 before 12pm ET	Day 2	Day 3
Orders received on day 1 after 12pm ET	Day 3	Day 4

Amgen Thousand Oaks (ATO) offices will be closed each year during the week of 04 July and prior to 25 December. During this time, there will be no shipments to clinical sites. Shipments to clinical sites will not occur from the Monday of the beginning of each shutdown, resuming the following Monday for 04 July, and the first business weekday of the New Year for 25 December. It is recommended that drug supply is assessed at each site and orders for (re)-supply are submitted prior to each shutdown.

The E1A11 Carfilzomib Drug Request Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format or found in Appendix IX.

Lyophilized Carfilzomib for Injection is using 2°C-8°C Credo shippers via UPS or FedEx. Credo is a re-usable shipping system and all shippers need to be returned to Amgen. See the return process details in the attachment. The returns costs are covered by Amgen. Please refer to the complete instructions for storage and use of Lyophilized Carfilzomib for Injection which may be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org).

As part of Amgen's shipper performance monitoring system, temperature of the shipments will be monitored on an ad hoc basis. In case that a temperature logger is included in the shipment, the receiving site is asked to follow instructions included.

Each site will need to complete and return the POR to the email on the form.

If needed, the Temperature Excursion Disposition Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format or found in Appendix X.

Drug Destruction and Return

At the completion of all patients' treatment randomized to Arm B at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried.

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CLINICAL PRODUCT COMPLAINT

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, reliability, safety, effectiveness, or performance of a drug after it is released for distribution to clinic. If you have a product complaint, please submit Form-0314341 in the *Other Study-Specific Tools and Information* section.

8.1.11 Site of Administration

Patients must receive drug at enrolling institution.

8.1.12 Side Effects

Adverse event listing for Carfilzomib (Derived from Investigator Brochure version 16.1) and safety alerts:

NOTE: The below listing is NOT A CAEPR and should not be treated as one.

Likely (> 20%)	Less Likely (<=20%)	Rare but Serious (< 3%)
Anemia	Leukopenia	Congestive heart failure
Thrombocytopenia	Neutropenia	Tumor lysis syndrome
Lymphopenia	Blurred vision	Acute Renal failure
Nausea	Abdominal pain	Posterior reversible encephalopathy syndrome (PRES)
Diarrhea	Abdominal distension	Hypertension including hypertensive crises
Vomiting	Dyspepsia	Pulmonary Hypertension
Constipation	Chills	Interstitial Lung Disease (including pneumonitis)
Fatigue	Asthenia	Acute Respiratory Failure
Fever	Pain	Acute Respiratory Distress Syndrome (ARDS)
Edema limbs	Pneumonia	Gastrointestinal perforation
Upper respiratory infection	Urinary tract Infection	Pericarditis
Lymphocyte count decreased	Nasopharyngitis	Pericardial effusion
Blood creatinine increased	Neutrophil count decreased	
Platelet count decreased	White blood cell decreased	
Back pain	AST increased	
Headache	ALT increased	
Dyspnea	Blood uric acid increased	
Cough	Blood phosphorous decreased	
	Weight decreased	
	Anorexia	
	Arthralgia	

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	Anorexia	
	Hypokalaemia	
	Hypomagnesaemia	
	Hyperglycaemia	
	Hyponatraemia	
	Hypophosphataemia	
	Hypercalcaemia	
	Hyperkalaemia	
	Dehydration	
	Hypocalcaemia	
	Decreased appetite	
	Hyperuricaemia	
	Hypoalbuminaemia	
	Arthralgia	
	Muscle spasms	
	Pain in extremity	
	Chest wall pain	
	Shoulder pain	
	Myalgia	
	Bone pain	
	Dizziness	
	Hypoaesthesia	
	Paraesthesia	
	Neuropathy, peripheral	
	Insomnia	
	Anxiety	
	Confusional state	
	Epistaxis	
	Pharyngolaryngeal pain	
	Dyspnoea, exertional	
	Productive cough	
	Rhinorrhoea	
	Nasal congestion	
	Rash	
	Pruritus	
	Hypertension	
	Hypotension	

NOTE: Second cancers have been reported in patients receiving therapy with carfilzomib. Its relationship with the drug is not clear at this time.

8.1.13 Nursing/Patient Implications

- Monitor CBC. Instruct patient to report any signs or symptoms of infection, unusual bruising, or bleeding to the health care team.
- Counsel patient in weight maintenance dietary regime. Small frequent meals with an increased protein and carbohydrate content may work best.

- GI side effects are commonly seen, but are usually mild in nature (nausea, diarrhea). Treat symptomatically and monitor for effectiveness. Instruct patient to report symptoms promptly.
- Pneumonia has been seen. Instruct patient to report any shortness of breath, cough and/or chest pain to the study team.
- Elevated creatinine and isolated cases of renal failure (some associated with tumor lysis syndrome) have been seen. Make sure patient is well hydrated prior to administration and monitor creatinine levels closely.
- Fatigue is the most commonly reported side effect. Instruct patient in energy conserving lifestyle and monitor for effectiveness.
- There is a possibility of drug-drug interaction with substrates of the CYP3A4 cytochrome. Take a detailed history of patient's concomitant medications including OTC and herbal preparations. Instruct patients not to start any new medications without checking with the study first.
- Instruct patient to report any cardiac palpitations, increased pulse, lightheadedness, visual changes, feelings of weakness or dizziness.
- Periodically assess vital signs.
- Instruct patient to report any numbness, tingling, or pain in the hands and/or feet to the health care team.

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8.1.14 References

1. Demo SD, Kirk CJ, Aujay MA, et al. Anti-tumor activity of PR 171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007; 67(13):6383-91.
2. Kuhn DJ, Chen Q, Voorhees PM, Strader JS, Shenk, KD, Sun CM, Demo SD, Bennett, SD, van Leeuwen, F, Chanan-Khan, A and Orlowski, RZ. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007 Nov 1;110(9):3281-90.
3. Badros AZ, Vij R, Martin T, Zonder JA, Kunkel L, Wang Z, Lee S, Wong AF, Niesvizky R. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. Leukemia. 2013;27(8):1707-14. doi: 10.1038/leu.2013.29. PubMed PMID: 23364621; PMCID: PMC3740399.
4. Niesvizky R, Martin TG, 3rd, Bensinger WI, Alsina M, Siegel DS, Kunkel LA, Wong AF, Lee S, Orlowski RZ, Wang M. Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clin Cancer Res. 2013;19(8):2248-56. doi: 10.1158/1078-0432.CCR-12-3352. PubMed PMID: 23447001; PMCID: PMC4149337.

5. Niesvizky R, Martin TG, 3rd, Bensinger WI, Alsina M, Siegel DS, Kunkel LA, Wong AF, Lee S, Orlowski RZ, Wang M. Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clin Cancer Res. 2013;19(8):2248-56. doi: 10.1158/1078-0432.CCR-12-3352. PubMed PMID: 23447001; PMCID: PMC4149337.
6. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, Hajek R, Rosinol L, Siegel DS, Mihaylov GG, Goranova-Marinova V, Rajnics P, Suvorov A, Niesvizky R, Jakubowiak AJ, San-Miguel JF, Ludwig H, Wang M, Maisnar V, Minarik J, Bensinger WI, Mateos MV, Ben-Yehuda D, Kukreti V, Zojwalla N, Tonda ME, Yang X, Xing B, Moreau P, Palumbo A, Investigators A. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-52. doi: 10.1056/NEJMoa1411321. PubMed PMID: 25482145.
7. Carfilzomib Investigator Brochure Version 16.1

8.2 Bortezomib

8.2.1 Other Names

Velcade®, PS341, MLN-341, LDP-341

8.2.2 Classification

Proteasome inhibitor.

8.2.3 Mode of Action

Proteasome inhibition.

8.2.4 Storage and Stability

Storage: The intact vials should be stored at room temperature and protected from light.

Stability: Shelf life surveillance of the intact vials is ongoing. The solution as reconstituted is stable for 43 hours at room temperature.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

8.2.5 Dose Specifics

For Arm A patients only: Bortezomib will be administered at doses of 1.3 mg/m^2 or lower on days 1,4,8 and 11 (cycles 1-8); days 1 and 8 (cycles 9-12).

8.2.6 Preparation

For SC administration, each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood), within 8 hours before dosing, with 1.4 mL of normal (0.9%) saline, sodium chloride injection, so that the reconstituted solution contains

bortezomib at a concentration of 2.5 mg/mL. For intravenous administration, dilute each 3.5 mg vial with 3.5 ml of 0.9% NaCl resulting in a 1 mg/mL solution of bortezomib.

8.2.7 Route of Administration

Bortezomib may be administered intravenously (rapid push, 3-5 seconds) or subcutaneously

8.2.8 Pharmacokinetics

Distribution: 498-1884 L/m2. Distributes widely to peripheral tissues.

Protein binding, plasma: ~83%

Metabolism: Hepatic primarily via CPY2C19 and 3A4 and to a lesser extent CYP1A2; forms metabolites (inactive) via deboronization followed by hydroxylation. Total exposure to bortezomib is increased in patients with moderate to severe hepatic impairment; consider reduction of starting dose in these patients.

Half-life elimination: Single dose: 9-15 hours; multiple dosing: 1 mg/m2: 40-193 hours; 1.3 mg/m2: 76-108 hours.

8.2.9 Incompatibilities

Cytochrome P450 Effect: Substrate of CYP1A2 (minor), 2C9 (minor), 2C19 (major), 2D6 (minor), 3A4 (major); Inhibits CYP1A2 (weak), 2C9 (weak), 2C19 (moderate), 2D6 (weak), 3A4 (weak).

Increased Effect/Toxicity: Bortezomib may increase the levels/effects of other CYP2C19 substrates. Levels/effects of bortezomib may be increased by CYP2C19 and CYP3A4 inhibitors. Patients should be closely monitored when given bortezomib in combination with strong CYP3A4 inhibitors (such as ketoconazole and ritonavir).Decreased Effect: Levels/effects of bortezomib may be decreased by CYP2C19 and CYP3A4 inducers.

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St John’s wort may decrease bortezomib levels.

8.2.10 Availability

Commercially available bortezomib will be used.

8.2.11 Site of Administration

Patients can receive bortezomib under care of local oncologist, returning to the enrolling institution only at the beginning of each cycle.

8.2.12 Nursing/Patient Implications

- Monitor CBC. Instruct patient to report any signs or symptoms of infection, unusual bruising, or bleeding to the health care team.
- Counsel patient in weight maintenance dietary regime. Small frequent meals with an increased protein and carbohydrate content may work best.

- Diarrhea was a dose limiting toxicity in Phase I trials. Instruct patient to report diarrhea and treat symptomatically.
- Provide symptomatic relief of nausea and vomiting and evaluate effectiveness.
- Instruct patient to report any cardiac palpitations, increased pulse, lightheadedness, visual changes, feelings of weakness or dizziness.
- Periodically assess vital signs.
- Instruct patient to report any numbness, tingling, or pain in the hands and/or feet to the health care team.
- Instruct patient to report any rash.
- Advise patient that fatigue may be a side effect. Instruct patient in energy conserving techniques.
- The following SC injection guidelines will be observed:
  - one SC dose will be given as a single injection
  - anatomical sites of SC administration are thighs (right or left) or abdomen (right or left)
  - the SC injection site will be rotated for successive injections
  - within the same cycle, injections at the same site should be avoided; it is recommended to alternate between right and left abdomen, upper and lower quadrant, or between right and left thigh, proximal and distal sites.
  - the selected SC injection site should be free from any skin condition that might interfere with the assessment of injection site reactions

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8.2.13 References

1. VELCADE® (bortezomib) for Injection [package insert]. Cambridge, MA:

   Millennium Pharmaceuticals, Inc.; 2012 January.

2. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, Stewart AK, Turturro F, Rifkin R, Wolf J, Estevam J, Mulligan G, Shi H, Webb IJ, Rajkumar SV. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119(19):4375-82. doi: 10.1182/blood-2011-11-395749. PubMed PMID: 22422823.

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therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679-86. doi: 10.1182/blood-2010-02-268862. PubMed PMID: 20385792; PMCID: PMC3324254.

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5. Bortezomib Investigator Brochure Edition 19, July 8, 2016

8.3 Lenalidomide

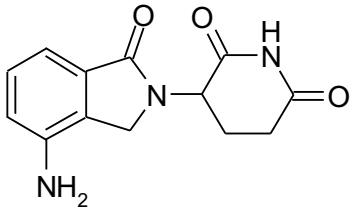
8.3.1 Other Names

IMiD™ compound CC-5013, Revlimid® (formerly Revimid™)

8.3.2 Classification

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

Chemical Structure of Lenalidomide



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

The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. 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.

8.3.3 Mode of Action

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and anti-angiogenic properties. Lenalidomide inhibited the secretion of pro-

inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

8.3.4 Storage and Stability

Lenalidomide will be supplied as capsules for oral administration. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

8.3.5 Dose Specifics

Lenalidomide will be administered at doses of 25 mg during the induction phase and 15 mg during the maintenance phase.

8.3.6 Preparation

No preparation required

8.3.7 Route of Administration

Lenalidomide will be administered orally

8.3.8 Pharmacokinetics

Absorption: 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.

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.

Distribution: In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion: 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.

8.3.9 Incompatibilities

None

8.3.10 Availability

Lenalidomide will be provided in accordance with the RevAssist program of Celgene Corporation. Per standard RevAssist requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled on this trial, must be registered in and comply with all requirements of the RevAssist® program.

Scheduling Considerations:

Lenalidomide cannot be shipped to patients until all of the steps outlined below have been completed. Due to the multiple steps involved in ordering lenalidomide we ask that sites allow adequate time for order processing to ensure patient treatment is not delayed.

Sites should educate patients that they must register in and comply with all requirements of the RevAssist® program including the patient survey and patient education in order for drug orders to be approved.

Please note that lenalidomide will be shipped directly to patients.

There will be no weekend or holiday delivery of drugs.

Prescriptions must be filled within 7 days and only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

No Starter Supplies are available for this protocol.

Strengths Available and Order Recommendations:

Lenalidomide is available as a 5mg, 10mg, 15 mg, or 25mg capsule for oral administration. Only enough lenalidomide for one cycle of therapy will be supplied to the patient at a time.

Initial Orders:

Please note that lenalidomide cannot be shipped to patients until all of the following steps have been completed. Steps 1 through 4 can be completed at any time after randomization. These steps register the patient and physician into the RevAssist program. Once it is determined the patient is eligible to proceed on to Arms A, B, C or D, sites can complete the remaining steps. Step 5 begins the prescription process and all subsequent steps must be completed within 7 days.

1. Prescribing physician registers in the RevAssist® program by either calling 1-888-423-5436 or registering through www.REVLIMID.com.
2. Patient must be randomized and eligible.
3. Prescribing physician assists patient to enroll in the RevAssist® program by obtaining and signing a Patient-Physician Agreement

Form (PPAF) either through calling Celgene Customer Care at 1-888-423-5436 or via www.REVLIMID.com

4. Patient signs the appropriate PPAF and agrees to follow all the procedures of the commercial RevAssist® Program. The prescribing physician will then fax the completed PPAF to Celgene at 1-888-432-9325
5. Patient and prescriber complete the phone surveys as required by the RevAssist® Program by calling Celgene Customer Care at 1-888-423-5436 or utilizing the RevAssist online® access.
6. At the completion of the survey, the prescribing physician is given a RevAssist® authorization number. The prescription containing the authorization number should be faxed to the pharmacy of choice.
7. Prescribing physician advises the patient that a representative from a RevAssist® contract pharmacy will contact them by phone within 24 hours.
8. RevAssist® contract pharmacy calls patient to conduct patient education.
9. RevAssist® contract pharmacy calls Celgene Customer Care for confirmation number.
10. RevAssist® contract pharmacy approves the order and ships lenalidomide and FDA-approved Medication Guide directly to the patient. Once the order is approved, patient will receive lenalidomide via FedEx in 1-2 business days.

Reorders:

Please note that lenalidomide cannot be shipped to patients until all of the following steps have been completed:

1. Patient and prescriber complete the phone surveys as required by the RevAssist® Program by calling Celgene Customer Care at 1-888-423-5436 or utilizing the RevAssist online® access.
2. At the completion of the survey, the prescribing physician is given a RevAssist® authorization number. The prescription containing the authorization number should be faxed to the pharmacy of choice. The list of pharmacies in the RevAssist network can be found at http://www.celgene.com/patient-support/pharmacy-network.aspx
3. Prescribing physician advises the patient that a representative from a RevAssist® contract pharmacy will contact them by phone within 24 hours.
4. RevAssist® contract pharmacy calls patient to conduct patient education.
5. RevAssist® contract pharmacy calls Celgene Customer Care for confirmation number.

6. RevAssist® contract pharmacy approves the order and ships lenalidomide and FDA-approved Medication Guide directly to the patient. Once the order is approved, patient will receive lenalidomide via FedEx in 1-2 business days.

Scheduling Considerations:

Lenalidomide cannot be shipped to patients until all of the steps above have been completed. Due to the multiple steps involved in ordering lenalidomide we ask that sites allow adequate time for order processing to ensure patient treatment is not delayed.

Drug Destruction and Return:

Sites are to instruct patients to return any unused lenalidomide to Celgene for destruction. Instructions for return of drug are included with each shipment of lenalidomide and instruct patients to call Celgene Customer Care at 1-888-423-5436 to begin the return process. Once notified, Celgene will provide patients with a pre-paid UPS label to return unused lenalidomide to the company.

Celgene Patient Support Program:

Celgene has a Celgene Patient Support (CPS) team that is focused on providing assistance accessing lenalidomide to patients who are insured, uninsured and/or underinsured. CPS can work with patients, caregivers, and/or physicians' offices who opt in for support.

For patients who are uninsured, the patient will be evaluated for free Revlimid. If they meet the Celgene free product criteria, they will have Revlimid shipped to them within 3 days. If the patient does not qualify for free Revlimid, CPS will work with the patient and the physicians' office to identify alternative coverage options.

For patients who are underinsured and cannot afford their co-pay, CPS can provide the patient with options for co-pay support through the Celgene Commercial Co-pay Program, as well as the various non-profit foundations in the U.S.

Celgene Patient Support contact information:

Telephone: 1-800-931-8691
Email: patientsupport@celgene.com
Fax: 1-800-822-2496

8.3.11 Nursing/Patient Implications

- The most common side effects are neutropenia and thrombocytopenia.
- Due to the highly teratogenic potential of the closely related thalidomide, it is highly recommended that all women of childbearing age group and all men use effective contraception during therapy (see Section 5.1.6 and Appendix V for complete details). All staff who are pregnant or who can become pregnant should not handle this drug outside of its original packaging.
- Instruct patient to report any rash immediately to the study team.

- Lenalidomide capsules should be swallowed whole with water, and should not be broken, chewed or opened.
- 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.

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8.3.12 References

1. Lenalidomide Investigator Brochure Edition 15, December 8, 2011
2. Revlimid US Package Insert:

   http://www.revlimid.com/pdf/REVLIMID_PI.pdf (accessed 17 Oct 2011).
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4. Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, Thakuri M, Reu F, Reynolds CM, Sexton R, Orlowski RZ, Barlogie B, Dispenzieri A. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519-27. doi: 10.1016/S0140-6736(16)31594-X. PubMed PMID: 28017406.

8.4 Dexamethasone

8.4.1 Other Names

Decadron

8.4.2 Classification

Dexamethasone is an adrenal corticosteroid compound

8.4.3 Mode of Action

Dexamethasone induces myeloma cell apoptosis, but the exact mode of action is not well known.

8.4.4 Storage and Stability

Dexamethasone tablets should be stored at room temperature and are stable for at least 2 years.

8.4.5 Dose Specifics

For Arm A patients: Dexamethasone will be administered orally at 20 mg (cycles 1-4), and 10 mg (cycles 5-8) days 1, 2, 4, 5, 8, 9, 11 and 12. Dexamethasone will be administered orally cycles 9-12 at 10 mg days 1, 2, 8 and 9.

For Arm B patients: Dexamethasone will be administered orally at 40 mg (cycles 1-4) and 20 mg (cycles 5-9) days 1, 8, 15 and 22.

8.4.6 Preparation

Dexamethasone tablets are available as 4 mg and 10 mg tablets

8.4.7 Route of Administration

Dexamethasone will be administered orally

8.4.8 Incompatibilities

None

8.4.9 Availability

Commercially available dexamethasone will be used.

8.4.10 Side Effects

Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

8.4.11 Nursing/Patient Implications

- Monitor regularly for hypertension, CHF and other evidence of fluid retention.
- Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.
- Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.
- Evaluate signs of infection, particularly local candidal infections and treat appropriately.
- Monitor blood glucose frequently.
- Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team
- Advise patient that easy bruising is a side effect.

9. Statistical Considerations

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9.1 Study Design and Objectives

This two-stage randomized study is designed and powered to investigate both a maintenance and an induction question: (#1) following induction with a proteasome inhibitor-IMiD combination, whether indefinite versus limited lenalidomide maintenance therapy is superior; and (#2) whether CRd versus VRd induction treatment is superior. To implement these two comparisons, 1,080 patients are first randomized (R1) equally to either 12 cycles of VRd induction (Arm A) or 9 cycles of CRd induction (Arm B). Patients who have completed induction without experiencing disease progression or patients who have received at least 6 cycles on Arm A and 4 cycles on Arm B but stopped induction therapy early due to adverse events will be randomized again (R2) equally to 24 cycles of R maintenance and then observation (Arm C) or indefinite R maintenance until disease progression (Arm D). Patients will be stratified by intent to SCT at disease progression (R1) and by induction arm (R2).

The statistical design was revised substantially with Addendum #11. By September 2015, nearly 2 years since study activation, it was apparent that the number of patients continuing on to Step 2 after going off Step 1 treatment was below expectations. At that time, the Step 2 enrollment yield approximated 50% versus the 85% yield assumed in the original design. This trend continued for another year at which point the DSMC recommended the study team formally address the problem. In this amendment, the Step 2 enrollment yield is lowered from 85% to 65% and the overall sample size increased by 324 to 1,080 patients. Addendum #11 also includes measures expected to enhance Step 2 enrollment yield including the following: expanding the window for Step 2 registration from 28 days to 6 weeks and allowing both patients who have completed induction without experiencing disease progression *and* patients who received at least 6 cycles on Arm A and 4 cycles on Arm B but withdrew early due to adverse events to be eligible for Step 2. At the same time, research from randomized phase III trials has served to heighten interest in the PFS induction comparison. Results from the S0777 trial clearly showed that the VRd induction combination improved PFS and OS over Rd.[92] Results from the IFM2009 study confirmed the lack of any disadvantage to deferring transplant, thus potentially allowing more patients to delay transplant on this trial.[99] Carfilzomib was approved in the setting of relapsed or refractory multiple myeloma based on results from the ENDEAVOR study.[100] Lastly, results from the Clarion trial evaluating induction with a melphalan plus prednisone backbone and carfilzomib versus bortezomib in patients with newly diagnosed multiple myeloma ineligible for hematopoietic stem-cell transplant were negative with a treatment hazard ratio close to 1.0 for the primary PFS comparison.[101] Given these reasons, it was resolved that induction PFS become a co-primary endpoint with maintenance OS. Key revisions to the statistical design are presented in the sections on the sample size calculation (9.4), projected accrual (9.5) and the monitoring plan (9.7).

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9.2 Study Endpoints

9.2.1 Co-Primary Endpoints

9.2.1.1 Overall survival for the maintenance analysis; Defined as the time from the maintenance randomization (R2) to death due to any cause or, censored at the date last known alive.

9.2.1.2 Progression-free survival for the induction analysis; Defined as the time from the induction randomization (R1) until the earlier of progression or death due to any cause. Patients alive without disease progression will be censored at date of last disease evaluation. Only deaths that occur within 3 months of the last disease evaluation are considered events.

9.2.2 Secondary Endpoints

9.2.2.1 Progression-free survival for the maintenance analysis; Defined as the time from the maintenance randomization (R2) until the earlier of progression or death due to any cause. Patients alive without disease progression will be censored at date of last disease evaluation. Only deaths that occur within 3 months of the last disease evaluation are considered events.

9.2.2.2 Overall survival for the induction analysis; Defined as the time from induction randomization (R1) to death due to any cause, or censored at the date last known alive.

9.2.2.3 Response rates including partial response (PR), very good partial response (VGPR), immunofixation negative complete response (IF-CR) and complete response (CR) at 2.8 and 8.3 months after induction randomization (R1).

9.2.2.4 Time to progression (TTP) for the induction analysis; Defined as the time from the induction randomization (R1) to progression, or censored at the date of last disease evaluation for those without progression reported.

9.2.2.5 Duration of response (DOR) for the induction analysis; Defined as the time from first objective response (partial response or better) since induction randomization (R1) until the earlier of progression or death due to any cause, or censored at date of last disease evaluation for those without events reported.

9.2.2.6 Incidence of overall grade 3 or higher non-hematologic toxicity and grade 3 or higher toxicity by type during induction, active maintenance and observation phases.

9.2.2.7 Incidence of grade 2 or higher peripheral neuropathy and cardiac toxicity during induction phase.

9.2.2.8 MRD negative rates at 8.3 months after induction randomization (R1).

9.2.3 Quality of Life Endpoints

9.2.3.1 Change for the transition to maintenance analysis; Defined as the change in the FACT-Ntx TOI from the end of induction therapy to the end of cycle 6 maintenance.

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9.2.3.2 Change for the short-term maintenance analysis; Defined as the change in the FACT-Ntx TOI from the end of 2 years of maintenance (cycle 24) to 3 years (cycle 36 of maintenance/observation month 33) post R2.

9.2.3.3 Change for the long-term maintenance analysis; Defined as the change in the FACT-Ntx TOI from the end of 2 years (cycle 24) of maintenance to 5 years (cycle 60 of maintenance/observation month 55) post R2.

9.2.3.4 Change for the end of induction analysis; Defined as the change in the FACT-Ntx TOI from the induction randomization (R1) to the end of induction therapy (month 8.3).

9.2.3.5 Change for the early induction analysis; Defined as the change in the FACT-Ntx TOI from the induction randomization (R1) to 2.8 months of induction therapy.

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9.2.3.6 Levels and changes in the FACT-Ntx TOI and FACT-MM during induction, active maintenance and observation phases.

9.2.3.7 Time to worsening of FACT-Ntx TOI for the induction analysis; Defined as the time from the baseline assessment at induction randomization (R1) to a decrease of 7 points. Patients with at least one post-baseline assessment are censored at the date of last assessment. Patients without a baseline assessment or a post-baseline assessment are censored at date of maintenance randomization.

9.2.3.8 Time to worsening of FACT-MM for the maintenance analysis; Defined as the time from the baseline assessment at maintenance randomization (R2) to a decrease of 4 points. Patients with at least one post-baseline assessment are censored at the date of last assessment. Patients without a baseline assessment or a post-baseline assessment are censored at date of maintenance randomization.

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9.2.4 Correlative Endpoints

9.2.4.1 MRD negative rates at 2.8 months after induction randomization (R1).

9.2.4.2 MRD negative rates at 2 and 3 years after maintenance randomization (R2).

9.2.4.3 MRD levels and changes during induction, active maintenance and observation phases.

9.2.4.4 Mutation status at pre-registration, disease progression and suspected complete response.

9.2.4.5 Gene expression levels at pre-registration, disease progression and suspected complete response.

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9.3 Statistical Analysis Plan

9.3.1 Co-Primary Endpoints

9.3.1.1 Maintenance Overall Survival

For the co-primary endpoint of overall survival from the maintenance randomization (R2) to death, the Kaplan-Meier (KM) method will be used to describe the overall survival function by arm.[66] All patients in the maintenance randomization (R2) will be classified according to their randomized treatment assignment irrespective of actual treatment received (ITT: intent-to-treat). The primary analysis is a superiority test of OS in Arm D against Arm C, which is performed at one-sided 0.025 significance level using a stratified logrank test, where the stratification factor is the induction arm.[67] Full information of 364 deaths is expected at 9 years follow-up from R2. The table below outlines expectations which will be monitored around number of cases censored at various time points prior to the cutoff date of 9 years and after full accrual (accrual duration estimated to be 5 years).

Year from R2	No. Censored Cases	No. Deaths
4	447	116
5	531	173
6	472	232
7	422	282
8	378	326
9	340	364

Sensitivity analysis will be done to evaluate OS in the subset of eligible patients, and censoring patients at time of non-protocol therapy. Material differences may be reported.

The primary analysis compares OS regardless of response on first randomization. As secondary analyses, KM plots by maintenance arm will also be estimated within each induction arm and within induction response categories (dichotomized at VGPR) and these relationships will be assessed with interaction terms in Cox proportional hazards (PH) regression models.[68] Analyses will also be conducted to check consistency of the treatment effect within gender and ethnicity subgroups.

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Because there is no difference in maintenance treatment for the first 24 cycles, the proportional hazards assumption is not valid. We will thus estimate the absolute difference in OS rates at 2-, 3- and 4- years from R2.

As an exploratory analysis, a stratified Cox PH regression model will be used to estimate the hazard ratio (HR) [Arm D/Arm C] and 95% confidence interval in a landmark analysis after 2 years from R2 unadjusted for potential confounders. Adjusted models will incorporate known baseline prognostic factors including but not limited to age, race, ISS Stage and ECOG PS along with stem cell transplant as a time-varying covariate. This analysis will also be performed in the subset of patients with MRD status at 2 years from R2.

9.3.1.2 Induction Progression Free Survival

The main analysis dataset for the co-primary endpoint of the induction PFS comparison (Arm A versus Arm B) will be all patients randomized (R1). A stratified logrank test will be used to compare PFS distributions between induction arms.

The Kaplan-Meier method will be used to describe the progression-free survival function by arm using all data while ignoring maintenance. A stratified Cox regression model will be used to estimate the hazard ratio [B/A], where all patients (regardless of maintenance treatment) will be combined by induction arm, unadjusted for potential confounders. Adjusted models will incorporate known baseline prognostic factors including but not limited to age, race, ISS Stage and ECOG PS along with stem cell transplant as a time-varying covariate.

Sensitivity analyses will be done to evaluate PFS according to treatment received, in the subset of eligible patients, and censoring patients at time of non-protocol therapy. Material differences may be reported. We will also evaluate PFS distributions by arm within intent to transplant at disease progression stratification status.

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It is important to note that this hazard ratio [B/A] regarding induction treatment is the one when patients are supposed to receive either 24 cycles R maintenance (Arm C) or indefinite R maintenance (Arm D) equally likely. Therefore, in addition, weighted Cox regression will be used to estimate: (1) the hazard ratio if all patients were supposed to receive indefinite R maintenance and also (2) the hazard ratio if all patients were supposed to receive up to 24 cycles of R maintenance.[69-71]This approximately doubles the information for the maintenance arm being analyzed. The resulting representation depends on the proportion of dropout within each arm.

9.3.2 Secondary Analyses

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9.3.2.1 Induction Response

The primary response analysis dataset is comprised of all patients that start protocol induction treatment. Response will be tabulated by category (sCR, CR, VGPR, PR, SD, PD, unevaluable). PR and VGPR rates will be compared between induction arms using the chi-square test for association. The null hypothesis is no difference in these response rates. A two-sided 0.05 significance level will be split between these two tests. PR and VGPR rates are expected to be 81.5% and 43.5%, respectively, on the VRd arm based on results from S0777 trial. Given 540 patients per arm and assuming a two-sided 0.025 significance level, there is 89% power to detect a difference of 7.5% in PR rates (CRd 89%) and 88% power to detect a difference of 10.5% in VGPR rates (CRd 54%). Sensitivity analyses will be conducted to exclude ineligible patients. Assuming 10% ineligibility or 972 patients, the power is reduced to 85% in each analysis, respectively. Response after 2.8 months will also be evaluated with a two-sided 95% exact confidence interval calculated for each rate. We will also estimate the treatment odds of VGPR response over induction using logistic regression in univariate and adjusted models including known baseline prognostic factors. Duration of response will be estimated using Kaplan-Meier methods in the subset of patients achieving partial response or better while on induction therapy.

9.3.2.2 Induction Time to Progression

The induction time to progression analysis dataset will include all randomized patients (R1). TTP distributions will be estimated by induction arm using Kaplan-Meier methods.

9.3.2.3 Toxicity

We will monitor the toxicities experienced by all treated patients. To compare toxicity between induction arms, we are specifically interested in the grade 3 or higher treatment-related (attribution possible, probable or definite), non-hematologic event rate while on induction treatment. With 540 treated patients per arm, there is 90% power to detect a difference in toxicity rates of 7% from an estimated rate of 82% on the VRd arm based on S0777 results to 89% on the CRd arm using the chi-square test for association. Global non-hematological toxicity rates after 2 and 3 years of R maintenance will be calculated with a two-sided 95% exact confidence interval. Interim analyses for toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are made available to the ECOG-ACRIN Principle Investigator

or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required as described in Section 5.2.

9.3.3 Quality of Life Analyses

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9.3.3.1 Primary Analysis

Health-related quality of life will be prospectively measured using the following instruments: the FACT-Physical, FACT-Functional, FACT-Ntx and FACT-MM.[73] The average total score for each instrument will be recorded for each arm and each time point. QoL assessments will first be administered at induction registration (+/- 7 days) prior to initiation of treatment. During the induction phase, there will be 4 assessments for each arm as follows: for the VRd arm (Arm A), QoL will be measured at the end of cycles 1, 4 (month 2.8), 8 (month 5.5) and 12 (month 8.3 induction end) and for the CRd arm (Arm B), at the end of cycles 1, 3 (month 2.8), 6 (month 5.5) and 9 (month 8.3 induction end). QoL will also be assessed at early discontinuation of induction therapy for any reason. During the maintenance therapy phase, there will be 7 assessments as follows: for the limited lenalidomide maintenance arm (Arm C), QoL will be assessed at the end of cycles 6, 12 and 24 of therapy and at observation months 28, 33, 44 and 55 post R2 and for the indefinite lenalidomide maintenance arm (Arm D) at the end of cycles 6, 12, 24, 30, 36, 48 and 60 of therapy. Again, there will be an assessment at time of early therapy discontinuation for any reason.

At each QoL analysis timepoint, the sample size depends on estimated progression, drop-out and participation rates. There are 4 primary QOL treatment group comparisons and 2 primary response group comparisons stated below. The 2-sided significance level will be 0.05/4=0.0125 and 0.05/2=0.025 for these analyses, respectively. Differences which can be detected with 80% power between groups are computed using a 2-sided t-test (or Wilcoxon Rank Sum test if scores are not normally distributed) assuming a) instrument standard deviation (SD) of 11.5, 16 and 20.5; b) correlation 0.6 and 0.4 between measurements; and c) 70% and 90% compliance. As a general guideline, a minimally important difference (MID) is 0.2-0.3 points per question, thus given the length of the FACT-Ntx TOI, the MID is 6-8 points. This parallels half SD of change observed in a similar cohort of MM patients (5-7 points).[74,75] We believe the differences in mean change score outlined below in the base case (SD=16) that can be detected with satisfactory power are plausible and reasonable within the context of associated hypotheses.

Treatment Comparison: Transition to Active Maintenance

For the transition to active maintenance question, the mean change in health related QoL measured by the FACT-Ntx TOI from end of induction to the end of 6 cycles of maintenance will be compared between induction treatment arms. Given the assumed PFS hazard rates for Arms A and B, potential dropout and participation rates, it is estimated there will be 406 patients at the end of 6 cycles of R maintenance. With 406 patients, the difference in mean change score between induction treatment arms that can be detected with 80% power under various scenarios of SD, compliance and correlation is from 3.6-8.9 points (Table 9.3.3.1.1). Assuming a SD of 16, the range is 5-7 points.

Table 9.3.3.1.1

			Differences between Induction Treatment Arms in Mean Change FACT-Ntx TOI Score during Transition to Active Maintenance Phase (power=80%, 2-sided alpha=0.0125)	
standard deviation (SD)	correlation	SD of change	70% compliance n=284 (142/arm)	90% compliance n=364 (182/arm)
11.5	0.6	10.3	4.1	3.6
	0.4	12.6	5.0	4.4
16.0	0.6	14.3	5.7	5.0
	0.4	17.5	7.0	6.2
20.5	0.6	18.3	7.3	6.4
	0.4	22.5	8.9	7.9

Treatment Comparison: Maintenance versus Observation-Short Term

For the short-term comparison of the two strategies of lenalidomide maintenance of limited duration versus indefinite maintenance therapy until disease progression, the mean change in health-related QoL measured by the FACT-Ntx TOI from the end of 2 years (cycle 24) of maintenance to 3 years (cycle 36 of maintenance/observation month 33) post R2. Given the assumed PFS hazard rates for Arms A and B, potential dropout and participation rates, it is estimated there will be 210 patients after 3 years post maintenance randomization. With 210 patients, the difference in mean change score between maintenance arms that can be detected with 80% power under various scenarios of SD, compliance and correlation is from 5.1-12.5 points (Table 9.3.3.1.2). Assuming a SD of 16, the range is 7-9.8 points.

Table 9.3.3.1.2

			Differences between Maintenance Treatment Arms in Mean Change FACT-Ntx TOI Score from End of 2 Years to End of 3 Years Post Maintenance Randomization (power=80%, 2-sided alpha=0.0125)	
standard deviation (SD)	correlation	SD of change	70% compliance n=146 (73/arm)	90% compliance n=188 (94/arm)
11.5	0.6	10.3	5.7	5.1
	0.4	12.6	7.0	6.2
16.0	0.6	14.3	8.0	7.0
	0.4	17.5	9.8	8.6
20.5	0.6	18.3	10.2	9.0
	0.4	22.5	12.5	11.0

Treatment Comparison: Maintenance versus Observation – Long Term

For the long term comparison of the two strategies of lenalidomide maintenance of limited duration versus indefinite maintenance therapy until disease progression, the mean change in health-related QoL measured by the FACT-Ntx TOI from the end of 2 years (cycle 24) of maintenance to 5 years (cycle 60 of maintenance/ observation month 55) post R2. Given the assumed PFS hazard rates for Arms A and B, potential dropout and participation rates, it is estimated there will be 147 patients after 5 years post maintenance randomization. With 147 patients, the difference in mean change score between maintenance arms that can be detected with 80% power under various scenarios of SD, compliance and correlation is from 6.1-15.1 points (Table 9.3.3.1.3). Assuming a SD of 16, the range is 8.4-11.8 points.

Table 9.3.3.1.3

			Differences between Maintenance Treatment Arms in Mean Change FACT-Ntx TOI Score from End of 2 Years to End of 5 Years Post Maintenance Randomization (power=80%, 2-sided alpha=0.0125)	
standard deviation (SD)	correlation	SD of change	70% compliance n=102 (51/arm)	90% compliance n=132 (66/arm)
11.5	0.6	10.3	6.9	6.1
	0.4	12.6	8.5	7.4
16.0	0.6	14.3	9.6	8.4
	0.4	17.5	11.8	10.3
20.5	0.6	18.3	12.3	10.8
	0.4	22.5	15.1	13.2

Treatment Comparison: Induction

The mean change in health-related QoL measured by the FACT-Ntx TOI from registration to end of induction will be compared between induction treatment arms. Given the assumed PFS hazard rates for Arms A and B, potential drop-out and participation rates, it is estimated there will be 448 patients at the end of induction (month 8.3). With 448 patients, the difference in mean change score between induction treatment arms that can be detected with 80% power under various scenarios of SD, compliance and correlation is from 3.4-8.5 points (Table 9.3.3.1.4). Assuming a SD of 16, the range is 4.8-6.6 points.

Table 9.3.3.1.4

			Differences between Induction Treatment Arms in Mean Change FACT-Ntx TOI Score over Induction Phase (power=80%, 2-sided alpha=0.0125)	
standard deviation (SD)	correlation	SD of change	70% compliance n=314 (157/arm)	90% compliance n=402 (201/arm)
11.5	0.6	10.3	3.9	3.4
	0.4	12.6	4.8	4.2
16.0	0.6	14.3	5.4	4.8
	0.4	17.5	6.6	5.9
20.5	0.6	18.3	6.9	6.1
	0.4	22.5	8.5	7.5

Response Comparison: Early Induction

Patients will be evaluated for response using standard criteria after 2.8 months corresponding to 4 cycles of VRd and 3 cycles of CRd. Patients will be classified by very good partial response or partial response or better status: responders (R) vs. non-responders (NR). Unevaluable patients are counted in the denominator but ineligible patients are excluded. Given the assumed PFS hazard rates for Arms A and B, potential drop-out and participation rates, it is estimated there will be 700 patients at the end of 2.8 months of induction therapy. Assuming 10% ineligibility then this drops to n=630 patients. It is assumed 90% of these patients will have complete data (n=566). The expected overall VGPR and PR rates are 33% and 70%, lower than the response rates assumed by end of induction. Patients on the CRd arm, nevertheless, are expected to have a more rapid response. The difference in mean change score between responder groups that can be detected under various scenarios of SD and correlation is from 2.8-6.2 for the VGPR analysis and 2.9-6.4 for the PR analysis (Table 9.3.3.1.5).

Table 9.3.3.1.5

standard deviation (SD)	correlation	SD of change	Differences between Responder Groups in Mean Change FACT-Ntx TOI Score at Early Induction Assessment (power=80%, 2-sided alpha=0.025) VGPR 90% compliance n=566 (187 R/ 379 NR)	PR 90% compliance n=566 (396 R/ 170 NR)
11.5	0.6	10.3	2.8	2.9
	0.4	12.6	3.5	3.6
16.0	0.6	14.3	4.0	4.1
	0.4	17.5	4.8	5.0
20.5	0.6	18.3	5.1	5.2
	0.4	22.5	6.2	6.4

9.3.3.2 Secondary Analyses

Descriptive statistics (mean, SD, median, range) will be used to evaluate the distribution of levels and changes for the set of health-related QoL evaluations associated with each phase, by treatment arm and within early discontinuation of treatment status subgroups. Levels and changes will also be assessed graphically. Correlations among instruments (FACT-MM, FACT-Ntx TOI and the related individual subscales) will be assessed at each time point with Pearson's correlation coefficient (or Spearman, if data display significant non-normality).

Changes from baseline will be analyzed using linear mixed models based on restricted maximum likelihood estimation with covariance matrix maximizing Akaike information criteria. Models with treatment, assessment time, and treatment by assessment time interaction with and without other predictors will be fit. If there is substantial missingness, we will analyze the data according to the methods described in Schluchter and Schluchter, Greene and Beck.[76,77] These methods take into account jointly modeling longitudinal data and survival time to dropout. Time to worsening while on either induction or maintenance will be analyzed with KM methods and Cox regression with the related treatment arm as the only factor. Correlation between time to worsening of symptoms with PFS and OS will be assessed with Kendall's Tau adjusted for censored observations.[78]

We will evaluate whether patients with poor treatment adherence during maintenance have a reduced health-related QoL. Treatment adherence will be measured by the percent full protocol dose of lenalidomide over a given interval and evaluated both as a continuous and binary variable dichotomized at adherence less than 75% full

protocol dose (poor adherence). There are 7 maintenance intervals as follows:

Interval #1: End of Induction to end of cycle 6

Interval #2: End of cycle 6 to end of cycle 12

Interval #3: End of cycle 12 to end of cycle 24

Interval #4: End of cycle 24 to end of cycle 30 (Arm D only)

Interval #5: End of cycle 30 to end of cycle 36 (Arm D only)

Interval #6: End of cycle 36 to end of cycle 48 (Arm D only)

Interval #7: End of cycle 48 to end of cycle 60 (Arm D only)

Correlation between continuous percent full protocol dose for a given interval and quality of life score measured at the end of the interval will be assessed graphically with scatter plots and using Pearson correlation coefficients (or Spearman, if data display significant non-normality). For each primary maintenance treatment comparison, there will be a parallel analysis for treatment adherence. For the transition to maintenance analysis, all patients receive treatment and the associated QoL sample size as stated above is 406 patients. For the maintenance versus observation short-term and long-term comparisons, only arm D patients receive treatment and, therefore, the relevant sample sizes for the analysis of the relationship between QoL change score and treatment adherence are 105 patients and 73 patients, respectively. At the end of a given period, patients will be segmented into high and low FACT-Ntx TOI score groups based on the group median score. The proportion of patients with poor treatment adherence will be computed within groups and compared using Fisher's exact test.[72] This analysis of treatment adherence is exploratory and nominal p-values will be reported without adjusting for multiple comparisons. The overall poor adherence rate is estimated to be 25%. Assuming 2-sided 0.05 significance and 90% of patients with complete data, there is approximately 85% power to detect a difference in poor adherence rates between high and low FACT-Ntx TOI score groups of 14% (i.e. high score poor adherence of 18% vs. low score 32% poor adherence) for the transition to active maintenance analysis with n=182 patients per score group. In the other two analyses with only data from Arm D, the difference in poor adherence rates between high and low score groups that can be detected with satisfactory power widens to 26%-32%.

Reliability of the FACT-MM will be assessed with Cronbach's alpha. We will evaluate the relationship between the FACT-MM and the individual elements of the

FACT-Ntx TOI to discern criterion validity. We are also interested in the relationships between baseline clinical measures and will segment patients according to ECOG PS (0-1 versus > 1), presence of bone disease, ISS stage (I-II versus III) and renal function (creatinine < 2 versus > 2). Within each group, mean changes over time will be presented graphically. We will estimate the effects of these characteristics on the patterns of QoL over time with mixed models.[70]

9.3.4 Laboratory Analyses

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9.3.4.1 Minimal residual disease

Samples for evaluation of minimal residual disease will be prospectively collected during induction therapy at 2.8 months (end of cycle 4 Arm A and cycle 3 Arm B) and induction end at 8.3 months (end of cycle 12 Arm A and cycle 9 Arm B). During the maintenance therapy phase, samples will be collected 2- and 3-y post R2. MRD evaluation by multiparametric flow cytometry will be conducted and patients classified as MRD negative, MRD positive or not evaluable as described in Section 11.2. At each time point, MRD negative rates with two-sided 95% exact confidence intervals on each arm will be estimated. Patterns of change over time in MRD will also be evaluated using longitudinal regression analysis with general linear mixed effects models and GEE semi-parametric models.

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MRD negative rates will be compared between either induction or maintenance arms depending on the assessment time point using the Mantel-Haenszel test stratified either on intent to transplant at progression or induction arm (Step 1 and 2 stratification factors, respectively). It is hypothesized that a greater proportion of patients on the CRd arm will be MRD negative at both induction timepoints and that a greater proportion of patients on the indefinite lenalidomide arm will be MRD negative at the maintenance timepoint 3-y post R2. While no adjustment for multiple testing will be performed, the end of the induction therapy is the most important time point of interest in this correlative study. We use the planned sample size for the Step 2 randomization after induction (n=704) as the basis for estimating sample size in the MRD analysis at induction end. Given a 60% participation rate and 90% evaluable sample yield, there will be 380 patients for the MRD evaluation at induction end. There is approximately 85% power to detect a common odds ratio of 2.46 given a two-sided 0.05 significance level. The overall MRD negative rate is assumed to be 15% (CRd 20.5% vs. VRd 9.5%). For estimating power, these MRD negative rates are held constant across strata and sample size is split evenly

between arms. Logistic regression models will be used to compare proportions of MRD negative between induction arms in multivariable models adjusted for known baseline prognostic factors. Stepwise selection procedures will be used for model building with all covariates significant at the 0.05 level included in the final model.

With respect to the transition to maintenance, the proportion of patients with detectable MRD at induction end who convert to undetectable MRD at 2-y post R2 will be calculated overall and by induction arm. The probability of conversion accounting for death and progression as competing risks will be assessed separately by induction arm.

MRD assessment will also be evaluated in the context of disease response based on IMWG criteria. At each timepoint, the proportion of patients with undetectable MRD across IMWGresponse categories (VGPR, CR, sCR) will be calculated and these proportions will be compared using a chi-square test. Disease free status based on MRD versus IMWG assessment (CR, sCR) will be evaluated in 2x2 tables and the percent agreement and disagreement calculated. The kappa statistic will be used to describe agreement between the methods.[102] With 380 pairs at induction end, an intraclass kappa of 0.90 compared to 0.75 with 88% power and 2-sided 0.05 significance can be established assuming an MRD negativity rate of 15%. A scale to interpret kappa considers 0.01-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.90 substantial and 0.81-0.99 almost perfect agreement.[103] Measures of association (sensitivity, specificity) will also be calculated presuming one or the other method is the gold standard to elucidate the value of multiparametric flow cytometry to detect presence of disease beyond IMWG criteria.

We also will evaluate the ability of MRD at induction end with and without established risk factors to predict short-term (2 years from R2) and long-term (4 years from R2) overall and progression-free survival. Logistic regression adjusted for censoring will be used to derive a prediction model in two-thirds of the data and the remaining data will comprise the validation dataset to evaluate the prediction rule using random cross-validation estimated C-statistics. It is noted that calculating the C-statistic for time-to-event data with censoring will result in not-usable pairs of data.[84,85,97] Considering the completeness of follow-up, a binary outcome may be considered for the short-term analysis. As exploratory, we will evaluate differences of patient and disease characteristics in discordant and concordant cases.

9.3.4.2 Genomic Sequencing

Computational analyses will be performed according to the CoMMpass protocol (Section 11.3). Biological sample submissions are requested at pre-registration, at the time of disease progression and at the time of suspected complete response. Approximately 60% of enrolled E1A11 patients have consented to participate in laboratory research studies. Further, in a recent CoMMpass interim analysis (IA7) (ASH 2015), 75% of enrolled CoMMpass patients were molecularly characterized. Given these estimates, the pre-registration analysis dataset will have an estimated 486 patients. Descriptive statistics (absolute frequencies, percentages, mean, SD, median, range) will be used to characterize the study cohort by mutation incidence and expression levels at all time-points. Association of genotype data (binary) with categorical baseline patient and disease characteristics will be evaluated using chi-squared test or, if appropriate, Cochran-Armitage trend test. For example, assuming an overall ISS3 rate of 30% at baseline, there is satisfactory power (>80%) to detect a difference in ISS3 rates between mutation subgroups of 22% (50% vs 28%) and 12.5% (37.5% vs 25%) if the mutation incidence is 10% and 40%, respectively. The Wilcoxon-rank sum test or, if appropriate, the Jonckheere-Terpstra test for trend will be used to assess differential expression levels with baseline patient and disease characteristic groups. Given 480 patients, there is 85% power to detect a 0.28 standardized mean difference in levels between 2 baseline groups of equal sizes (50-50%) or a 0.4 standardized mean difference between unequal groups (15-85%) at a 2-sided 0.05 significance level. Mantel-Haenszel test will be used for the MRD negativity rate and PR/VGPR rate comparisons between genotype groups. The Mantel-Haenszel estimator will be used to estimate the odds ratio (95% confidence intervals). The Kaplan-Meier method will be used to estimate progression-free and overall survival distributions and Cox regression to estimate hazard ratios by genotype status. There is 80% power to detect a 1.63 and 2.0 hazard ratio assuming genotype prevalence of 25% and 10%, respectively, at a 2-sided 0.05 significance level with approximately 480 patients and 177 events (event proportion at final PFS analysis ~37%). While most of these analyses are exploratory, false discovery rate (FDR) control methods will be employed due to the multiple testing of genes and mutations from these high throughput data methods.

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9.3.4.3 Circulating Plasma Cells and Plasma Cell Proliferation

With samples submitted pre-registration, multiparametric flow cytometry will quantify circulating plasma cells (cPC) in terms of number of clonal events/150,000 collected total events and plasma cell proliferation in terms of the plasma cell labeling index (PCLI) percentage. Given a 60% participation rate and an estimated evaluable sample yield of 85%, 550 patients will be included in these analyses. The Kaplan-Meier method will be used to estimate induction progression-free survival and overall survival distributions and Cox regression used to estimate hazard ratios by dichotomized cPC and PCLI. A quantity of 3% or greater for PCLI and 150 events or greater for cPC is associated with a more aggressive disease course. There is 80% power to detect a 1.55 and 1.75 hazard ratio assuming prevalence of 30% and 15%, respectively, at a 2-sided 0.05 significance level with approximately 550 patients and 200 events (event proportion at final PFS analysis ~37%).

9.4 Sample Size Considerations

9.4.1 Maintenance Overall Survival

The planned sample size is based on power calculations for the maintenance comparison of overall survival. Calculations assume no interaction between induction and maintenance therapies. We estimate 65% of patients would be eligible to begin maintenance. Assuming exponential distribution and a median PFS of 3 years corresponding with 12 cycles of VRd + 24 cycles of lenalidomide versus a median PFS of 4 years for 9 cycles of CRd + 24 cycles of lenalidomide, the PFS rates at end of induction (8.3 months) are 85% and 89%. Power calculations target a 50% improvement in median OS (Hazard Ratio (HR) = 0.667). More specifically, we estimate an annual hazard rate on limited R maintenance (Arm C) of 0.1386 versus 0.0924 on R indefinite (Arm D). Assuming exponential distribution of failures from the start of maintenance randomization, this corresponds to a median OS of 5 years versus 7.5 years, respectively (4-y OS rate of 57% vs. 69%). There is 80% power using a stratified logrank test to detect this HR given 9 years of follow-up from R2, a 1-sided 0.025 alpha, 395 patients and 204 events. To account for progression and dropout during the first 2 years of maintenance after R2 (i.e. patients randomized to indefinite R essentially crossing over), we inflate the sample and event size according to Lachin-Foulkes non-compliance adjustment.[86] Assuming 25% non-compliance, the sample size for the maintenance comparison increases to n=704 patients and full information to 364 deaths. Backing into the induction comparison assuming 35% progression/drop-out before R2, the overall sample size is 1080 patients. It is noted that the power calculation assumes proportional hazards although there is no difference in maintenance treatment for

the first 24 cycles. Further, given the uncertainty around the number of patients that will enroll onto maintenance, we will build in potential sample size re-estimation if the yield is too low or shorten follow-up duration if the yield is above expectations.

Before this amendment (Addendum #11), the Step 2 enrollment yield was assumed to be 85%. As of February 2017, the observed Step 2 enrollment yield approximated 50% but measures to enhance Step 2 enrollment yield have been incorporated in this addendum. The revised Step 2 yield resulted in a slight increase in Step 2 sample size of 64 patients to 704 patients and correspondingly an increase in full information from 356 to 364 deaths with the same follow-up duration of 9 years, Assumptions regarding the effect size and component median OS estimates along with Type I error, power and the non-compliance margin were unchanged.

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9.4.2 Induction Progression Free Survival

Median PFS on VRd (Arm A) is expected be 3 years. Assuming exponential distribution of events, this corresponds to an annual hazard rate of 0.231. With 1,080 patients randomized at induction, there is 80% power at a 1-sided 0.025 significance level to detect a 25% reduction in the hazard rate to 0.1733 on the CRd arm (33% improvement in median PFS to 4 year; hazard ratio=0.75). Full information under the alternative hypothesis is 399 PFS events expected after 5 years.

As outlined above with this redesign (Addendum #11), there is a substantial increase in overall sample size by 324 patients, from 756 to 1,080. The power calculation for the now co-primary induction PFS endpoint changed with respect to accrual duration extended by 1.5 years, follow-up duration shortened from 5.5 to 5 years and the timing for interim analyses (see Section 9.7). Assumptions regarding the effect size and component median PFS estimates along with Type I error, and power were unchanged. The resulting full information is increased by 7 PFS events from 392 to 399.

9.5 Projected Accrual

Accrual duration is expected to be approximately 5 years with the revised accrual target of 1,080 patients given the accrual rate of 18 patients per month (ppm). Observed accrual as of the time of this amendment (Addendum #11) has exceeded estimates (averaging 24 ppm for the previous 6 months) due to the strong collaboration among ECOG-ACRIN, the Southwest Oncology Group (SWOG), and Alliance.

9.6 Randomization Scheme

At the induction randomization (R1), patients will be stratified by intent to transplant at progression. At maintenance randomization (R2), patients will be stratified by induction arm. Patients will be randomized at R1 and R2 with 1:1 treatment allocation using permuted blocks methods within strata and dynamic balancing within main institution.[87]

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9.7 Monitoring Plan

All patients will be on-study for 15 years from time of randomization, during which they will be monitored for effects of treatment through regular clinic visits and data submitted to ECOG-ACRIN. Interim analyses for efficacy and futility will be conducted as described below.

9.7.1 Maintenance Overall Survival

Interim analyses of the OS comparison will be performed annually coincident with ECOG-ACRIN Data Safety Monitoring Committee (DSMC) meetings beginning when approximately 32% of the planned full information has occurred, continuing until either criteria for early stopping are met or full information is reached. At each scheduled interim analysis, a stratified logrank test statistic and one-sided p-value are computed. To preserve the overall type I error rate, critical values at the interim analyses will be determined using a truncated version of the Lan-DeMets error spending function corresponding to the O'Brien-Fleming boundary.[88,89] Boundary values at a nominal significance less than 0.0005 will be truncated at 0.0005, with the boundary also adjusted to preserve the overall type I error rate of 2.5% (Table 9.7.1.1). Under the accrual and failure rate assumptions above, interim analyses would be expected to occur from years 4 through 8 after the second randomization corresponding with information times of 32%, 48%, 64%, 77% and 89%. The final analysis occurs at full information (364 events) after 9 years of follow-up. Because of delays in initiation of accrual and delays in data submission and processing, it is likely that actual analysis times will be 3 months later.

Table 9.7.1.1

Repeated Analysis	Time from R2 (years)	Information Time (%)	Failures under Alternative	Critical Value	Nominal Significance
1	4	32%	116	3.291	0.0005
2	5	48%	173	3.148	0.0008
3	6	64%	232	2.617	0.0044
4	7	77%	282	2.357	0.0092
5	8	89%	326	2.192	0.0142
6	9	100%	364	2.077	0.0189

Coupled with the interim analysis for early stopping for superiority of R indefinite, the study will be monitored for harm and inefficacy. At 32% information, the DSMC may consider stopping the maintenance component of the study (if induction PFS has not been completed yet) early for harm if the lower bound of a 95% confidence interval on the hazard ratio (R indefinite/R ltd) is above 1.0. Interim inefficacy analyses are also planned starting at 48% information based on the approach described by Freidlin et al.98 The study will be stopped if there is not at least a small trend in favor of the alternative hypothesis starting at this time. Specifically, an inefficacy boundary will begin at the second interim analysis with a hazard ratio near 1.0 and will

gradually decrease to 20% of targeted benefit at full information, subject to the requirement that the two-sided 95% confidence interval for the hazard ratio does not contain the design-alternative hazard ratio of 0.667. This plan is summarized below. The aforementioned stratified Cox regression model will be used to estimate the hazard ratio. If the hazard ratio exceeds the cutoff value at the corresponding information proportion, the study may be stopped for inefficacy.

Table 9.7.1.2

Information Proportion	Cutoff Hazard Ratio
48%	1.000
64%	0.977
77%	0.957
89%	0.939
100%	0.922

Before this amendment (Addendum #11), interim analyses for the maintenance OS comparison occurred at 41%, 56%, 70%, 81%, 91% information. With changes to the timing of interim analyses and sample size, the expected count of failures under the alternative hypothesis, critical value, nominal significance for the efficacy analysis along with the cutoff hazard ratio for futility analysis were revised.

9.7.2 Induction Progression-Free Survival

There will be three interim analyses of the induction PFS comparison. Starting at 54% of full information estimated at 3.5 years from R1, these interim analyses will occur every 6 months coincident with scheduled DSMC meetings. Similar to the maintenance overall survival endpoint, to preserve the overall type I error rate, the critical value at the interim will be determined using Lan-DeMets error spending rate function corresponding to the O'Brien Fleming boundary (truncated at 0.0005).The final analysis will occur after 5 years of follow-up with full information of 399 PFS events.

Table 9.7.2.1

Repeated Analysis	Time from R1 (years)	Information Time (%)	Failures under Alternative	Critical Value	Nominal Significance
1	3.5	54%	215	2.834	0.002
2	4	68%	272	2.515	0.006
3	4.5	84%	333	2.254	0.012
4	5	100%	399	2.048	0.020

We will also incorporate an interim futility analysis for the induction PFS using the Wieand rule.[91] At each interim analysis, the treatment hazard ratio [B/A] is estimated with a stratified Cox regression model. If the hazard ratio equals or exceeds 1, consideration will be given to

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early termination of the induction comparison. Although it is unlikely, if the induction comparison were to be stopped for futility before accrual was completed, the protocol would be amended to directly assign patients to VRd induction to complete the accrual for the maintenance comparison.

Before this amendment (Addendum #11), interim analyses for the maintenance PFS comparison occurred at 30% and 68% information. With changes to the timing of interim analyses, sample size and follow-up duration, the expected count of failures under the alternative hypothesis, critical value, nominal significance for the interim efficacy analysis were revised. Additionally, the method formerly used to evaluate futility, conditional power, was replaced.

9.7.3 Toxicity

There will be one early interim analysis for toxicity when 100 patients on the CRd arm have been treated for 6 cycles. We are specifically interested in the rate of grade 4 or higher cardiac, pulmonary or renal toxicity, either directly or at least probably related to treatment. The CRd arm would be of interest if the toxicity rate is no worse than 25%. If 32 or more patients experience this level of toxicity, consideration will be given to modifying the treatment regimen. Under this monitoring rule, there is less than 7% probability of meeting this boundary if the true rate is 25% but 96% probability of meeting the boundary if true rate is unacceptable (40%).

9.8 Gender and Ethnicity

Based on previous data from the newly diagnosed ECOG MM trial, E4A03, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	9	6	15
Not Hispanic or Latino	474	591	1065
Ethnic Category: Total of all subjects	483	597	1,080
Racial Category			
American Indian or Alaskan Native	4	3	7
Asian	3	4	7
Black or African American	56	76	132
Native Hawaiian or other Pacific Islander	0	0	0
White	420	514	934
Racial Category: Total of all subjects	483	597	1,080

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.9 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

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10. Biological Sample Submissions

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Bone marrow and peripheral blood are to be submitted from patients who agree to participate in the protocol defined laboratory research studies. Follow-up bone marrow aspirates are required to be submitted for the MRD analysis outlined in Section 11.2. Background for the research studies is outlined in Section 1.6 and rationale and methodology described in Section 12. Additional peripheral blood and bone marrow are to be submitted from patients who consent to allow specimens to be submitted for future undefined research studies.

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10.1 Submissions to the Mayo Clinic Myeloma Reference Laboratory

Myeloma Tumor Biology Kits are available to order, and will include materials necessary for the preparation and shipment of samples. Kits should be ordered at least 24 hours in advance of each sample time point. To order kits call Kim Henderson at the Mayo Clinic Myeloma Reference Laboratory at (507) 284-3805 or e-mail henderson.kimberly@mayo.edu.

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ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System and an STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.3. **A current white blood count and differential** is to be included with each sample submission, entered via the Sample Tracking System.

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If your shipment was not logged into the ECOG-ACRIN STS please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number (E1A11), the FedEx tracking number, and name and phone number of the contact person.

Any questions concerning sample collection and shipment can be directed to Kim Henderson at (507) 284-3805.

10.1.1 Sample Submission Schedule

The blood and bone marrow collections are to occur at the time of those performed for clinical assessments. Additional procedures to collect the research specimens should not be required. Fresh specimens are to be shipped day of collection. **FRIDAY AND PRE-HOLIDAY COLLECTION AND SHIPMENTS SHOULD BE AVOIDED.**

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Sample submission schedule is outlined in the table below:

NOTE: Unstained core biopsy slides can be mailed later if they are not available at the time of shipping the bone marrow aspirate and peripheral blood.

Rev. 5/14, 9/14, 9/17	Biological Materials	Pre-Registration[1]	After Induction Cycle Three [Arm B]	After Induction Cycle Four [Arm A]	After Induction Cycle Nine [Arm B]	After Induction Cycle Twelve [Arm A]	After Maintenance Cycles 24 and 36	Confirmation of CR[2]	Disease Progression
	MANDATORY *for Defined Laboratory Research Studies*								
	Bone Marrow Aspirate (1) 1mL Streck Cell Preservative® vial		X		X		X	X	
	From Patients Who Answer *"YES"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*								
	Bone Marrow Aspirate (1) 1mL Streck Cell Preservative® vial	X							
Rev. Add11	Peripheral Blood (1) 8.5mL ACD (yellow top) tube	X	X		X		X	X	X
	From Patients Who Answer *"YES"* to *"I agree to provide additional specimens for research."*								
Rev. Add11	Bone Marrow Aspirate (2) 6mL ACD (yellow top) tubes	X	X		X		X	X	X[3]
Rev. 9/17	Peripheral Blood (1) 10mL Red Top tube	X	X		X		X		X
	Bone Marrow Core Biopsy Slides (5)	X	X		X		X	X	X

1. Prior to treatment. The blood and bone marrow collections are to occur at the time of those performed for clinical assessments. Additional procedures to collect the research specimens should not be required.
2. Any subsequent marrow performed for CR confirmation.
3. Or excessive toxicity for Arm D patients.

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10.1.2 Sample Preparation Guidelines

All samples must be clearly labeled with the protocol number E1A11, the patient's initials (last name, first name), ECOG-ACRIN patient sequence number, date of collection, and type of sample (PB or BM).

A. Peripheral Blood

- Draw 8.5mL of peripheral blood into **one (1) ACD (yellow top) vacutainer** tube provided in the Myeloma Tumor Biology Kit. Ship the day of collection.
- Draw 10mL of peripheral blood **into one (1) clot (red top) tube** provided in the Myeloma Tumor Biology Kit. Ship the day of collection.

B. Bone Marrow Aspirate

This redirect bone marrow aspirate should be drawn at the same time that a bone marrow aspiration/biopsy is being done for clinical and diagnostic purposes and should be done through the same skin puncture site that the clinical sample was obtained.

- Draw 12mL of a 'redirect' bone marrow aspirate into **two (2) ACD (yellow top) vacutainer tubes** provided in the Myeloma Tumor Biology Kit. Ship the day of collection.
- Draw 1mL of a 'redirect' bone marrow aspirate and place in the **Streck Cell Preservative®** screw-top vial provided in the Myeloma Tumor Biology Kit. Secure vial top tightly and immediately mix by gentle inversion 3 times. Ship the day of collection.

C. Bone Marrow Core Biopsy Slides

- Five (5) air-dried, unstained "charged" slides from the paraffin block of a bone marrow core biopsy are to be submitted at each time point indicated in the above table.
- Slides should be sent with the bone marrow aspirate and peripheral blood samples if possible. If slides are unavailable to send at that time, they may be sent separately within one month of collection.

10.1.3 Shipping Procedures

Samples should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. The samples from multiple patients may be shipped together, but must be placed in separately labeled tubes and bags.

Follow packing guidelines listed in the kit. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

It is requested that the bone marrow core biopsy slides be sent with the other samples in the Myeloma Tumor Biology Kit. However, they

may be shipped separately, within one month of collection, if they cannot be prepared on the same day as the other samples are collected.

Packing instructions:

- Place the slightly thawed Kool-PAK in bottom of Styrofoam container (Kool-PAK should be frozen at least 24 hours in advance). Allow the frozen ice pack to thaw at room temperature for 2–3 hours before preparing the specimen for shipment.
- Place absorbent toweling on top of the Kool-PAK.
- Place specimens in their individual plastic bags provided, wrap in paper toweling and place them in the Styrofoam container and close the lid. Do not place the specimen(s) directly on the ice pack.
- Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
- Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx air bill and adhere to the exterior lid of the box. Ship specimens priority overnight delivery the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Please call Kim Henderson at (507) 284-3805 or e-mail henderson.kimberly@mayo.edu to notify the Mayo Clinic Myeloma Reference Laboratory when specimen(s) are being shipped if your shipment was not logged into the ECOG-ACRIN STS. Indicate the ECOG-ACRIN protocol number (E1A11), the FedEx tracking number, and name and phone number of the contact person.

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The samples in prepared kits should be shipped to the following address:

Kim Henderson
Mayo Foundation
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

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An STS shipping manifest form must be generated and shipped with all sample submissions.

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10.2 Submissions for Genomic Sequencing through the CoMMpass Study

From patients who answer *"YES"* to *"I agree to participate in the genomic sequencing laboratory research study."*

10.2.1 Collection Kits

Collection kits are available to order, and will include materials necessary for the preparation and shipment of the samples. Kits should be ordered at least 24 hours in advance of each sample time

point. To order kits send an e-mail request to mmrf.commpass@vai.org and **include "E1A11" in the subject line**.

Kits are shipped by FedEx and will arrive the next day.

All samples should be shipped the day of collection using the kits. Follow the shipping and packing instructions provided in the kits carefully.

Please verify the shipping kit contains the following:

- One (1) pre-labeled 6mL green top vacutainer tubes (inside smaller box)
- Two (2) pre-labeled 6mL purple top vacutainer tubes (inside smaller box)
- Plastic Biohazard Ziploc bag with absorbent (inside smaller box)
- Collection & Shipping Instructions (MMRF.0001)
- Sample Collection Form (MMRF.0002)
- Pre-printed FedEx air bill
- Two (2) cold packs

Confirm that the Kit ID sticker on the included Sample Collection Form (MMRF.0002) corresponds to the Kit ID sticker on the outside of the small inner cardboard kit box as well as the outer insulated shipping box.

Confirm that all 3 vacutainer tubes are labeled with a bar-coded ID and that the first 8 digits (e.g. MMRF---00001) of each tube label match the Kit ID.

Remove the 2 cold packs and freeze at -20°C for at least 2 hours. Cold Packs should remain frozen until shipment.

10.2.2 Sample Submission Schedule

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ECOG-ACRIN requires that all biological specimens submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System and an STS shipping manifest form must be generated and shipped with the specimen submissions.

Biological Materials	Pre-Registration	Confirmation of CR	Disease Progression/ Relapse
From Patients Who Answer *"YES"* to *"I agree to participate in the genomic sequencing laboratory research study."*			
Bone Marrow Aspirate (1) 5mL Green Top Sodium Heparin Vacutainer Tubes[3]	X	X[1,2]	
Peripheral Blood (2) 5mL Purple Top EDTA Vacutainer Tubes[3]	X	X[1,2]	

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1. At relapse/progression and suspected CR. For any given patient, samples at relapse/progression are not required beyond the second episode (first and subsequent relapse) during the follow-up period.
2. Bone marrow samples at relapse/progression must be obtained before a new therapeutic regimen is begun.
3. **Both bone marrow and peripheral blood must be submitted together on the day of collection. The sequencing cannot be performed without both specimen types.**

10.2.2.1 Peripheral Blood

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Draw 10mL of peripheral blood, 5mL into each of ***two,*** 6mL purple top, EDTA vacutainer tubes provided in the collection kit. *Please use vacutainers labeled "Peripheral Blood".* Ship day of collection.

a. Write the ECOG-ACRIN protocol number (E1A11) and ECOG-ACRIN patient sequence number on each label.
b. Immediately after aliquoting, invert vacutainers 10 times to ensure proper mixing.
c. Refrigerate samples at 2-8°C until shipment.

10.2.2.2 Bone Marrow Aspirate

Draw 5mL of bone marrow from the aspirate needle and aliquot 5mL into the ***one,*** 6mL green top, sodium heparin vacutainer tube provided in the collection kit. *Please use vacutainers labeled "Bone Marrow".* Ship day of collection

a. Write the ECOG-ACRIN protocol number (E1A11) and ECOG-ACRIN patient sequence number on each label.
b. Immediately after aliquoting, invert the vacutainer tube 10 times to ensure proper mixing.
c. Refrigerate sample at 2-8°C until shipment.

Collect the bone marrow sample immediately after the diagnostic sample has been obtained. To obtain a sample of adequate quality, **re-positioning the needle is required.**

Given the volume of bone marrow to be collected, we request that you submit the first available aspirate sample once all clinically required procedures are complete.

We highly recommend that the bone marrow aspirate needle bevel be repositioned (i.e. turned 180°) or turned radially by 90° after each 2.5mL of sample for collection of the aspirate.

To minimize clotting associated with large aspirates and late order draw aspirates, we highly recommend the aspirate syringe contain sodium heparin.

PLEASE NOTE: If additional purple-top or green-top tubes are required, pull these tubes

from the "bulk supply" and hand write the ECOG-ACRIN protocol number (E1A11) and ECOG-ACRIN patient ID number and Kit ID on each tube.

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10.2.3 Kit Packaging and Shipping

NOTE: Bone marrow and peripheral blood must be submitted together on the day of collection. The sequencing cannot be performed without both specimen types.

1. Complete Sample Collection Form (MMRF.0002). Circle the appropriate visit type: baseline, relapse/progression, suspected CR, or other. Complete all fields on the form including the immunoglobulin information.
2. Make a copy of the Sample Collection Form (MMRF.0002) and retain for study records.
3. Place all collection vacutainer tubes in the small, inner box. The Styrofoam insert will need to be removed and dismantled for tube placement. Please return all unused vacutainer tubes in the box.
   a. Each side of the Styrofoam compartment in the smaller inner box holds 4 tubes.
   b. Place the Peripheral Blood vacutainers in the 2 grooves on one side.
   c. Place the Bone Marrow vacutainer in the groove on the opposite side.
4. Place the fully assembled Styrofoam insert into the provided Biohazard Ziploc bag with absorbent paper and seal the Ziploc bag.
5. Place the Ziploc bag with the Styrofoam insert inside the small cardboard box and close the box.
6. Place the small box inside the larger plastic Ziploc bag then place it in the large, outer insulated shipper.
7. Retrieve the 2 frozen cold packs, ensure they are completely frozen, and place them on either side of the small inner box.
8. Place the Styrofoam lid on the insulated shipper and place the completed Sample Collection Form on top of the lid.
9. Close the cardboard flaps and seal the package. Be sure to remove the pre-printed FedEx air bill from the outer insulated shipper prior to sealing the package.
10. **For Monday through Thursday Shipments,** place the included FedEx air bill on the TOP of the insulated shipper.
11. **For Friday Shipments (Saturday Delivery), the included FedEx air bill CANNOT be used. Please refer to the Friday Shipping (Saturday Delivery) Instructions (MMRF.0003) in**

the Friday Shipments (Saturday Delivery) envelope provided separately from the collection kits.

12. Remove the colored sticker (pink, blue, or green) covering the FedEx Label prior to shipping.
13. Peel off the yellow removable label covering the UN3373 sticker on the outside of the insulated shipper.
14. Notify the Advance Technologies Laboratories at Spectrum Health via phone call (616-486-6233) of each impending shipment on the day of shipment.
15. Send a shipment notification via email to mmrf.commpass@vai.org on the day of shipment. Please include the following information:
    a. Subject line: "E1A11 MMRF shipment from (collection site)"
    b. Email body:
        i. Ship date
        ii. FedEx tracking number (found on pre-printed air bill)
        iii. Collection site name and ID number
        iv. ECOG-ACRIN protocol number (E1A11) and ECOG-ACRIN patient ID number
        v. Kit ID number (located on the outside of the kit box; e.g. MMRF-00001)
        vi. Collection date
        vii. Contact information (name and telephone number)
16. Arrange for SAME DAY FedEx pickup (1-800-463-3339).

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    a. If FedEx is unable to pick up due to a late collection, refrigerate specimens until next available FedEx shipment.

    Ship specimens to:

    Spectrum Health
    Advanced Technologies Laboratory
    145 Michigan NE, Suite 6210
    Grand Rapids, MI 49503
    (616) 486-6233

For any additional questions or to request collection kits for Friday Shipments (Saturday Delivery) envelopes, contact VARI (Van Andel Research Institute) at (616) 234-5122 or mmrf.commpass@vai.org and include "E1A11" in the subject line.

10.2.4 Banking

Any residual cells and/or derivatives (isolated RNA/DNA and any unused material) of specimens remaining after the completion of the studies in the CoMMpass protocol will be batched and routed to an ECOG-ACRIN designated central repository for possible use in ECOG-ACRIN approved future studies. If future use is denied or

withdrawn by the patient, the specimens will be removed from consideration for use in any future study.

10.3 ECOG-ACRIN Sample Tracking System

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It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

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Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link:

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http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

A Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at the time of sample submission, along with the Patient Information Form (Appendix I) for samples going to Mayo Clinic Myeloma Reference Laboratory.

Retroactively enter all collection and shipping information when STS is available.

10.4 Use of Specimens in Research

Specimens will be distributed to investigators for the laboratory research studies defined in Section 12.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained in an ECOG-ACRIN designated central repository.

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

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If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.5 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used will be submitted electronically via secure web application to the ECOG-ACRIN Operations Office – Boston on a monthly basis or upon request by any laboratory holding and/or using any specimens associated with this study.

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11. Laboratory Research Studies

The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

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11.1 Plasma Cell Proliferation

Presence of circulating plasma cells and plasma cell proliferation will be assessed by a CD38/CD45 immunofluorescence flow cytometry assay performed on peripheral blood or bone marrow respectively.

The analysis will be performed at the Hematology Research Laboratory at Mayo Clinic.

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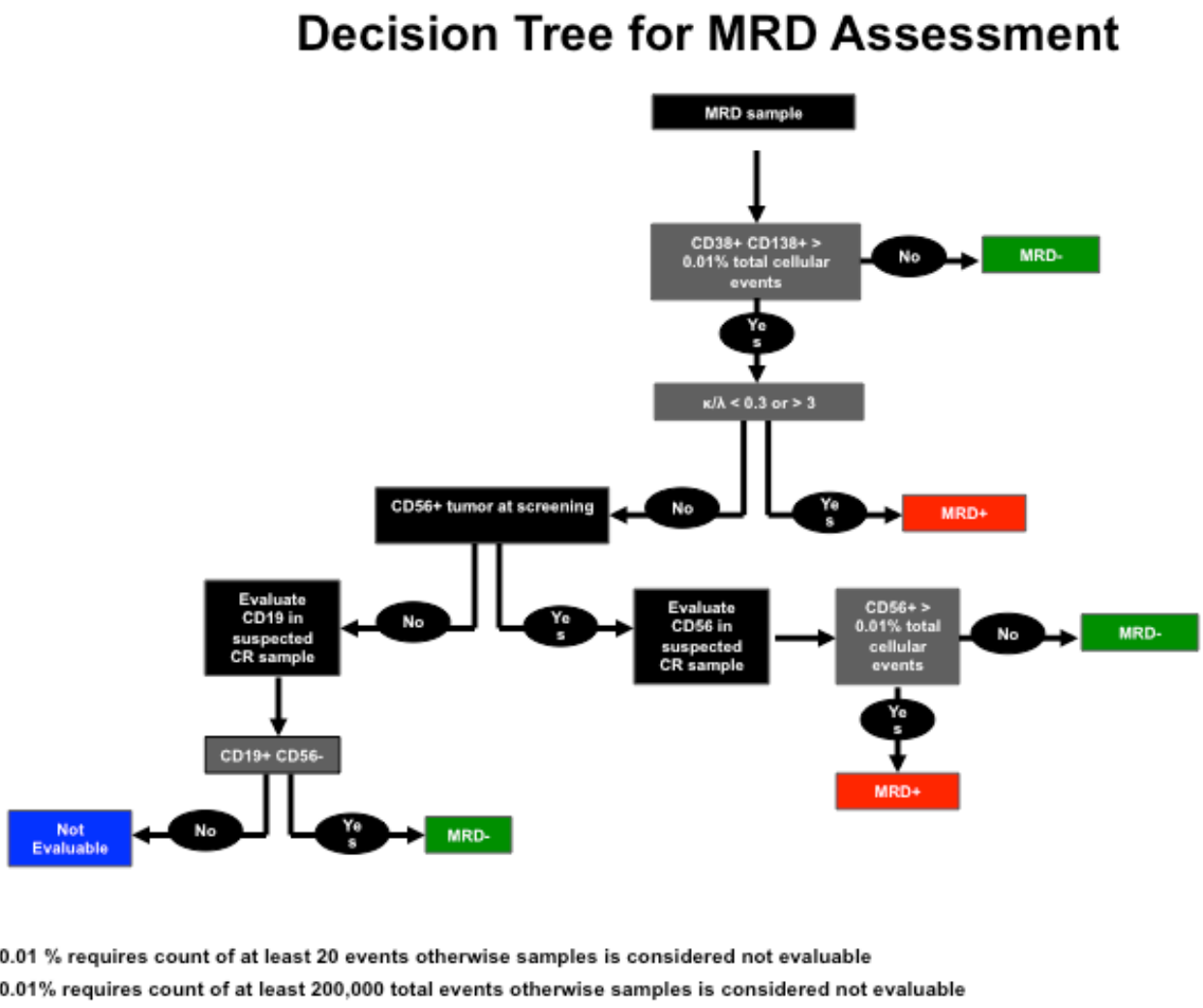
11.2 Minimal Residual Disease Analysis

The analysis will be performed at the Hematology Research Laboratory at Mayo Clinic.

For each sample, one milliliter whole bone marrow diluted 1:1 in STRECK stabilization reagent (Streck, Inc. Omaha, NE) is pulled one time through a 27 gauge needle to reduce cellular aggregation. This aliquot is washed one time in PBS (phosphate buffered saline) and lysed in ammonium chloride buffer (ACK). The cells are counted and the concentration is adjusted to 10 million cells per ml. Two million cells are added to each of the three MRD (minimal residual disease) panel tubes. CD38 APC, CD45 APC-H7 and CD138 percp cy5.5 are included in each tube for gating purposes. Tube-2 also includes CD19 PEcy7 and CD56 PE while tube-3 includes the appropriate isotype control reagents. After 15 minutes incubation in the dark the tubes are washed one time with PBS. Tube-1 is further fixed and permeabilized, then stained with kappa FITC and lambda PE in order to determine the light chain restriction of the gated plasma cells. The samples are resuspended in 0.5 ml of stabilizing fixative and held at 4 degrees in the dark until run on the Canto II flow cytometer (BD Biosciences, San Jose, CA). Acquisition is done in a single step with the instrument set to collect 2 million events or until the entire sample has been used up.

The gating strategy and the algorithm for determination of MRD status is as shown in the flow diagram below. > 0.01% requires at least 100 malignant plasma cell events and < 0.01% requires at least 1 million total events collected.



>0.01 % requires count of at least 20 events otherwise samples is considered not evaluable

<0.01% requires count of at least 200,000 total events otherwise samples is considered not evaluable

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11.3 Integrated Genomic Sequencing *(collaboration with MMRF through the CoMMpass Study)*

These analyses will be performed at Spectrum Health, Van Andel Research Institute, and Translational Genomics Research Institute.

11.3.1 ***Rationale*:** It is increasingly clear that the genomic abnormalities seen in the myeloma cells increase overtime and play a critical role in driving the disease course. These changes underlie the inevitable development of resistance seen in these patients to all available therapies over time. Understanding these changes during the initial treatment of myeloma will be extremely valuable, as it will help us improve the initial therapies to better deal with and potentially prevent these early changes, thus altering the natural history of the disease and improving survival. Doing these studies in the context of E1A11 is particularly relevant, as it utilizes a triplet regimen that is currently considered standard and another regimen that is likely to become a new standard if the results prove the hypothesis of this trial. The studies are time sensitive, and are likely to be productive if done concurrently with the study, as there are many other new classes of

drugs being developed and this information can be highly relevant when trying to decide the next best combinations to be tested for initial therapy of myeloma. The CoMMpass study provides a unique opportunity to not only bring to bear the resources that are lacking to comprehensively analyze the myeloma cell genome in the context of this study, but also allows us to compare the results with many of the other regimens being used in the community setting. This represents a unique and mutually beneficial collaboration, which will be invaluable in advancing the science. A protocol synopsis of the CoMMpass study is provided in Appendix XII.

11.3.2 *Assays Employed and Data Generated (TGen):*

Data Generation: As part of the MMRF CoMMpass study Translational Genomic Research Institute (TGen) is comprehensively characterizing each patient sample using three different assays. These approaches were conceived and reduced to practice prior to the onset of the CoMMpass study. For each and every patient submitted to TGen an attempt will be made to generate the following three libraries:

1. Whole genome long-insert libraries (Liang W et al Nuc Acid Res 2013)
   - Created from both Tumor and Constitutional DNA samples
   - Used to detect somatic structural alterations and copy number abnormalities
2. Whole exome libraries
   - Created from both Tumor and Constitutional DNA samples
   - Used to detect somatic single nucleotide variants (SNV) and indel events along with copy number abnormalities
3. mRNA libraries
   - Created from Tumor RNA only
   - Used to define expression estimates (gene and transcripts), splice junctions, fusion transcripts, and to determine if somatic mutations are expressed

Due to changes in commercial offerings and internal efforts to reduce the input DNA/RNA requirements at TGen, several modifications have been made as to how the sequencing libraries are created throughout the course of the study.

1. Whole genome long-insert
   - Illumina TruSeq DNA kits using 1000ng inputs
   - Kapa Biosystems kits using 500ng inputs: Minimal low input option of 250ng inputs
   - Kapa Biosystems Hyper kits using 200ng inputs: Minimal low input option of 100ng inputs Exome Methods:
2. Whole exome

a. Illumina TruSeq DNA using 1000ng followed by pooled (6-plex) Illumina TruSeq Exome capture
b. Kapa Biosystems kits using 500ng inputs followed by pooled (8- plex) Agilent SureSelect V5+UTR capture: Minimal low input of 150ng inputs
a. Kapa Biosystems Hyper kits using 200ng inputs followed by single-plex Agilent SureSelect V5+UTR capture (Library and Capture performed on an Agilent Bravo liquid handler): Minimal low input of 50ng for diagnostic samples and 10ng for sequential samples

3. mRNA Methods:
   i. Illumina TruSeq RNA (mRNA unstranded) using 2000ng inputs
   ii. Illumina TruSeq RNA (mRNA unstranded) using 500ng inputs: Minimal low input of 150ng

All libraries are sequenced on Illumina HiSeq2000 or HiSeq2500 sequencers at TGen. Exome and RNA assays are typically sequenced using paired-end 83x83bp (TruSeqExome/RNA and Agilent V5+UTR single-plex) or 82x82bp (Agilent V5+UTR 8-plex pools) sequencing. Long-inserts are typically sequenced using 86x86bp sequencing. In rare situations any samples may be included on flowcells with a mixture of different assays that may require 82x82, 83x83, or 100x100bp sequencing.

Data Analysis:

1. Fastq files are generated using bcl2fastq-1.8.4 from raw illumina run folders.
2. All Fastq files are aligned to the GRCh37 reference human genome. The reference used in this version of the pipeline includes the entire hs37d5 based genome used by the 1000 genome project.
   a. hs37d5.fa
      i. ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/technical/reference/phase 2_reference_assembly_sequence/
   b. To this base genome, the ERCC contigs, numerous virus genomes known to cause cancer, and a copy of the ribosomal subunit have been added.
      i. hs37d5_plusRibo_plusOncoViruses_plusERCC.fa
3. All annotation and gene models are based on Ensembl version 74. Any gene models associated with contigs that do not exist in the hs37d5 base genome have been removed. Also, gene models for the cancer specific EGFR VIII isoform have been added.

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11.4 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned laboratory research studies will be submitted electronically via secure data portal to the ECOG-ACRIN Operations Office – Boston by the central laboratory on a quarterly basis.

12. Electronic Data Capture

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Please refer to the E1A11 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave and EASEE-PRO (for tobacco use assessment).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be conducted under an IND. All records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

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13. References

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Appendix I

Myeloma Tumor Biology Kit

Specimen Checklist and Shipping Instructions

****PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- 5 lb Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx air bill with pre-printed return address
- 6ml ACD (yellow top) collection tubes
- 8.5ml ACD (yellow top) collection tube
- 10ml Red Top tube
- Streck Cell Preservative® vial
- Zip lock specimen bags
- (1) Kool-PAK. Place the ice pack in the freezer for at least 24 hours prior to specimen shipment. Allow the frozen ice pack to thaw at room temperature for 2-3 hours **before** preparing the specimen for shipment.

Packing and Shipping Instructions:

1. Collect the following specimens:
    1. Peripheral blood - Draw 8.5ml of peripheral blood into one (1) ACD (yellow top) tube.
    2. Peripheral blood – Draw 10ml of peripheral blood into one (1) Red Top tube.
    3. Bone marrow aspirate - Draw 12ml of a 'redirect' bone marrow aspirate into two (2) 6ml ACD tubes.
    4. Bone marrow aspirate - Draw 1ml of a 'redirect' bone marrow aspirate and place in the Streck Cell Preservative® screw-top vial. Gently mix by inversion 3 times.
    5. Bone marrow core biopsy slides – Five (5) air-dried unstained biopsy slides (plus or charged slides).

       Exception: Unstained core biopsy slides can be mailed later if they are not available at the time of shipping the bone marrow aspirate and peripheral blood.
2. All specimens are to be clearly labeled with the protocol number E1A11, the patient's initials (last name, first name), ECOG-ACRIN patient sequence number, sample type (PB, BM) and date of collection.
3. Place the slightly thawed Kool-PAK in bottom of Styrofoam container.
4. Place absorbent toweling on top of Kool-PAK.

5. Place specimens in the plastic bags provided, wrap in paper toweling and place them in the Styrofoam container and close the lid. Do not place the specimen(s) directly on the ice pack.
6. Place the Styrofoam container and the Sample Tracking System shipping manifest form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx air bill and adhere to the exterior lid of the box. Ship specimens via overnight delivery the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

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The ECOG-ACRIN Sample Tracking System will automatically contact the Myeloma Reference Laboratory. If you did not use the ECOG-ACRIN Sample Tracking System please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person.

The samples in prepared kits should be shipped to the following:

Kim Henderson
Mayo Foundation
221 4th Avenue SW
613 Stabile
Rochester, MN 55905

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Patient Information Form

It is required that samples submitted from patients participating in E1A11 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 10.3). This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Specimen Date: / /

Patient Initials (last name, first name):

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ECOG-ACRIN Protocol #: E1A11

ECOG-ACRIN Patient Sequence #:

Contact Person:

Institution:

Address:

City State Zip

Phone #:

FAX #:

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PLEASE INCLUDE A CURRENT WHITE BLOOD COUNT AND DIFFERENTIAL

WBC _____

% of Lymphocytes: _____

% of Monocytes: _____

Please indicate which samples are being shipped at this time:

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1. Pre-Study or Baseline
2. End of Cycle 3 (Arm B)
3. End of Cycle 4 (Arm A)
4. End of Cycle 9 (Arm B)
5. End of Cycle 12 (Arm A)
6. End of Cycle 24
7. End of Cycle 36
8. Confirmation of CR
9. Disease Progression

Any questions concerning these samples or to obtain a Myeloma Tumor Biology kit, please contact:

Kim Henderson
henderson.kimberly@mayo.edu
(507) 284-3805

Affiliates who anticipate participating in this study should please call in advance for kits.

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

Patient Medication Calendar

Medication Calendar Directions

1. Take your scheduled dose of each medication.
2. If you forget, the missed medication will not be taken later.
3. Please bring the empty bottle or any leftover medication and your medication calendar to your next clinic visit.

CTEP-assigned Protocol #_____
Local Protocol # _____

Patient Medication Calendar

Today's date _____ Study: E1A11 Cycle _____

Patient Name_____ (*initials acceptable)* **Patient Study ID_____**

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take lenalidomide capsules by mouth. Dose: Take _____# of capsules once daily.
3. You will take dexamethasone tablets by mouth. Dose: Take _____# tablets every morning
4. Record the date that you took you medication and when you took it.
5. If you have any comments or develop any side effects, please record them and anything you would like to tell your doctor in the Comments column provided.
6. Please bring this form and any unused lenalidomide and dexamethasone medication to your doctor's visit.

Day	Date	Time of dose	# of Capsules/Tablets Taken		Comments
			Lenalidomide capsules	Dexamethasone tablets	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

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Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 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.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix V

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

Risks Associated with Pregnancy

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 RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

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

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding

- Acknowledge the aforementioned requirements
- For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

  Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):
- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

  Contraception

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

  The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. 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

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.

Before starting lenalidomide:

Female Subjects:

- FCBP must have two negative pregnancy tests (combined sensitivity of at least 50 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10-14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During study participation and for 28 days following discontinuation from the study:

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.

Male Subjects:

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and at the time that lenalidomide treatment is discontinued. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.

- 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 this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.
- Patients randomized to Arm B utilizing carfilzomib must also agree to use effective contraception or abstinence while taking carfilzomib. Female patients must continue to use contraception for 30 days after the last dose of carfilzomib and male patients must continue to use condoms while having intercourse for 90 days after the last dose of carfilzomib.

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Appendix VI

Cancer Screening Guidelines

(Adapted from American Cancer Society Guidelines)

Breast cancer

- Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health
- Clinical breast exam (CBE) about every 3 years for women in their 20s and 30s and every year for women 40 and over

Colorectal cancer and polyps

Beginning at age 50, both men and women should follow one of these testing schedules:

Tests that find polyps and cancer

- Flexible sigmoidoscopy every 5 years*, or
- Colonoscopy every 10 years, or
- Double-contrast barium enema every 5 years*, or
- CT colonography (virtual colonoscopy) every 5 years*

Tests that primarily find cancer

- Yearly fecal occult blood test (gFOBT)**, or
- Yearly fecal immunochemical test (FIT) every year**, or
- Stool DNA test (sDNA), interval uncertain**

* If the test is positive, a colonoscopy should be done.

** The multiple stool take-home test should be used. One test done by the doctor in the office is not adequate for testing. A colonoscopy should be done if the test is positive.

Cervical cancer

- Cervical cancer screening (testing) should begin at age 21. Women under age 21 should *not* be tested.
- **Women between ages 21 and 29** should have a Pap test every 3 years. Now there is also a test called the HPV test. HPV testing should *not* be used in this age group unless it is needed after an abnormal Pap test result.
- **Women between the ages of 30 and 65** should have a Pap test plus an HPV test (called “co-testing”) every 5 years. This is the preferred approach, but it is also OK to have a Pap test alone every 3 years.
- **Women over age 65** who have had regular cervical cancer testing with normal results should *not* be tested for cervical cancer. Once testing is stopped, it should not be started again. Women with a history of a serious cervical pre-cancer should continue to be tested for at least 20 years after that diagnosis, even if testing continues past age 65.

- **A woman who has had her uterus removed (and also her cervix)** for reasons not related to cervical cancer and who has no history of cervical cancer or serious pre-cancer should *not* be tested.
- **A woman who has been vaccinated against HPV** should still follow the screening recommendations for her age group.

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Randomized Phase III Trial Of Bortezomib, Lenalidomide And Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed By Limited Or Indefinite Lenalidomide Maintenance In Patients With Newly Diagnosed Symptomatic Multiple Myeloma

Appendix VII

RevAssist Prescription Form

Today's Date _____ Date Rx Needed_____ Patient Last Name_____ Patient First Name_____ Phone Number ( )_____ Shipping Address _____ City _____State_____ Zip_____ Date of Birth _____Patient ID#_____ Language Preference: ☐ English ☐ Spanish ☐ Other Best Time to Call Patient: ☐ AM ☐ PM Patient Diagnosis (ICD-9 Code) _____ Patient Allergies _____ _____ Other Current Medications _____ _____	Prescriber Name_____ State License Number _____ Prescriber Phone Number ( )_____ Ext._____ Fax Number ( ) _____ Prescriber Address _____ _____ City _____State_____ Zip_____ **Patient Type Form PPAF** (Check one) ☐ Adult Female – NOT of Childbearing Potential ☐ Adult Female – Childbearing Potential ☐ Adult Male ☐ Female Child – Not of Childbearing Potential ☐ Female Child – Childbearing Potential ☐ Male Child

PRESCRIPTION INSURANCE INFORMATION

Fill out entirely and fax a copy of patient's insurance card, both sides)

Primary Insurance _____

Insured_____

Policy # _____

Group # _____

Phone # _____

Rx Drug Card # _____

Secondary Insurance_____

Insured_____

Policy # _____

Group # _____

Phone # _____

Rx Drug Card # _____

TAPE PRESCRIPTION HERE PRIOR TO FAXING REFERRAL, OR COMPLETE THE FOLLOWING:

Recommended Starting Dose: See below for dosage

Myelodysplastic Syndromes: The recommended starting dose of REVLIMID® is 10 mg/day with water. Dosing is continued or modified based upon clinical and laboratory findings.

Multiple Myeloma: The recommended starting dose of REVLIMID® is 25 mg/day orally for Days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical

REVLIMID®

Dose	**Quantity**	**Directions**
☐ 5 mg	_____	_____
☐ 10 mg	_____	_____
☐ 15 mg	_____	_____
☐ 25 mg	_____	_____

☐ Dispense as Written ☐ Substitution Permitted

NO REFILLS ALLOWED (Maximum Quantity = 28 days)

Prescriber Signature_____**Date**_____

Authorization #_____**Date**_____
(To be filled in by healthcare provider)

Pharmacy Confirmation #_____**Date**_____
(To be filled in my pharmacy)

IMPORTANT INFORMATION ABOUT RevAssist®

- To avoid fetal exposure, REVLIMID® (lenalidomide) is only available under a special restricted distribution program called "RevAssist®"
- Only prescribers registered with RevAssist® can prescribe REVLIMID® (lenalidomide)
- Only RevAssist® contract pharmacies can dispense REVLIMID® (lenalidomide)
- In order to receive REVLIMID® (lenalidomide), patients must enroll in RevAssist® and agree to comply with the requirements of the RevAssist® program
- Information about REVLIMID® (lenalidomide) and the RevAssist® program can be obtained by calling the Celgene Customer Care Center toll-free at 1-888-423-5436, or at www.REVLIMID.com

HOW TO FILL A REVLIMID® (Lenalidomide) PRESCRIPTION

1. Healthcare Provider (HCP) instructs patient to complete patient survey
2. HCP completed survey
3. HCP completes patient prescription form
4. HCP obtains RevAssist® authorization number
5. HCP provides authorization number on patient prescription form
6. **HCP faxes form, including prescription, to one of the Celgene Pharmacy Network participants (see below)**
7. HCP advises patient that a representative from the pharmacy will contact them
8. Pharmacy conducts patient education
9. Pharmacy calls for confirmation number
10. Pharmacy ships REVLIMI® to patient with a FDA-approved MEDICATION GUIDE

Please see www.celgene.com/PharmacyNetwork for the list of pharmacy participants

Randomized Phase III Trial Of Bortezomib, Lenalidomide And Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed By Limited Or Indefinite Lenalidomide Maintenance In Patients With Newly Diagnosed Symptomatic Multiple Myeloma

Appendix VIII

Rev. 5/14
Rev. Add12

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on carfilzomib/lenalidomide, or within 28 days of the patient's last dose of carfilzomib/lenalidomide must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERs): http://ctep.cancer.gov

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as “A death in utero.”

It must be reported via CTEP-AERS as Grade 4 “Pregnancy loss” under the System Organ Class (SOC) “Pregnancy, puerperium and perinatal conditions”.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient’s death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as “A death occurring during the first 28 days after birth” that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to carfilzomib/lenalidomide must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 “Death Neonatal”under the System Organ Class (SOC) “General disorder and administration site conditions”.

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient’s death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix IX

Rev. 5/14
Rev. 5/17
Rev. Add11

E1A11 (Amgen 20159843) Carfilzomib Study Drug Request Form – Arm B Patients Only

Site Instructions: Complete all sections above the shaded area before forwarding the drug request to the ECOG-ACRIN Operations Office as an email attachment to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu or fax to 617-589-0919. The ECOG-ACRIN Drug Team will approve and email the order to Amgen Thousand Oaks (CA).

Secondary Contact (Research Nurse/Study Coordinator/Pharmacist):			
Name:		**Title:**	
Telephone:		**Email:**	
Investigator Name:		**Institution Name:**	
Investigator Phone:		**Investigator Email:**	
Ship Supplies To:			
Institution Name:			
Address:			
City, State, Zip:			
Email:		**Telephone:**	

ECOG-ACRIN Patient Sequence Number:	
Date Requested: (MM/DD/YY)	
Shipment Must Reach Destination By: (MM/DD/YY) **Please note:** if your institution has not ordered drug before, initial shipments may take up to **8-9 business days**. All subsequent orders will be shipped within **3-4 business days** Deliveries are **not** made on Mondays, Weekends or Holidays**.**	

Study Drug: Carfilzomib (4 single-use 60 mg vials per carton); Please order 2 cycles at a time	
# Vials Requested: Please order drug in quantities of 4 (max of 24 vials)	

To Be Completed By The ECOG-ACRIN Drug Team	
Cgroup/Inst/Affil: **CTEP ID #:** **IRB Approval Date:**	**Patient Randomized to Arm B:** **Amgen Site Number:** **Completed By:** **Date:**

Randomized Phase III Trial Of Bortezomib, Lenalidomide And Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed By Limited Or Indefinite Lenalidomide Maintenance In Patients With Newly Diagnosed Symptomatic Multiple Myeloma

Appendix X

Rev. 9/17
Rev. Add13

Temperature Excursion Disposition Form

AMGEN	Investigator Sponsored Studies		DOCUMENT NO. FORM-001512I
STATUS EFFECTIVE	EFFECTIVE DATE 13-May-2016	VERSION NO. 6.0	PAGE NO. Page 1 of 3
TITLE Investigator Sponsored Studies Temperature Excursion Submission Form			

FORM INSTRUCTIONS

1. Check the guidance provided by Amgen for time outside acceptable temperature storage range.
2. QUARANTINE the medicinal product under the required storage conditions and DO NOT USE. Do NOT mark on the product in any way. When Amgen receives the form, an assessment will be performed to approve or reject the material. The product MUST remain in quarantine until you have received a product impact memo confirming whether or not the medicinal product is suitable for use.
3. If any medicinal product impacted by the TE has been dosed, notify your Amgen representative immediately.
4. Complete the form electronically. If the form cannot be completed electronically use black ink and ensure the print is neat and legible.
5. Complete a separate form for each medicinal product if you are reporting a TE for more than one medicinal product.
6. If more space is needed to document the lot and box/unit information you may submit multiples of page 2 (Part A).

Example of how to complete the table in Part A

PART A - Required for TE Assessment

MEDICINAL PRODUCT NAME:

Lot NUMBER	AFFECTED BOX NUMBER ☐ N/A (no unique box number)	Quantity and Type of Affected Units* *vials, syringes, blister packs, bottles	Were any affected units administered to a subject? ☐ No ☒ Yes If Yes, NOTIFY the AMGEN REPRESENTATIVE IMMEDIATELY and complete columns below		Document the extreme lowest and/or the extreme highest temperature that was captured. Report the total time the product was out of range ABOVE the specified time duration in the IPIM/equivalent.			
					Extreme Low ☒ N/A (no extreme low)		Extreme High ☐ N/A (no extreme high)	
			How many affected units were dosed? (If not applicable – mark N/A)	Date Dosed DD-MMM-YYYY (If not applicable – mark N/A)	Lowest Temperature	Time outside storage condition	Highest Temperature	Time outside storage condition
1062121	KG0413872	90 vials	3	11-MAR-2016	°C	hrs min	32°C	2 hrs 35 min
1062121	KG0413873	89 vials	N/A	N/A	°C	hrs min	32°C	2 hrs 35 min
1057821	KG0410245	3 vials	N/A	N/A	°C	hrs min	32°C	2 hrs 35 min
1057821	KG0410246	2 vials	N/A	N/A	°C	hrs min	32°C	2 hrs 35 min

AMGEN	Investigator Sponsored Studies		DOCUMENT NO. FORM-001512I
STATUS EFFECTIVE	EFFECTIVE DATE 13-May-2016	VERSION NO. 6.0	PAGE NO. Page 2 of 3
TITLE Investigator Sponsored Studies Temperature Excursion Submission Form			

SUBMIT FORM TO: GCTE@AMGEN.COM AND YOUR AMGEN REPRESENTATIVE

PART A - Required for TE Assessment

MEDICINAL PRODUCT NAME:

Lot NUMBER	AFFECTED BOX NUMBER □ N/A (no unique box number)	Quantity and Type of Affected Units* *vials, syringes, blister packs, bottles	Were any affected units administered to a subject? ☐ No ☐ Yes If Yes, NOTIFY the AMGEN REPRESENTATIVE IMMEDIATELY and complete columns below		Document the extreme lowest and/or the extreme highest temperature that was captured. Report the total time the product was out of range ABOVE the specified time duration in the IPIM/equivalent.			
					Extreme Low ☐ N/A (no extreme low)		Extreme High ☐ N/A (no extreme high)	
			How many affected units were dosed? (If not applicable – mark N/A)	Date Dosed DD-MMM-YYYY (If not applicable – mark N/A)	Lowest Temperature	Time outside storage condition	Highest Temperature	Time outside storage condition
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min
					°C	hrs min	°C	hrs min

AMGEN	Investigator Sponsored Studies		DOCUMENT NO. FORM-001512I
STATUS EFFECTIVE	EFFECTIVE DATE 13-May-2016	VERSION NO. 6.0	PAGE NO. Page 3 of 3
TITLE Investigator Sponsored Studies Temperature Excursion Submission Form			

PART B - Required for TE Assessment				
Medicinal Product:		**Amgen reference number:** 20159843	**Amgen site number:** 66001	Date product was **QUARANTINED** under correct storage conditions: (DD-MMM-YYYY)
Was the guidance provided by Amgen checked for reporting requirements? ☐YES ☐NO		**Country:** US	**Principal Investigator:** Kumar, Shaji	**(FOR FROZEN PRODUCTS ONLY) Has the product been refrozen?** ☐YES ☐NO (Note: In all cases submit temp logs for frozen product)
		Date TE occurred:		
Reporter details:	**Name:**	**Title:**		**Is a resupply needed within the next 2 weeks?** ☐No ☐Yes If 'Yes' please order resupply through the Drug Shipment Request (DSR)
	Telephone:	**Email:**		

PART C				
Has the Amgen representative been notified?: ☐YES ☐NO	**Amgen Representative**	**Name:** Maria Bloodgood Lorie Bruno Kim Malys	**Telephone:** MB: 610-268-5074 LB: 570-778-8765 KM: 805- 447-5390	**Email:** mbloodgo@amgen.com; lorieb@amgen.com; kmalys@amgen.com
Who discovered the TE? ☐Site Staff ☐Other (if other specify)			Who Quarantined the product?	
Possible Cause				
☐Opening and Closing Door/left open ☐Storage Unit Malfunction ☐Human Error ☐Environmental / Weather Related	☐Missed Temperature Readings ☐Air Conditioning/Heating System ☐Missed Temperature Readings ☐Other, please explain		Has the cause been fixed? ☐Yes (how was it fixed?) ☐No (why was it not fixed?)	

Comments:

Randomized Phase III Trial Of Bortezomib, Lenalidomide And Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed By Limited Or Indefinite Lenalidomide Maintenance In Patients With Newly Diagnosed Symptomatic Multiple Myeloma

Appendix XI

Instructions for Storage and Use of Lyophilized Carfilzomib for Injection

For Investigator Sponsored Trials (IST's)

23 July 2013

Version 3.0

New Drug – Limited by Federal (or United States) Law to Investigational Use.
Investigational Drug to be used only by a Qualified Investigator.
For Clinical Study Use Only

1. HOW DRUG IS SUPPLIED

Lyophilized Carfilzomib for Injection is an investigational therapeutic agent provided in a single-dose vial as a sterile, lyophilized powder in the following dosage:

- 60 mg Single-Use Glass Vial / 4 pk Carton

  Each single-dose vial provides 60 mg of Carfilzomib in a 50 cc labeled glass vial with an elastomeric stopper and a flip-off lid. Flip-off lid colors may vary:

  - Green or Purple flip-off lid colors may be provided.

  The product is supplied in labeled carton(s) containing four (4) single-use vials per carton and is shipped and stored between 2°C - 8°C (36°F - 46°F).

Rev. 5/17
Rev. Add11

2. DRUG SUPPLY AVAILABILITY

Carfilzomib is an investigational agent (IND# 118503) available free of charge from Amgen, Inc and distributed by Amgen Thousand Oaks (CA). Carfilzomib for injection is supplied as cartons of 4 single-use 60 mg vials. **Carfilzomib should only be ordered for patients randomized to Arm B.**

Initial Drug Orders for Each Patient

Following randomization to Arm B a supply of Carfilzomib may be ordered. Investigators must email a completed E1A11 Carfilzomib Study Drug Request Form (Appendix IX) to the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu who will then forward the drug request to Amgen NASCR (US) for site shipment set-up; upon completion of site set up, Amgen NASCR will forward to Amgen Clinical Customer Service for order fulfillment. If email is not available, the completed form may be faxed to ATTN: ECOG-ACRIN Drug Team at 617-589-0919. **No starter supplies are available for this protocol.**

Rev. 2/15

Carfilzomib will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution. Sites should order enough vials to complete 2 cycles of treatment (maximum of 6 cartons totaling 24 vials).

Institutions should allow 8-9 business days for INITIAL shipment of drug from Amgen Thousand Oaks from receipt of the E1A11 Carfilzomib Drug Request Form by the ECOG-ACRIN Drug Team. Shipments will be made from Amgen Thousand Oaks on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Any order that would fall on a Friday under the lead time criteria below is scheduled for Monday. Any order that has a ship date that falls on a holiday will default to the next available shipping day according to the lead time criteria below.

Rev. 5/14

Date Request Received By ECOG-ACRIN Drug Team	Site Set Up Complete	Ship Date	Receipt of Drug at Institution
Orders received on day 1 before 12pm ET	Day 5	Day 7	Day 8
Orders received on day 1 after 12pm ET	Day 6	Day 8	Day 9

Amgen Thousand Oaks (ATO) offices will be closed each year during the week of 04 July and prior to 25 December. During this time, there will be no shipments to clinical sites. Shipments to clinical sites will not occur from the Monday of the beginning of each shutdown, resuming the following Monday for 04 July, and the first business weekday of the

New Year for 25 December. It is recommended that drug supply is assessed at each site and orders for (re)-supply are submitted prior to each shutdown.

The E1A11 Carfilzomib Drug Request Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format and is also located in Appendix IX.

Lyophilized Carfilzomib for Injection is using 2°C-8°C Credo shippers via UPS or FedEx. Credo is a re-usable shipping system and all shippers need to be returned to Amgen. See the return process details in the attachment. The returns costs are covered by Amgen. Please refer to the complete instructions for storage and use of Lyophilized Carfilzomib for Injection which may be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org).

As part of Amgen's shipper performance monitoring system, temperature of the shipments will be monitored on an ad hoc basis. In case that a temperature logger is included in the shipment, the receiving site is asked to follow instructions included.

Each site will need to complete and return the POR to the email on the form.

If needed, the Temperature Excursion Disposition Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format and can also be found in Appendix X.

IMPORTANT REORDER INSTRUCTIONS

Once it is determined that the patient will continue treatment, please reorder **2 cycles** of study drug immediately. Institutions should keep in mind the number of vials used per cycle, and that Carfilzomib is provided in cartons of 4 single-use 60 mg vials.

Institutions should allow 3-4 business days for shipment of drug from Amgen Thousand Oaks (CA) from receipt of the E1A11 Carfilzomib Drug Request Form by the ECOG-ACRIN Drug Team. Shipments will be made from Amgen Thousand Oaks on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Any order that would fall on a Friday under the lead time criteria below is scheduled for Monday. Any order that has a ship date that falls on a holiday will default to the next available shipping day according to the lead time criteria below.

Rev. 5/14

Date Request Received By ECOG-ACRIN Drug Team	Ship Date	Receipt of Drug at Institution
Orders received on day 1 before 12pm ET	Day 2	Day 3
Orders received on day 1 after 12pm ET	Day 3	Day 4

Amgen Thousand Oaks (ATO) offices will be closed each year during the week of 04 July and prior to 25 December. During this time, there will be no shipments to clinical sites. Shipments to clinical sites will not occur from the Monday of the beginning of each shutdown, resuming the following Monday for 04 July, and the first business weekday of the New Year for 25 December. It is recommended that drug supply is assessed at each site and orders for (re)-supply are submitted prior to each shutdown.

The E1A11 Carfilzomib Drug Request Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format or found in Appendix IX.

Lyophilized Carfilzomib for Injection is using 2°C-8°C Credo shippers via UPS or FedEx. Credo is a re-usable shipping system and all shippers need to be returned to Amgen. See the return process details in the attachment. The returns costs are covered by Amgen. Please refer to the complete instructions for storage and use of Lyophilized Carfilzomib for Injection which may be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org).

As part of Amgen's shipper performance monitoring system, temperature of the shipments will be monitored on an ad hoc basis. In case that a temperature logger is included in the shipment, the receiving site is asked to follow instructions included.

Each site will need to complete and return the POR to the email on the form.

If needed, the Temperature Excursion Disposition Form can be downloaded from the E1A11 Study Specific Tools section on the ECOG website (www.ecog.org) in WORD format or found in Appendix X.

To report any problems with drug supply or shipments, please email GCCS@amgen.com and include the Amgen Study number 20159843.

Rev. Add11

3. SHIPMENT AND RECEIPT OF DRUG

Lyophilized Carfilzomib for Injection is shipped in a refrigerated shipper with cold packs and a temperature monitor enclosed.

Carfilzomib should be considered a potentially toxic compound and appropriate procedures should be used when handling and preparing Carfilzomib solutions. Always wear hand protection when handling Carfilzomib for Injection.

Upon receipt of a drug shipment, perform the following:

- Open the shipper and ensure that all product cartons and vials are cold and have been received intact without damage.
- Turn off the temperature monitor and follow instructions under "TempTale 4 Temperature Monitor Instructions" – Section 3.2.
- After inspection of the shipment, place the drug cartons in a temperature-monitored refrigerator (2°C– 8°C / 36°F–46°F).
- If any vials are cracked or damaged, proceed to the directions under "Damaged Vials" – Section 3.4.

3.1 ACCOUNTABILITY AND CONFIRMATION OF RECEIPT

- Upon receipt of a drug shipment, document the required information as required per procedures at your institution.

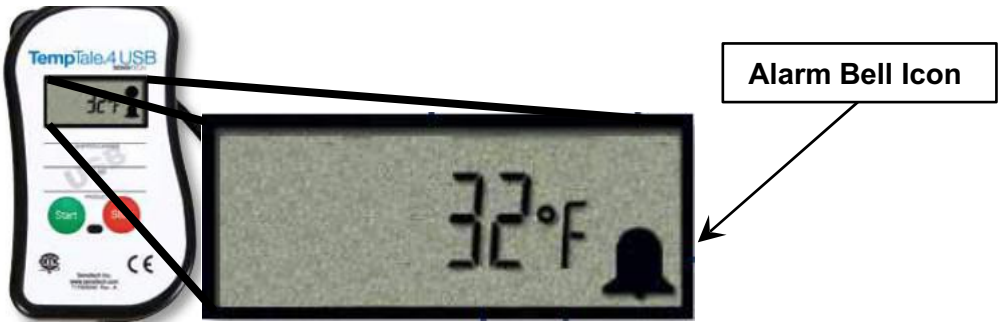
3.2 TEMPTALE 4 TEMPERATURE MONITOR INSTRUCTIONS

The temperature monitor included with shipment has a USB (Universal Serial Bus) cable to facilitate connection and downloading into computers. Instructions for downloading and retrieval of the data will be included with every shipment.

3.2.1 BELL ALARM ICON – NOT PRESENT

- No Bell Icon Alarm: If no Bell Icon appears on screen of the TempTale 4USB, the drug has been transported within the specified temperature range. No confirmation is required from the Sponsor and the drug is available for clinical use. Discard the TempTale4 USB with regular waste.

3.2.2 BELL ALARM ICON – PRESENT



- Bell Icon Alarm: If a Bell Icon appears on the screen of the TempTale 4USB **DO NOT USE THE DRUG** and perform the following steps:
  1. Transfer the drug carton(s) to a plastic bag and clearly label as "Quarantined" with the date. Store labeled quarantined drug in a temperature-monitored refrigerator (2°C–8°C / 36°F–46°F) and ensure that the drug is physically separated from drug available for use
  2. Contact Amgen (formerly Onyx) at GCTE@amgen.com to notify of the event. Provide a completed Appendix X – Temperature Excursion Disposition Form to Amgen (formerly Onyx) when notifying of the event. Please note that a completed Temperature Excursion Disposition Form is required for evaluation and disposition of all temperature excursion by Amgen (formerly Onyx) QA
  3. Download the information from the TempTale Temperature Monitor: follow the TempTale Download instructions that were included with the drug shipment.
     - In the event that the TempTale temperature data cannot be downloaded, sites can return the TempTale to Fisher utilizing the prepaid envelope and return documentation provided with the shipment.
  4. Send completed Temperature Excursion Disposition Form and temperature monitor data via email to GCTE@amgen.com.
  5. The temperature profile will be evaluated by Amgen (formerly Onyx) on the following timelines:
     - Within 24–48 hours for urgent situations (provided all relevant information has been provided by the site).
     - 5 business days for non-urgent situations. Should a formal investigation be required, timelines may increase.
     - Amgen (formerly Onyx) will notify the site in writing of the final disposition of the drug product (if the product can be removed from quarantine for clinical use or must be destroyed).
  6. If additional drug shipment is required, re-order via the instructions provided in Section 8.1.10 of the protocol.

3.3 QUARANTINED VIALS

Amgen (formerly Onyx) will determine if any quarantined vials are acceptable for use or whether they should be rejected.

If product is deemed acceptable by Amgen (formerly Onyx), Amgen (formerly Onyx) will notify site and ECOG-ACRIN in writing of the final disposition of the quarantine materials.

If the quarantined materials are deemed unusable, please destroy the vials per your Institution's procedure, and ensure that this is properly recorded the appropriate accountability logs.

3.4 DAMAGED VIALS

In the event that a shipment is received and any vial breakage is observed, document the incident in the appropriate Investigational Product Accountability Log. For example, if a shipment is received and one (1) vial is damaged in the kit (carton), all 4 vials are recorded as damaged. Once documented, please destroy the entire kit (carton) per the site SOP.

In the event during storage, if a drug vial(s) is cracked or the seal is disfigured, place the damaged vial(s) in Quarantine and document the incident in the appropriate Investigational Product Accountability Log. Once logged, please destroy the vials per the site SOP. STORAGE

3.5 LYOPHILIZED DRUG PRODUCT

Lyophilized Carfilzomib for Injection must be kept in the labeled drug cartons and stored at 2°C–8°C (36°F–46°F) in a refrigerator.

Vials must be kept in cartons in order to protect from light until ready for reconstitution.

- The refrigerator should be monitored daily (at minimum) and temperature records retained for review.
- The refrigerator should also be on a backup generator and alarmed for temperature deviations if available.

Any temperature excursions during storage must be reported to Amgen (formerly Onyx) for evaluation and disposition. Please complete Temperature Excursion Disposition Form and send along with temperature monitoring data via email to GCTE@amgen.com.

3.6 RECONSTITUTED DRUG PRODUCT

Once a drug vial is reconstituted and inspected, the clear solution can be stored in a refrigerator (recommended) controlled from 2°C–8°C (36°F–46°F) or at room temperature from 15°C–30°C (59°F–86°F) until use. Once reconstituted, Carfilzomib for Injection must be used within the stability timeframe (not greater than 24 hours when stored at 2°C–8°C (36°F–46°F) and not greater than 4 hours when stored at 15°C–30°C (59°F–86°F) or else it must be destroyed. DO NOT FREEZE LYOPHILIZED OR RECONSTITUTED DRUG.

If reconstituted Carfilzomib for Injection has been frozen, please discard material and prepare a new solution. Record discarded vials as damaged in the Investigational Product Accountability Log.

For any questions regarding drug storage, please contact Amgen (formerly Onyx) at GCTE@amgen.com. Include your site name, the protocol number (IST-CAR-558), and your detailed question.

4 CALCULATION OF DOSE

- Each dose will consist of Carfilzomib for Injection administered on a mg/m^2 basis, and should be based on the patient's actual calculated body surface area (BSA).
- Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.
- Dose adjustments do not need to be made for weight gains/losses of ≤ 20%.
- The concentration of reconstituted Carfilzomib for Injection is 2 mg/mL.
- The amount of Carfilzomib administered is determined based on the assigned dose level using the algorithm below:
  - X (dose level) mg/m^2 × BSA = mg to be administered
  - mg to be administered divided by 2 = mL to be administered
- Please ensure all calculations of dose are maintained either in the pharmacy records or subject's medical records.

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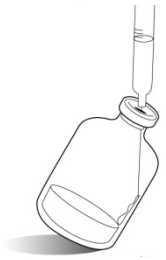
5 PREPARATION FOR ADMINISTRATION

Below are instructions for the preparation and administration of Carfilzomib for Injection. *Avoid use of bacteriostatic diluents or any other diluents other than Sterile Water for Injection USP.*

5.1 INSTRUCTIONS FOR RECONSTITUTION

60 mg Single-Use Glass Vial
Remove vial from refrigerator just prior to use.



1. Aseptically reconstitute each vial by slowly injecting 29 mL Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming. DO NOT USE alternative diluents, such as 0.9% Sodium Chloride Injection, USP, for reconstitution.

2. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides.

3. After reconstitution, Carfilzomib is ready for administration. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product.

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4. When administering in an IV bag, withdraw the calculated dose from the vial and dilute into **50 mL or 100 mL** 5% Dextrose Injection, USP (D5W) IV bag.

Amgen (formerly Onyx) does not have any data to support the use of closed-system drug transfer devices other than a standard syringe needle, therefore use of closed-system drug transfer devices are to be avoided.

5.2 INSPECTION

- The reconstituted drug solution in the vial should be a clear, colorless solution.
- Inspect all vials for the presence of any suspended particles, particulate matter, discoloration, or hazy solution prior to administration.
- If the solution is not clear or particles exist in inspected vials, notify Amgen (formerly Onyx) immediately via GCTE@amgen.com. Include your protocol number and site number (i.e. PX-171-XXX– Site YYY).
    - DO NOT USE THE DRUG. Proceed to reconstitute an alternate vial. Ensure that this is documented on the drug accountability log.
    - Place the vial(s) into a plastic bag labeled as “Quarantined” with the date. Store labeled quarantined drug in a temperature-monitored refrigerator at recommended storage temperature and ensure they are physically separated from the drug that is available for use.
    - Amgen (formerly Onyx) will provide further instructions to the site on next steps with quarantined vials.

5.3 STABILITY OF RECONSTITUTED DRUG

Stability of Reconstituted Carfilzomib for Injection, 60mg/vial

Storage Conditions of Reconstituted Carfilzomib	Stability (in Hours) per Container		
	Vial	Syringe	IV Bag (D5W)
Refrigerated (2°C to 8°C; 36°F to 46°F)	24	24	24
Room Temperature (15°C to 30°C; 59°F to 86°F)	4	4	4

Total time from reconstitution to administration should not exceed 24 hours.

6 ADMINISTRATION

6.1 INFUSION ADMINISTRATION

Materials required:

- Carfilzomib for Injection reconstituted as described in Section 6.1.
- 50 cc IV infusion bag containing 5% Dextrose Injection, USP (D5W). If a 50 cc bag is not available, 100cc bags are acceptable, provided instructions below in Section 7.1.2 are followed for the dilution.

  If 50 cc or 100 cc IV infusion bag containing 5% Dextrose Injection is not available, it is also acceptable to use 5% glucose solution that is equivalent in quality (ie, sterile, for injection, and intended for human use). It must be assured that only 5% glucose solution intended for human use will be used and that it will be used according to the Summary of Product Characteristics.

Instructions:

1. Aseptically withdraw the appropriate amount of the reconstituted Carfilzomib for Injection, calculated as discussed in Section 5.
2. If a 100cc bag is used, prior to transfer of this volume of Carfilzomib for Injection to the 100 cc IV infusion bag containing 5% Dextrose (or 5% glucose) Injection, withdraw equivalent volume of D5W from the IV bag. Carfilzomib should not be diluted or mixed with any other IV solutions except for 5% glucose solution that is equivalent in quality.
3. Dilute the Carfilzomib dose into the IV bag.
4. Administer IV infusion solution to the patient using an appropriate infusion set; deliver the entire volume as a continuous infusion over a period of time specified in protocol under ambient room temperature and lighting conditions.
5. If dextrose and/or glucose are contraindicated for an individual patient, contact your study coordinator.
6. Patients should have a dedicated infusion line for drug administration whenever possible. The line should be flushed with approximately 20 mL normal saline or D5W immediately before and after drug administration.
7. If a dedicated infusion line is not used, the existing infusion line must be flushed with approximately 20 mL normal saline or D5W immediately before and after drug administration.

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6.2 30 MINUTE INFUSION

- Carfilzomib for Injection is administered by injection for a period of up to approximately 30 minutes.
- Patients should have a dedicated infusion line for drug administration whenever possible. The line must be flushed with approximately 20 mL normal saline or D5W immediately before and after drug administration.
- If a dedicated infusion line is not used, the existing infusion line must be flushed with a minimum of 20 mL normal saline or D5W immediately before and after drug administration.

7 IMPORTANT REMINDERS

- Carfilzomib for Injection must be thoroughly reconstituted prior to administration.
- Reconstituted drug must be discarded if not used within the stability timeframe, according to the procedures outlined in Section 9.
- Reconstituted drug exposed to temperatures exceeding 30°C / 86°F must be discarded as outlined in Section 9.
- Do not freeze lyophilized or reconstituted Carfilzomib for Injection.
- Carfilzomib is a potent antineoplastic drug and procedures for the proper handling and disposal of anticancer drugs in accordance with institution and industry guidelines should be followed.

8 DISCARDING USED VIALS

All used vials of Carfilzomib for Injection need to be accounted for on your accountability logs.

9 CLEANUP IN THE EVENT OF VIAL BREAKAGE OR SPILLAGE

In the event of vial breakage or spillage, the drug powder or solution should be cleaned up immediately. Care should be taken to avoid injury from any broken glass. Appropriate personal protective equipment should be worn while handling broken vials of Carfilzomib for Injection. Refer to the Carfilzomib Material Safety Data Sheet (MSDS) as required.

- For powder spills, carefully sweep the contents into a closed container for hazardous waste disposal. Ventilate spill area and wash with an aqueous detergent solution after material pickup is complete.
- For solution spills, cover the liquid with an activated carbon absorbent mat and carefully place absorbed spill mat into a closed container for hazardous waste disposal. Ventilate spill area and wash with an aqueous detergent solution after material pickup is complete.

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10 CONTACTS

ECOG-ACRIN is the lead cooperative group conducting this trial under NCI. Carfilzomib is supplied by Amgen (formerly Onyx) and distributed by Fischer. All questions pertaining to ordering or status of an order should be directed the ECOG-ACRIN Drug Team at 900.drugorder@jimmy.harvard.edu

To report any problems with drug supply, storage and/or safety, please email Amgen (formerly Onyx) at GCTE@amgen.com. Please include your site number and protocol number (IST-CAR-558).

All issues will be resolved as soon as possible.

Randomized Phase III Trial Of Bortezomib, Lenalidomide And Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed By Limited Or Indefinite Lenalidomide Maintenance In Patients With Newly Diagnosed Symptomatic Multiple Myeloma

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Appendix XII

CoMMpass Study: Protocol Synopsis

Study Title	A prospective, longitudinal, observational study in newly diagnosed multiple myeloma (MM) patients to assess the relationship between patient outcomes, treatment regimens and molecular profiles.
Recruitment Period	3-year Target to start Q2 2016 and end Q2 2019
Follow-up Period	Full data will be collected on each patient for 5 years or until death, whichever comes first. All patients alive at the end of the initial 5-year period will be followed for an additional 5 years for survival and incidence of secondary primary malignancies only (10 years in total).
# Patients to be Enrolled	1,500 patients with multiple myeloma; Up to 200 patients with smoldering multiple myeloma to have tissue banking
# Sites	Target 100
Countries	U.S., Canada and Europe
Primary Objective	To identify the molecular profiles and clinical characteristics that define subsets of myeloma patients at initial diagnosis and at relapse of disease.
Secondary Objectives	• To study utility of molecular profiles and clinical characteristics as predictors of clinical benefit (response rate, PFS, and OS) in myeloma. • To evaluate the utility of potential biomarkers from blood and bone marrow samples to assess response and relapse. • To identify potential targets for novel myeloma therapeutics. • To characterize bone disease and response to bone directed therapies in genomically defined subsets of myeloma. • To assess patient-reported health-related quality of life (HRQoL) and resource utilization observed across genomically defined subsets of myeloma. • To measure severe/CTCAE grade 3–4 adverse events and observe across genomically defined subsets of myeloma.
Protocol Design	This is a long-term, prospective, observational study of newly diagnosed myeloma patients that will include serial clinical and molecular profiling assessments.

Key Inclusion Criteria	• Patient is at least 18 years old. • Patient has been diagnosed with symptomatic MM with measurable disease that includes at least one of the following: o Serum M protein ≥ 1g/dl o Urine M protein ≥ 200 mg/24 hrs o Involved free light chain level ≥ 10 mg/dl and an abnormal serum free light chain ratio (<0.26 or >1.65). • The patient is a candidate for systemic therapy that includes an IMiD® and/or proteasome inhibitor as part of the initial regimen. • No more than 30 days from baseline bone marrow evaluation as per this protocol to initiation of first-line therapy. • Patient has read, understood and signed informed consent. Patient is already receiving systemic therapy for MM (a single dose of bisphosphonates and up to 100 mg total dose of dexamethasone or equivalent corticosteroids are permitted prior to registration on study). • Patient had another malignancy within the last 5 years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix). Patient is enrolled in a blinded clinical trial for the first-line treatment of multiple myeloma or is expected to receive an investigational agent in a clinical trial for the first-line treatment of multiple myeloma. Patients may be enrolled in subsequent clinical trials as long as continued access to data and tissue, as per this protocol, is not prohibited.
Endpoints	Response rate (as defined by IMWG criteria), progression-free survival (PFS), overall survival (OS), HRQoL, and biologic profiling and genomic marker studies on bone marrow tumor cells and peripheral blood at baseline pretreatment, and at first and subsequent relapse.
Baseline Data Elements	• Patient demographics (age, gender, ethnicity, race, height, weight) • Family history of cancer • Medical history and comorbidities • Verified diagnosis of active myeloma by clinical, laboratory and bone marrow assessment, ruling out : a) monoclonal gammopathy of undetermined significance (MGUS); b) smoldering (asymptomatic) MM not requiring systemic anti-myeloma treatment; c) systemic amyloidosis in the absence of myeloma; d) POEMS syndrome; and e) solitary plasmacytoma • MM symptoms, signs, and findings • CBC, clinical chemistry, serum and urine immunology labs • Monoclonal protein quantification (including M-protein, FLC ratios, Bence-Jones protein) • Disease staging (ISS) • Cytogenetics – metaphase and FISH • Bone marrow aspirate and peripheral blood samples for molecular and genomic tests • EORTC QLQ- C30 and MY20 to assess HRQoL.

Initial Follow-up Data (Years 1-5)	• Treatment regimen, doses and dates of administration • Other therapy specific to multiple myeloma and supportive multiple myeloma care • Treatment response using IMWG criteria • Survival status • MM symptoms, signs, and findings • CBC, clinical chemistry, serum and urine immunology labs • Monoclonal protein quantification (including M-protein, FLC ratios, Bence-Jones protein) • Bone marrow aspirate and peripheral blood at relapse/progression and suspected CR for molecular and genomic tests • EORTC QLQ-C30 and MY20 • Resource utilization: hospitalization, ER visits • Adverse events (checklist)
Extended Follow-up Data (Years 6-10)	• Survival status • Bone marrow aspirate and peripheral blood at first relapse/progression for those who are in first remission at end of initial 5-year follow-up period • Incidence of secondary primary malignancies
Sample Size and Power	The proposed sample size for analysis in this study is 1000 patients with evaluable clinical and baseline molecular data. In order to achieve this goal it is estimated that 1500 patients will be screened, including 300 patients with inadequate bone marrow samples and 200 patients who are screen failures or have inadequate clinical data. The exploratory nature of this study will allow for expanding enrollment or ending enrollment early depending on the needs of the overall study. If strong trends suggest that a particular cohort should be expanded, the overall study sample size could increase to more than 1500 or subsequent enrollment to other cohorts could be restricted. This study will have excellent power to detect differences of 30% or more in progression-free survival and response rates between two treatments within subgroups of patients of size 100 or greater across a range of risk categories.
Statistical Methods	A statistical analysis plan (SAP) including all statistical methodologies will be developed. In an appendix to the SAP, table shells will detail the analyses to be run and how the results will be presented. Interim statistical analyses will be conducted every 6 months after the first patient is enrolled through the duration of the study. After 12, 18, and 24 months of patient enrollment, we anticipate that approximately 100, 300, and 500 patients, respectively, will have enrolled. At these analyses we may look at distributions of treatment patterns and genetic characteristics. If these analyses suggest that higher proportions of patients in one or more subgroups are required, recruitment will be adjusted accordingly. At the 24-, 30-, and 36-month interim analyses we anticipate a minimum of 100, 300, and 500 patients, respectively, with at least one-year of follow-up. At these analyses we will re-evaluate statistical assumptions and power of the study to detect clinically meaningful results. These re-evaluations will inform any changes in recruitment strategy.

Randomized Phase III Trial Of Bortezomib, Lenalidomide And Dexamethasone (VRd) Versus Carfilzomib, Lenalidomide, Dexamethasone (CRd) Followed By Limited Or Indefinite Lenalidomide Maintenance In Patients With Newly Diagnosed Symptomatic Multiple Myeloma

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Appendix XIII

Ancillary for Tobacco Use Assessment: EAQ16T

Study Co-Chairs: Elyse Park, Ilana Gareen, Lynne Wagner, Jamie Ostroff, Ben Herman

Patients registered to selected ECOG-ACRIN trials are eligible to participate in this ancillary study, once the appropriate amendment incorporating the study is activated.

The Ancillary for Tobacco Use Assessment is a project that seeks to address questions about patient-reported tobacco use and smoking behaviors that may span several studies and/or diseases. The tobacco use ancillary is embedded into parent protocols, with participation in the ancillary informed in the parent consent form and participation determined via providing email address to the sites. The general objectives of the tobacco use ancillary are not specific to any single parent protocol; however, specific objectives may be included in the parent or related parent protocols.

A significant proportion of cancer patients are current smokers at the time of cancer diagnosis,[1–5] and there are known risks associated with continued smoking following cancer diagnosis. These include decreased survival time; increased complications from surgery, radiation, and chemotherapy; and increased risk of second primary tumors.[6–11] As such, the National Comprehensive Cancer Network (NCCN), the American Association of Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) have identified persistent smoking as a modifiable risk factor and recommend cessation counseling for cancer patients who smoke. Although evidence-based guidelines for treating tobacco dependence exist,[12] they have not yet been well-integrated into cancer care settings. Moreover, knowledge regarding the scope and patterns of tobacco use among cancer patients is limited. As a critical step in closing this knowledge gap, the NCI-AACR Cancer Patient Tobacco Use Asssessment Task Force developed the Cancer Patient Tobacco Use [1–4,13,14] Questionnaire (C-TUQ). Through this ancillary, the modified C-TUQ measures will be administered to participants enrolling in selected Phase II and Phase III ECOG ACRIN (EA) therapeutic trials.

The major questions may be summarized:

5. What is the smoking status of cancer patients enrolled on EA clinical trials?
6. Do patients quit smoking or try to quit smoking after receiving a cancer diagnosis?
7. What forms of tobacco use do patients engage in?
8. What assistance do patients use or receive to try to quit?
9. How does tobacco use, other forms of tobacco use, and/or environmental tobacco exposure affect patient's treatment toxicity, patient-reported physical and psychological symptoms, trial adherence, and therapeutic outcomes?

When patients consent to participate, they will be asked to provide a contact email address and that address along with their registration information will be sent directly from the parent trial's registration system to ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO), and the patient will be automatically registered into EASEE-PRO for participation. To activate their account for self-directed web entry of surveys, the system will send an activation message to the contact email address that will explain how to activate their

account for self-directed web entry of surveys. After their account is activated, the patient will be able to complete questionnaires using a secure browser interface from any web enabled computer, tablet, or mobile device.

Measures

The selected Core and Extension C-TUQ items will be assessed. The 4-item Short Form PROMIS® for anxiety and depression, the Lung Cancer Stigma Scale, and six symptom items (general pain, fatigue, nausea, cough, insomnia, shortness of breath) from FACIT (Functional Assessment of Chronic Illness Therapy) together with modifications of these same six questions to address the degree of bother associated with each symptom will be administered as well. Additionally, we will ask participants' perceptions of how smoking improves or worsens each of the six symptom experience. All these items will be compiled into Survey of Tobacco Use (STU) (baseline and follow-up).

Contents and Corresponding Questions in Survey of Tobacco Use (STU)

Dimension	Source of Measures	Baseline STU	Follow-up STU
Basic Tobacco Use Information	C-TUQ	Q1 – Q5	Q1-Q2
Tobacco Use in Relation to Cancer Diagnosis and Treatment	C-TUQ	Q6 – Q7	Q3
Smoking Cessation, Cessation Products, and Assistance Methods	C-TUQ	Q8 – Q13	Q4-Q9
Use of Other Products	C-TUQ	Q14	Q10
Second-Hand Smoke Exposure	C-TUQ	Q15-Q16	Q11-Q12
Psychological Symptoms	PROMIS Lung Cancer Stigma Scale	Q17-Q18	Q13-Q14
Physical Symptoms	FACIT	Q19	Q15
Sociodemographics		Q20-21	

NOTE: In order to minimize ambiguity and assure that patients are oriented to answer appropriately, the specific phrasing of items may vary depending on specific cancer type and treatment.

Tobacco Use. The selected Core and Extension C-TUQ items (from categories of Basic Tobacco Use Information, Tobacco Use in Relation to Cancer Diagnosis and Treatment, Smoking Cessation/Cessation Products/Assistance Methods, Use of Other Products, and Second-Hand Smoke Exposure) will be assessed in the baseline and follow-up Survey of Tobacco Use.

Oncology Provider Assistance. C-TUQ Question 13 assesses "cancer doctors" Advise. We will add 4 As to assess participants' reported 5As (Ask (Q12a), Advise (Q12b), Assess (Q12c), Assist (Q12d-Q12f), and Arrange follow-up (Q12g), as in Baseline STU).[80]

Psychological Symptom Assessment. Anxiety & Depression: *(The Patient Reported Outcomes Measurement Information System (PROMIS®)).* We will administer the 4-item Short Form PROMIS® for anxiety and depression (Q17 in Baseline STU). Stigma: The Lung Cancer Stigma scale measures the extent to which shame is internalized (Q18 in Baseline STU).[81]

Physical Symptom Assessment *Physical Symptom Assessment (Functional Assessment of Chronic Illness Therapy (FACIT)). FACIT, a measurement system with a collection of quality-of-*

life questionnaires, expands the more familiar FACT (Functional Assessment of Cancer Therapy) questionnaires into other chronic illness and conditions. FACIT consists of many individual questions to assess various symptoms from the patient perspective. We will use 6 FACIT items, selected based on the therapeutic regimens, expected toxicity, and malignancy type of the parent trials. In addition, we have created modifications of these same six questions to address the degree of bother associated with each symptom" The symptoms of general pain, fatigue, nausea, cough, sleep difficulty, and shortness of breath will be assessed, first using the standard and validated FACT item, and then asking the degree of "bother" imposed by each symptom, on the same 5-point scale. These clusters of symptoms were specifically chosen based on potential interactions between tobacco use and longitudinal symptoms.

Sociodemographic Variables. Sociodemographic variables, including age, sex, zip code, and race/ethnicity are collected for all NCTN trial participants at registration. At baseline, participants will provide information on marital status (Q20 in Baseline STU) and education level (Q21 in Baseline STU) as part of the tobacco supplemental assessment.

Cancer Treatment Variables. Clinical variables including date of diagnosis, malignancy type (smoking related vs. non-smoking related, cancer stage), and treatment details (i.e. types and dates of surgery, chemotherapy, and/or radiation received), along with disease status and survival, will be captured in Medidata Rave via the parent protocol and will be available for analysis of the ancillary. Provider-assessed adverse events will also be captured via the parent protocol in Medidata Rave, using case report forms commonly used across the NCTN and using standard data elements.

Assessments

All items in Survey of Tobacco Use will be administered using the EASEE-PRO system. The advantage of our virtual electronic data capture system is that our proposed assessments will not be limited to, or dependent upon, patient trial visits. Confidential and potentially stigmatizing information can be provided without requiring direct contact with the care team.

Timing of Assessments

Given the critical questions that remain[13] about the timing of conducting tobacco use assessments, we have carefully chosen to collect tobacco assessment data at trial enrollment, 3 and 6 month follow-up. For tobacco treatment trials, 6 month follow-up is the recommended primary outcome time point. By 6 month follow-up, most cancer treatment-related quitting activity[62], cancer treatment initiation of therapy, and FDA-approved smoking cessation medication regimens will be completed. Adverse events during treatment will have been observed.

Statistical Considerations and Analysis Plans

The analysis plans described below are planned for a combined analysis of the data from the selected ECOG-ACRIN studies. Consistency in the effects over the studies would be examined in this analysis.

10. CHANGES IN SMOKING STATUS AND EXPOSURE. At baseline, combustible tobacco use (1a) will be characterized by smoking status (never smoker, former smoker, and current smoker based on Baseline STU Qs 1 and 5), other forms of tobacco use (1b) will be a composite variable determined by non-cigarette items (based on Baseline STU Q7 and Q14), and environmental tobacco smoke (ETS) level (1c) will be determined by current household and work exposure (Baseline STU Qs 15-16). At follow-up, combustible tobacco use (1a) will be examined by smoking status (Follow-up STU Qs 1 and 2), other forms of tobacco use (1b) will be determined by Follow-up STU Q10, and ETS level (1c) will be

determined by 30 day household and work exposure (Follow-up STU Qs 11-12). We will examine tobacco use at baseline, 3 and 6 month follow-up, and change in status (abstinence in combustible tobacco, abstinence of other forms of tobacco use, and change in exposure to smoke-free home and work) using summary statistics (frequency and proportion). We will explore the effects of sociodemographic and cancer treatment factors on smoking status using logistic regression (comparing smokers and non-smokers). We will also evaluate factors associated with changes in smoking status.

11. TREATMENT TOXICITY. The selected trials capture information about adverse events during treatment using NCI's Common Terminology Criteria for Adverse Events, Version 4. Toxicities are measured at each treatment visit and graded according to severity, with grade 1 corresponding to mild toxicity and grade 5 signifying a lethal adverse event. We will determine each patient's worst degree toxicity across all event types and treatment visits and will compare the distribution of worst degree grades between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure using exact tests. We will also examine the distribution of worst degree grades between users with different form of tobacco use. In addition, we will explore the effects of tobacco use on dose modifications (yes vs. no) using logistic regression, with each patient's dose modification status determined across all treatment visits.
12. SYMPTOM BURDEN. Tobacco variables will be conceptualized as described in the section of CHANGES IN SMOKING STATUS AND EXPOSURE. Tobacco use status (as measured at baseline, 3 and 6 month follow-up) will be compared to physical and psychological symptom burden (as measured at each corresponding time points). At 3 and 6 month follow-up, we will also examine the association between tobacco use changes and changes in symptom burden. We will explore the effects of sociodemographic and cancer treatment factors on symptom burden using repeated measures mixed effects models. As an example of statistical power, we consider the PROMIS SF-4 depression measure. We assume that 1500 patients will be enrolled across the 8 parent studies over 13 months, and that 20% are smokers. We assume that 85% of patients will have assessments at 6 months. Given groups of these sizes (26 quitters and 230 still-smokers) and standard deviation of 4.08 for the PROMIS SF-4 depression scale, there will be 83% power to detect a difference in change scores of 2.5 between groups using a two-sample t-test with Type I error of 5%. The minimally important difference for this instrument is 2.2.[79]
13. CESSATION PATTERNS AND TREATMENT. At baseline we will explore pre-treatment combustible tobacco use patterns (STU Q6a and Q6b), quitting behaviors (STU Q13), behavioral program utilization (STU Q11) and oncology provider support (5As, STU Q12), and smoking cessation medication use (STU Q10). At follow-up we will explore post-treatment combustible tobacco use patterns (STU Q3a-Q3e), quitting behaviors (STU Q9), behavioral program utilization (STU, Q7) and oncology provider support (5As, STU Q8), and smoking cessation medication use (STU Q6). We will explore the effects of sociodemographic and cancer treatment factors on these variables. We will examine associations of quitting behaviors and behavioral and medication utilization with tobacco use status (as outlined in the section of CHANGES IN SMOKING STATUS AND EXPOSURE) at baseline and on respective 3 and 6 month tobacco outcomes. These analyses will be descriptive in nature. Summary statistics (frequency, proportions, and 95% confidence intervals) will be used.
14. TRIAL OUTCOMES. We will compare treatment duration between smokers and non-smokers and between patients with environmental tobacco exposure and those without exposure. Cumulative incidence/competing risk methods will be used to estimate time to treatment discontinuation for adverse events, disease progression, completion per protocol,

or other causes. Gray's test will be used to test for differences in the cumulative incidence distributions.[78] Differences in the distribution of reasons for discontinuation of treatment will be examined using exact tests. Relative dose intensity is defined as the ratio of actually delivered dose intensity to the planned dose intensity. The effects of tobacco use and exposure on relative dose intensity (≥ 90% vs. < 90%) will be explored using logistic regression. Differences in the primary endpoint and important secondary endpoints will be examined using log rank test and exact test (as appropriate).

Data collected in the tobacco use project will support a range of analyses. Precise estimates of power will depend on the prevalence of smoking at baseline among study participants, the proportion whose smoking status changes, and the duration and adequacy of follow-up.

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