BMT CTN Protocol 07LT Statistical Analysis Plan (SAP)

BMT CTN 07LT: Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702

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Prepared by: _____ Date: 15 MAY 2019
Protocol Statistician (DDMMMYYYY)

Reviewed by: _____ Date: 16 MAY 2019
DCC Statistician Leadership (DDMMMYYYY)

Approved by: _____ Date: 17 MAY 2019
Protocol Chair/Protocol Officer (DDMMMYYYY)

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Protocol

BMT CTN #07LT is titled “Continued, Long-Term Follow-Up and Lenalidomide Maintenance Therapy for Patients Who Have Enrolled on BMT CTN 0702.”

1. General Review of Study Design and Process

1.1 Study Objectives

BMT CTN protocol 07LT is a follow-up study to BMT CTN 0702, which was a Phase 3, multi-center trial designed to compare progression-free survival and additional outcomes between patients randomized to one of three treatment arms:

- Autologous transplant followed by a second autologous transplant then maintenance therapy (Auto/Auto)
- Autologous transplant followed by consolidation therapy with lenalidomide (Revlimid), bortezomib (Velcade) and dexamethasone (RVD) then followed by maintenance therapy (Auto/RVD)
- A single autologous transplant followed by maintenance therapy (Auto/Maint)

1.1.1 Primary Objective

The primary objective of the study is to compare progression-free survival (PFS) as a time to event analysis between the three randomized treatment arms from the BMT CTN 0702 protocol as a pairwise comparison. The analysis will be conducted once all alive patients have been enrolled for 5 years post randomization on the BMT CNT 0702 protocol.

1.1.2 Secondary Objectives

The secondary objectives of the study are:

- Cumulative incidence of second primary malignancies (SPM)
- Probability of overall survival (OS)
- Probability of event-free survival (EFS)
- Health Quality of Life (QOL)

1.2 Study Design and Procedures

1.2.1 Primary Hypothesis and Primary Endpoint

The primary hypothesis of this study and the original BMT CTN 0702 study is that the use of novel anti-myeloma agents will improve long-term PFS after high-dose melphalan followed by autologous hematopoietic cell transplantation (HCT) as compared to a second autologous transplantation.

To correspond with the primary objective to compare progression-free survival (PFS) as a time to event analysis between the three randomized treatment arms from the BMT CTN 0702

protocol as a pairwise comparison, the main null and alternative hypotheses of the study are that the different treatment arms will have different rates of long-term PFS:

$$H_{01}: PFS_{Auto/Auto} = PFS_{Auto/RVD}$$

$$H_{A1}: PFS_{Auto/Auto} \neq PFS_{Auto/RVD}$$

$$H_{01}: PFS_{Auto/Auto} = PFS_{Auto/Maint}$$

$$H_{A1}: PFS_{Auto/Auto} \neq PFS_{Auto/Maint}$$

$$H_{01}: PFS_{Auto/RVD} = PFS_{Auto/\ Maint}$$

$$H_{A1}: PFS_{Auto/RVD} \neq PFS_{Auto/\ Maint}$$

These three hypotheses will each be tested with a two-sided stratified log rank test at the $\alpha=0.05 / 3$ level using a Bonferroni correction to control the overall type I error rate.

The primary endpoint is PFS. Patients are considered a failure of the primary endpoint if they die or suffer from disease progression. The time to this event is the time from randomization on the BMT CTN 0702 protocol until progression, death, or initiation of non-protocol anti-myeloma therapy, or until last myeloma follow-up through December 2018 if there is no event.

1.2.2 Accrual Plan and Randomization

Participants were eligible to accrue on to BMT CTN 07LT as soon as they finished the earlier of 3 years of maintenance therapy on BMT CTN 0702 or four years of follow up on BMT CTN 0702. The protocol was approved after some participants had already finished 3 years of maintenance on BMT CTN 0702 so they were eligible to enroll when the protocol was activated, and there may have been a period when the participant was on commercially-available lenalidomide or other treatment. The protocol was activated in March 2015, and accrual was targeted through the beginning of 2018 to allow a window of time after the last person enrolled on BMT CTN 0702 would be eligible for BMT CTN 07LT.

Randomization occurred on the parent BMT CTN 0702 trial, which had a 1:1:1 randomization ratio with permuted blocks. Randomization on the parent trial was also stratified by patient risk and center. There was no additional randomization on BMT CTN 07LT.

1.2.3 Duration of Follow-up

Participants will be followed for until death, progression, withdrawal from study, or the end of 2018. The randomization date on the BMT CTN 0702 trial will be the start time for most of the analyses, except for the secondary analysis of PFS which starts at initiation of maintenance therapy and includes discontinuation of lenalidomide as a time-varying covariate.

1.3 Inclusion and Exclusion Criteria

As a follow-on study, the 07LT protocol is open for enrollment of participants randomized on 0702 who have completed 3 years of maintenance therapy on 0702 or 4 years of follow-up on 0702, have not died or had clinical progression, and have signed the 07LT informed consent form.

Participants who have completed 3 years of maintenance therapy on BMT CTN 0702 are eligible for continued maintenance therapy on 07LT if they are willing and able to comply with the requirements of the Revlimid REMS® program, and have signed an informed consent. Participants who are pregnant, breastfeeding, unwilling to take DVT prophylaxis, had thromboembolic events while on full anticoagulation during lenalidomide use, or had secondary primary malignancies after initiation of lenalidomide on BMT CTN 0702 are ineligible for initiating BMT CTN 07LT maintenance therapy.

1.4 Treatment Description

Lenalidomide will be administered initially at the patient's last documented dose prior to discontinuation of BMT CTN 0702 lenalidomide maintenance therapy. Cycle duration is 28 days. Patients will continue lenalidomide until disease progression, or discontinuation due to toxicity, death, or withdrawal from the study. Patients who discontinue lenalidomide due to any reason other than death or withdrawal of consent will continue to be followed.

In the presence of lenalidomide-related non-hematologic toxicities, the study drug will be withheld until the toxicity resolves, then restarted at a reduced dose as described in the protocol. Dose modifications for hematologic toxicities are described in the protocol. If the patient is on DVT/PE prophylaxis or treatment, discontinuation or modifications of anticoagulation should be considered by the treating physician.

If a dose reduction has occurred and ANC ≥ 1000/μL and platelet count is ≥ 75,000/μL, the study drug dose may be re-escalated as shown in the protocol, one step per cycle to a maximum of 15 mg daily.

1.5 Response Variables and Data Collection Time Points

Participants are evaluated for the primary endpoint of progression-free survival (death, disease progression, initiation of non-protocol myeloma therapy) and for the following secondary endpoints:

- Overall survival
- Event-free survival (no progression, death, or SPM)
- Incidence of SPM
- Unexpected grades 3-5 adverse events
- Health quality of life

Patients have visits every six months until death, progression, withdrawal of consent, or the end of the study.

Participants who receive long-term lenalidomide maintenance therapy are required to report unexpected grades 3-5 adverse events until the patient progresses or until 28 days from their last dose of lenalidomide. These require expedited reporting within 24 hours – 3 business days of the site's knowledge of the event, depending on the type of event. The protocol specifies additional rules for reporting requirements of AEs after an SPM depending on the treatment received for the SPM, and for reporting serious expected adverse events and selected AEs of interest.

Participants who do not receive lenalidomide maintenance or have permanently discontinued lenalidomide maintenance not required to report adverse events except for SPMs.

For all participants on 07LT, SPMs must be reported within three business days of knowledge of the event and deaths must be reported within 24 hours of knowledge of the participant's death. Non-melanoma skin cancers are not required to be reported.

Health quality of life surveys are completed at visits corresponding to 5, 6, and 7 years from original randomization on 0702.

2. General Statistical Considerations

Unless stated otherwise:

- For continuous outcomes, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum.
- For categorical outcomes, frequencies and percentages will be displayed for categorical data.
- All statistical comparisons made using 2-sided pairwise tests will be compared to an $\alpha=0.05/3$ significance level.

2.1 Sample Size and Power Calculations

The projected sample size for this study was determined from the available sample size of the parent study, BMT CTN 0702, and the rate of progression-free survival on 0702. Seven hundred and fifty-eight participants enrolled on 0702, and it was anticipated that the sample size on 07LT could range from 417 to 569 for 3-year PFS ranging from 55% to 75%.

2.2 Handling Missing Data

All participants who were randomized on the parent protocol BMT CTN 0702 will be included in the analysis for BMT CTN 07LT. Data for patients not enrolled on the long-term follow-up protocol will be included with two parts combined: 1) 0702 data until their end of participation on the BMT CTN 0702 protocol; 2) follow up data provided through the Center for International Blood and Marrow Transplant Research (CIBMTR).

For time-to-event variables, participants who have not had an event or competing risk event will be censored at the time data for the endpoint is no longer available. For Quality of Life analyses, participants will be excluded at a particular time point if they do not complete the surveys within a +/- 90-day window for the particular time point in the analysis.

The time of progression that was adjudicated on BMT CTN 0702 by the 0702 Endpoint Review Committee (ERC) will be used for participants who progressed on BMT CTN 0702. There is no adjudication of progression on BMT CTN 07LT, so progression will be determined by site-reported responses.

For the primary endpoint of PFS and the secondary endpoints of EFS, overall survival and cumulative incidence of SPM, and for tabulation of cause of death, data from the BMT CTN 0702, BMT CTN 07LT, and from the CIBMTR will be used.

2.3 Multiple Comparisons

All tests for treatment group differences that compare 2 groups at a time will be compared at the 0.05/3 significance level to adjust for the pairwise testing. Kaplan Meier estimates, cumulative incidence estimates, and hazard ratios for treatment groups will be presented with 98.3% confidence limits.

2.4 Interim Analyses and Stopping Guidelines

There will be no interim analyses on BMT CTN 07LT and no adjustments for prior testing of the endpoints on the 0702 study.

There are no official stopping guidelines for BMT CTN 07LT. The BMT CTN DSMB monitors the safety and efficacy data on an approximate 6-month basis, and makes recommendations to the NHLBI regarding release of data to investigators and the general public.

2.5 Timing of Analysis

Follow-up for the BMT CNT 07LT protocol continues until the end of 2018; this is approximately when all living patients have been enrolled for 5-years post randomization on the BMT CTN 0702 protocol. The BMT CTN 07LT analysis will begin upon the completion of all data entry and cleaning including retrieval of CIBMTR data after the follow-up is finished.

2.6 Software

All analyses will be conducted using SAS version 9.4 or higher, or R version 3.3.2 or higher.

2.7 Analysis Populations

The following analysis populations will be used:

0702-enrolled	Will include all patients randomized on protocol BMT CTN 0702. Data from the BMT CTN 0702 protocol, BMT CTN 07LT protocol, and CIBMTR will be used
07LT-enrolled	Will include patients enrolled on protocol BMT CTN 07LT only. Data will be limited to data provided during 07LT follow-up. This population will be used for tabulation of unexpected grades 3-5 events, analysis of health quality of life, and study protocol deviations.

Some of the analyses will use a subset of these populations. These are described in the section for each endpoint.

2.7.1 Primary Analysis Population

0702-enrolled population

The primary analysis population, 0702-enrolled population, will include all participants randomized on the parent trial, BMT CTN 0702, in the arm to which they were assigned (intent-to-treat), regardless of treatment received. This population will be used for the analysis of the primary endpoint, PFS, as well as for the secondary endpoints of overall survival, EFS, and SPM. This population will be used to tabulate reasons for permanent withdrawal from lenlidomide maintenance therapy.

07LT-enrolled population

The 07LT-enrolled population will include all participants enrolled on BMT CTN 07LT. This population will be used for the analysis of adverse events and of health quality of life, and for descriptions of study accrual, and study protocol deviations.

No adjustments for post-randomization review of eligibility.

For analyses with the 0702-enrolled population, all participants for the BMT CTN 0702 trial will be included in the BMT CTN 07LT analysis, even those adjudicated to be ineligible by the BMT CTN 0702 Endpoint Review Committee or determined to be ineligible after data review post enrollment. Similarly, analyses limited to the 07LT population will include all participants enrolled on BMT CTN 07LT, including any participants determined post enrollment to be ineligible for BMT CTN 07LT.

2.7.2 Safety Analysis and Analysis Population

The 07LT-enrolled population is comprised of two groups of participants – those who are taking long-term lenalidomide maintenance therapy, and those who have never started maintenance therapy. Safety data is collected differently for participants taking lenalidomide and or patients who never stated lenalidomide on 07LT or discontinued it.

For participants enrolled on BMT CTN 07LT who are taking long-term lenalidomide maintenance therapy, unexpected, grades 3-5 adverse events will be reported through the expedited AE reporting system in AdvantageEDC using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Unexpected, grade 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event. Selected expected serious AEs (protocol Appendix F - Table F-1) require expedited reporting. Additionally, selected AEs of interest (protocol Appendix F - Table F-2) will require expedited reporting, if they fulfill serious criteria according to the Code of Federal Regulations Title 21 (21 CFR 312.32) and occur after the administration of lenalidomide and up to 30 days after the permanent discontinuation of lenalidomide. See protocol Appendix F for additional details on expedited reporting.

For participants enrolled on BMT CTN 07LT follow-up only, or for BMT CTN 07LT participants who have permanently discontinued lenalidomide maintenance for more than 28-30 days, or for participants who have met the protocol defined definition of progression, reporting of

unexpected grades 3-5 adverse events, selected serious AEs, or selected AEs of interest will not require reporting with the exception of second primary malignancies.

Deaths are required to be reported for all patients enrolled on 07LT within 24 hours of the site's knowledge of the patient's death.

Unexpected grades 3-5 adverse events will be tabulated and compared across treatment arms for the BMT CTN 07LT population. Summaries by type and severity of adverse events will be provided. Safety data will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) Coding Version 20.0 or above.

Secondary primary malignancies (SPMs) in the BMT CTN 0702 population will be analyzed as a secondary outcome using cumulative incidence curves and Gray's test for treatment group comparisons. SPMs will also be described by treatment group and histologic type.

Primary causes of deaths will be tabulated, and survival will be analyzed as a secondary outcome using Kaplan Meier curves and stratified log rank tests.

2.8 General Analysis Guidelines

There are no planned sub-group analyses or sensitivity analyses.

Any changes to the planned analyses or any ad hoc analyses will be documented and clarified in each analysis report (through the time of the report) and may be documented in updated versions of the SAP. Ad hoc analyses will be included as supplemental exhibits and noted to be analyses that are not part of the pre-planned analyses.

There are no pre-defined ancillary studies for the BMT CTN 07LT protocol. Optional research samples for future analysis are being collected for those enrolled in 07LT. Any analyses with these samples will be described separately and will be conducted at time points not affecting the analyses described in this SAP.

2.8.1 Changes to the planned analyses

Clarifications from the BMT CTN 07LT protocol

The protocol specified that for the primary endpoint of PFS, deaths will be counted as failures no matter when they occur. This is clarified to note that deaths that occur prior to the end of 2018 will be counted as failures and deaths that occur after progression will use time to progression rather than time to death for the primary analysis. Deaths through the end of follow-up in December 2018 will be counted, but deaths that occur between the end of BMT CTN 07LT in December 2018 and the database closure for the analysis will not be counted.

The protocol specified that for some of the secondary outcomes, the analysis would be completed once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol. This is clarified to note that the secondary outcomes will be analyzed at the same time as the primary analysis -- once all alive patients have been followed for 5-years post randomization on the BMT CTN 0702 protocol or the end of 2018.

The protocol specified that a Cox model would be used to analyze PFS data, but did not require that treatment group and risk strata be included in the model. These factors will be included in the models.

Supplemental analyses of EFS and OS have been added to incorporate a Cox model analysis adjusting for baseline risk factors for the 0702-enrolled population and to incorporate a Cox model investigating EFS, baseline risk factors, and discontinuation of lenalidomide among the population that initiated maintenance therapy. Additional cause-specific analyses will show the Cox model results for each component of EFS, with censoring at the time of the other components.

Additional supplemental landmark analyses of PFS, OS, and EFS have been added to explore these outcomes between those on long term lenalidomide and those not on long term lenalidomide.

3. Participant Characteristics and Compliance

3.1 Demographics and Baseline Characteristics

Descriptive statistics for demographics and baseline characteristics will be presented by randomized treatment group for participants enrolled on BMT CTN 0702 and separately for participants enrolled on BMT CTN 07LT.

Testing of treatment group differences among all participants enrolled on BMT CTN 0702 will be conducted to determine which characteristics to include the in the Cox regression model for PFS. Factors with a significance level <0.1 based on a chi-square test of differences using all three treatment arms (not pairwise tested) will be included in the Cox regression model. Factors to be summarized include, but are not limited to, those listed below. Factors to be considered for inclusion in the Cox regression model and tested for treatment group differences are limited to those marked in the second column below.

For the factor of ERC-adjudicated disease response at study entry, 2 categorizations will be considered: CR or greater vs less than CR, and VGPR or greater vs less than VGPR.

Factors for descriptive summary statistics	**Factors to consider for inclusion in Cox model**
Baseline data from 0702 randomization	
Baseline disease risk strata (as randomized)	Will be included even if no difference among treatment groups
Baseline disease risk strata (updated post randomization)	Will not be included
Gender	Will be considered for inclusion
Ethnicity	Will be considered for inclusion
Race	Will be considered for inclusion
Karnofsky performance score	Will be considered for inclusion
ERC-adjudicated disease response at BMT CTN 0702 study entry	Will be considered for inclusion
Age at 0702 enrollment	Will be considered for inclusion
Pre-0702 initial therapy for myeloma (doublets/triplets/other)	Will be considered for inclusion

Factors for descriptive summary statistics	Factors to consider for inclusion in Cox model
Baseline data for those enrolled on 07LT	
Baseline disease risk strata (as randomized)	Will not be included
Gender	Will not be included
Ethnicity	Will not be included
Race	Will not be included
Karnofsky performance score	Will not be included
ERC-adjudicated disease response at BMT CTN 0702 study entry	Will not be included
Age at 07LT enrollment	Will not be included

3.2 Participant Compliance

A table listing significant protocol deviations/violations will be provided separately for those who continued lenalidomide maintenance therapy and those who did not, by treatment group for participants enrolled on 07LT. Reasons for permanent withdrawal of lenalidomide maintenance therapy will be tabulated.

A consort diagram will be provided to illustrate BMT CTN 07LT accrual, disposition, and follow up.

4. Analysis Plan

4.1 Analysis of the Primary Endpoint

The primary analysis of PFS will include all randomized subjects from the BMT CTN 0702 protocol, classified according to their randomized treatment allocation, irrespective of treatment received [intent-to-treat]. The time to this event is the time from randomization on the BMT CTN 0702 protocol to progression, initiation of non-protocol anti-myeloma therapy (this includes lenalidomide if the dose is above 15mg), or death from any cause reported on BMT CTN 0702, BMT CTN 07LT, or to the CIBMTR. Patients will be censored at loss to follow-up or end of 2018, whichever comes first. For those lost to follow-up, if loss occurred during 0702, censoring will occur at last myeloma evaluation before loss to follow-up. For those lost to follow-up on BMT CTN 07LT, censoring will occur at the last contact date reported on the study status follow-up form. For those who completed BMT CTN 0702 but did not enroll on 07LT, censoring will occur at the last evaluation of progression provided by the CIBMTR.

The treatment arms will be compared with a two-sided log-rank test stratified on risk status. Tests will be performed pair-wise at the 0.05/3 level to maintain type I error at 0.05 for this endpoint in this analysis. A Kaplan-Meier plot of PFS and 5-year estimates of PFS will be provided by treatment group.

A secondary analysis of PFS will be conducted using Cox regression, with treatment arm and risk strata as covariates, and adjusting for demographic and baseline characteristics which are statistically different between treatment arms ($p<0.1$) for covariates specified in section 3.1. Start time will be randomization on BMT CTN 0702.

In another secondary analysis of PFS, discontinuation of lenalidomide maintenance will be considered as a time-varying covariate in a separate Cox regression model for those who initiated lenalidomide; in this model, the outcome will be the time to progression or death from initiation of lenalidomide. Initiation of maintenance lenalidomide on BMT CTN 0702 will be the start time for this analysis. CIBMTR data will be used to determine whether participants who discontinued study lenalidomide also discontinued commercial lenalidomide. The limited interpretation will be noted for this analysis, since it will include non-randomized comparisons and there may be bias in who enrolled in BMT CTN 07LT.

4.2 Analysis of the Secondary Endpoints

Overall Survival

The event is death from any cause. Overall survival (OS) time will be calculated as the time from randomization on the BMT CTN 0702 protocol to death, loss to follow-up or the end of the study, whichever comes first. CIBMTR data will be used to supplement BMT CTN 0702/07LT data. Patients alive at the time of last observation or lost to follow-up will be censored at the date of last contact either for CIBMTR-reported data or 0702/07LT-reported data. The Kaplan-Meier estimate of survival will be estimated at 5 years post randomization on the BMT CTN 0702 protocol along with corresponding 98.3% confidence intervals. Overall survival will be compared between treatment arms using a stratified two-sided log-rank test in pairwise comparisons of treatment groups. The analysis population will be the 0702-enrolled population, with data from CIBMTR included.

Event-Free Survival

Event-free survival (EFS) time will be calculated as the time from randomization on the BMT CTN 0702 protocol to death, progression, second primary malignancy, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation or lost to follow-up will be censored at the date of last contact. The analysis population will be the 0702-enrolled population with follow up data from the CIBMTR included as needed. The Kaplan-Meier estimate of EFS will be estimated at 5 years post randomization on the BMT CTN 0702 protocol along with corresponding 98.3% confidence intervals. Event-free survival will be compared between treatment arms using a stratified, two-sided log-rank test in pairwise comparisons of treatment groups.

Second Primary Malignancies

The event is the development of the first SPM post randomization on BMT CTN 0702, excluding non-melanoma skin cancers. Death without SPMs will be considered a competing risk for this event. The analysis population is the 0702-enrolled population, and CIBMTR data will be used to supplement BMT CTN 0702/07LT data. Start time is randomization on BMT CTN 0702. Cumulative incidence function will be used to calculate this endpoint and time of randomization on the BMT CTN 0702 protocol will be the starting point for the analysis. Estimates at 5 years will be described along with 98.3% confidence intervals. The cumulative incidence of SPMs will be compared between treatment arms using stratified two-sided Gray's test in pairwise comparisons of treatment groups. SPMs will also be described by histologic type. It will be

noted that reporting of SPM is not required after progression, and the CIBMTR data will be used to supplement 07LT data.

Unexpected Grades 3-5 Adverse Events

Unexpected grades 3-5 adverse events occurring post enrollment on BMT CTN 07LT will be tabulated and compared across treatment arms and lenalidomide status for participants enrolled in BMT CTN 07LT. CIMBTR data will not be used. AEs will be described using the Medical Dictionary for Regulatory Activities (MedDRA) and classified according to the system organ class and preferred term. Summaries by type and severity by treatment arm will be provided, and tabulations will be separated into tables for those who initiated maintenance on BMT CTN 07LT and those who did not.

Health Quality of Life

Health quality of life (HQL) will be compared between all treatment groups utilizing the FACT-BMT self-report, transplant-specific questionnaire and the generic quality of life tool, the SF-36. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial. Participants were not required to complete the HQL questionnaires after progression; therefore, only HQL completed prior to progression will be summarized. The limitations in interpretation of this analysis will be noted with the presentation of the results. HQL at each time point from BMT 0702 baseline through 5 years post randomization on BMT CTN 0702 will be summarized using simple descriptive statistics (median, mean, SD or SE). No formal statistical analyses will be conducted. As 5 year data is only available for those participants on 07LT, this analysis will focus solely on 07LT participants.

4.3 Supplemental Analyses

A supplemental analysis of OS will be included in which OS is analyzed using Cox regression, with treatment arm and risk strata as covariates, and will include demographic and baseline characteristics which are statistically different between treatment arms ($p<0.1$) for covariates specified in section 3.1. Start time will be randomization on BMT CTN 0702 and all participants randomized on 0702 will be included.

Supplemental analysis of EFS will be included.

- The first will analyze EFS using Cox regression, with treatment arm and risk strata as covariates, and will include demographic and baseline characteristics which are statistically different between treatment arms ($p<0.1$) for covariates specified in section 3.1. Start time will be randomization on BMT CTN 0702 and all participants randomized on 0702 will be included.
- The second will explore cause-specific hazards for each component of EFS. Cox models with treatment arm, risk strata, and demographic/baseline covariates as specified above will be used. Start time will be randomization on BMT CTN 0702 and all participants randomized on 0702 will be included. For each component, the other components of EFS will be considered censoring events.
- The third will analyze EFS using Cox regression in the subset of 0702 participants who initiated lenalidomide maintenance therapy. In this model, the outcome will be the time to

progression or death and the start time will be initiation of maintenance lenalidomide. Discontinuation of lenalidomide maintenance will be considered as a time-varying covariate. Treatment group, strata, and baseline covariates used in the first EFS regression analysis will also be included. The limited interpretation will be noted for this analysis, since it will include non-randomized comparisons and there may be bias in who enrolled in BMT CTN 07LT and continued on lenalidomide maintenance.

Supplemental landmark analyses will be included. The endpoints of PFS, OS, and EFS will be explored in the 0702-enrolled population who is alive four years post randomization (OS) or who is alive and progression- or event-free (for PFS and EFS respectively). A log rank test will compare each outcome for the groups determined by those who were taking lenalidomide at four years post randomization compared to those who were not. Kaplan meier estimates of each outcome at 5 years post randomization will be provided for each lenalidomide status group.

5. Template of Proposed Table/Figure/Listing (TFL) Shells

The templates for the Tables, Figures, and Listings are provided in the Appendix of this SAP. These templates are for illustration purposes only, and may not be the final layout or wording chosen for publications or presentations. Actual format of the tables and figures may differ and will be subject to change in the final analysis report and/or publication. Editorial changes in presentation or content will not necessarily be described in the changes to planned analyses section of the report or SAP updates.

6. References

Cox D. Regression models and lifetables (with discussion). Journal of the Royal Statistical Society 1972;Series B:187-220.

Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695-706.

Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals of Statistics 1988, 16: 1141-1154.

Appendix

Exhibit 07LT-1: Participant Disposition and Follow-Up

The consort diagram will start with the 0702-enrolled population and at a minimum will provide information about the number enrolled, transplanted with initial autologous transplant, and started lenalidomide maintenance therapy in each arm. Adiagram will be provided showing the number of participants enrolled on BMT CTN 0702/07LT, treatment assignment, and initiation of long-term lenalidomide maintenance therapy on BMT CTN 0702/07LT. A table will be provided with descriptive statistics on length of follow-up by assigned treatment arm.

Reasons for not enrolling on BMT CTN 07LT will be tabulated for participants on BMT CTN 0702.

Exhibit 07LT-2A: Participant Demographics and Baseline Characteristics

Baseline characteristics and demographics will be described for 0702-enrolled participants by frequencies and percentages for categorical covariates, and minimum, maximum, median, mean, and standard error for continuous covariates. The following covariates from 0702 study entry may be included:

- Treatment group assignment
- Baseline risk status (at time of randomization and updated to include any changes entered for baseline risk status)
- Gender
- Ethnicity
- Race
- Patient age at time of 0702 enrollment
- Endpoint Review Committee-adjudicated disease status at BMT CTN 0702 study entry
- Karnofsky performance score at time of 0702 enrollment

Other baseline covariates will be summarized at the request of the investigators. P-values for treatment group comparisons will not be provided.

	Treatment Arm			
	Auto/Auto (N=247) N (%)	**Auto/RVD (N=254) N (%)**	**Auto/Maintenance (N=257) N (%)**	**Total (N=758) N (%)**
Gender				
Female				
Male				

	Treatment Arm			
	Auto/Auto (N=247) N (%)	**Auto/RVD (N=254) N (%)**	**Auto/Maintenance (N=257) N (%)**	**Total (N=758) N (%)**
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Unknown				
Not Answered				
Race				
American Indian/Alaska Native				
Asian				
Hawaiian/Pacific Islander				
Black or African American				
White				
More than One Race				
Other, Specify				
Unknown				
Not Answered				
Karnofsky Performance Score				
90 - 100				
70 - 80				
Less than 70				
Baseline disease risk strata (at randomization)				
High				
Standard				
Baseline disease risk strata (data entry updated post randomization)				
High				
Standard				
Age group at 0702 enrollment, years				
20-29				
30-39				
40-49				
50-59				

	Treatment Arm			
	Auto/Auto (N=247) N (%)	**Auto/RVD (N=254) N (%)**	**Auto/Maintenance (N=257) N (%)**	**Total (N=758) N (%)**
60-70				
ERC-adjudicated 0702 baseline disease response				
Stringent complete response				
Complete response				
Near complete response				
Very good partial response				
Partial response				
Stable disease				
Progression				
Not evaluable				
Baseline response (grouped)				
CR or Stringent CR				
Baseline response (grouped)				
VGPR, near CR, CR, or stringent CR				
CIBMTR-collected pre-0702 initial myeloma therapy				
Doublets				
Triplets				
Other				

Age at 0702 enrollment, years				
Min				
Max				
Median				
Mean				
StdDev				

Exhibit 07LT-2B: Participant Demographics and Baseline Characteristics (07LT-enrolled participants)

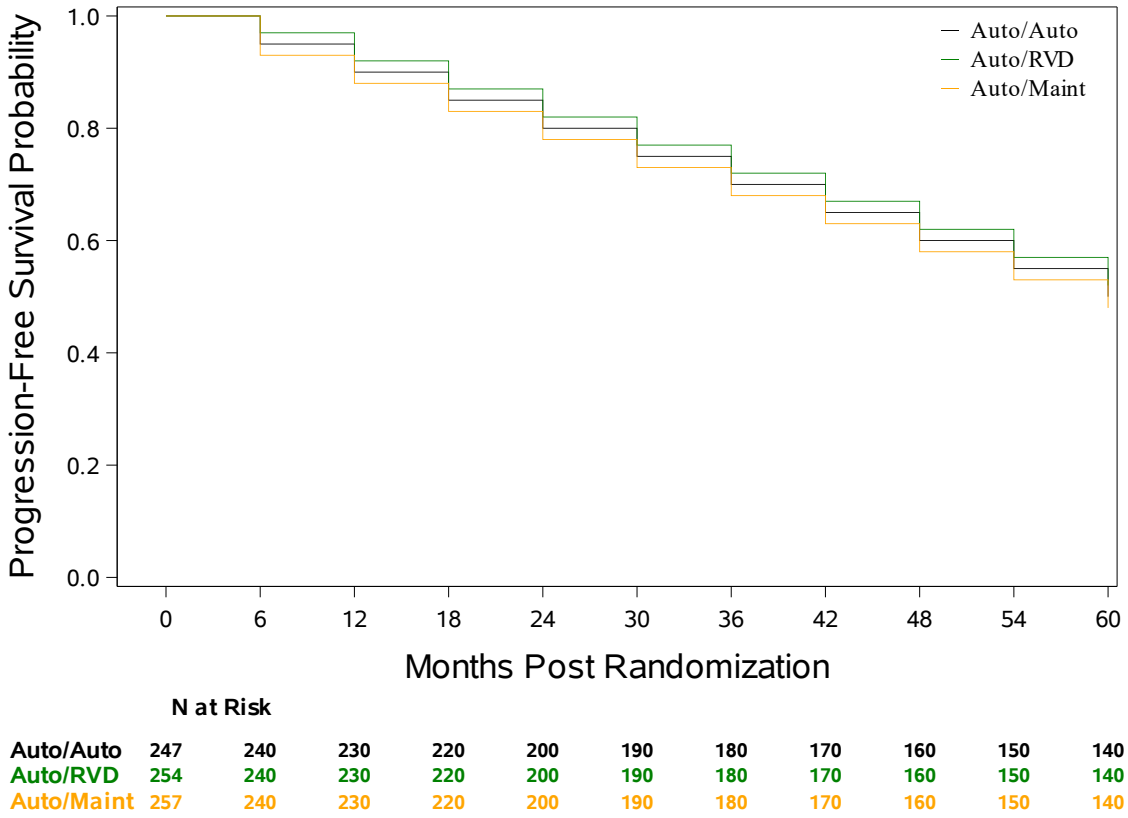
	Treatment Arm			
	Auto/Auto (N=) N (%)	**Auto/RVD (N=) N (%)**	**Auto/Maintenance (N=) N (%)**	**Total (N=) N (%)**
Gender				
Female				
Male				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Unknown				
Not Answered				
Race				
American Indian/Alaska Native				
Asian				
Hawaiian/Pacific Islander				
Black or African American				
White				
More than One Race				
Other, Specify				
Unknown				
Not Answered				
Karnofsky Performance Score at 0702 enrollment				
90 - 100				
70 - 80				
Less than 70				
Baseline disease risk strata at randomization				
High				
Standard				
Baseline disease risk strata (data entry updated post randomization)				
High				
Standard				

	Treatment Arm			
	Auto/Auto (N=) N (%)	**Auto/RVD (N=) N (%)**	**Auto/Maintenance (N=) N (%)**	**Total (N=) N (%)**
Age group at 07LT enrollment, years				
20-29				
30-39				
40-49				
50-59				
60-70				
ERC-adjudicated 0702 baseline disease response				
Stringent complete response				
Complete response				
Near complete response				
Very good partial response				
Partial response				
Stable disease				
Progression				
Not evaluable				
Baseline response (grouped)				
CR or Stringent CR				
Baseline response (grouped)				
VGPR, near CR, CR, or stringent CR				
CIBMTR-collected pre-0702 initial myeloma therapy				
Doublets				
Triplets				
Other				

Age at 07LT enrollment, years				
Min				
Max				
Median				
Mean				
StdDev				

Exhibit 07LT-3: Progression-free Survival (Primary Analysis of PFS)

Figure template for illustration only



Kaplan Meier Estimates and 98.3% Confidence Intervals

	Auto/Auto	Auto/RVD	Auto/Maint
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Pairwise Tests of Treatment Group Differences

		First Event[3]				
Comparison	N	Total Events	PRG or NPT	DTH	Stratified Log-rank (Abs(Z))[1]	p-value[2]
Auto/Auto to Auto/RVD	247 254	XXX XXX	XXX XXX	XXX XXX	X.X	0.XX
Auto/Auto to Auto/Maintenance	247 257	XXX XXX	XXX XXX	XXX XXX	X.X	0.XX
Auto/RVD to Auto/Maintenance	254 257	XXX XXX	XXX XXX	XXX XXX	X.X	0.XX

[1]Absolute value of the Z statistic is reported; does not indicate direction.
[2]P-values are compared to the α=0.05/3 level for statistical significance.
[3]Only the first event (clinical progression (PRG), non-protocol anti-myeloma therapy initiation (NPT), death) is counted.

Notes for primary analysis:

Analysis population: 0702-enrolled

Events:

- *Clinical progression*
- *initiation of non-protocol antimyeloma therapy*
- *death*

BMT CTN 0702 Endpoint Review Committee data will be used for events when available (in general, during the first 38 months of follow-up on 0702). CIBMTR data will be used.

Censoring:

- *the date of last myeloma data collected through 0702 or 07LT or from the CIBMTR*

Testing:

- *two-sided log-rank test stratified on risk status at randomization. Significance level for each pairwise test is 0.05/3.*

Exhibit 07LT-4A: Multivariate Cox Regression Analysis of Progression-free Survival (Secondary Analysis of PFS) – 0702 baseline factors

Maximum Likelihood Estimates and Hazard Ratios

			Hazard Ratio			
Covariate			Point Estimate	Lower Confidence Limit	Upper Confidence Limit	Model Parameter Estimate p-value
Auto/Auto treatment arm vs Auto/Maintenance arm[1]						
Auto/Auto treatment arm vs Auto/RVD arm[1]						
Auto/RVD treatment arm vs Auto/Maintenance arm[1]						
Risk strata—High risk vs Risk strata—Standard risk						
(other adjustment factor as needed)						
(other adjustment factor as needed)						
(other adjustment factor as needed)						

[1]P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Notes for this secondary analysis:

Model covariates:

- *Treatment group*
- *Randomized risk strata*
- *Any of the factors in column 2 of the table in Section 3.1 that have a test for treatment group differences that is significant at the 0.1 level*
- *No interactions will be included.*

Model building and testing:

- *Analysis population is 0702 participants*
- *Time to PFS is calculated from randomization*
- *proc phreg in SAS, no model selection procedures*

Exhibit 07LT-4B: Multivariate Cox Regression Analysis of Progression-free Survival from Initiation of Lenalidomide (Secondary Analysis of PFS)

Maximum Likelihood Estimates and Hazard Ratios

			Hazard Ratio			
Covariate			Point Estimate	Lower Confidence Limit	Upper Confidence Limit	Model Parameter Estimate p-value
Auto/Auto treatment arm vs Auto/Maintenance arm[1]						
Auto/Auto treatment arm vs Auto/RVD arm[1]						
Auto/RVD treatment arm vs Auto/Maintenance arm[1]						
Risk strata—High risk vs Risk strata—Standard risk						
Permanent discontinuation of lenalidomide (time-dependent)						
(other adjustment factor as needed)						
(other adjustment factor as needed)						
(other adjustment factor as needed)						

[1] P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Notes for this secondary analysis:

Model covariates:

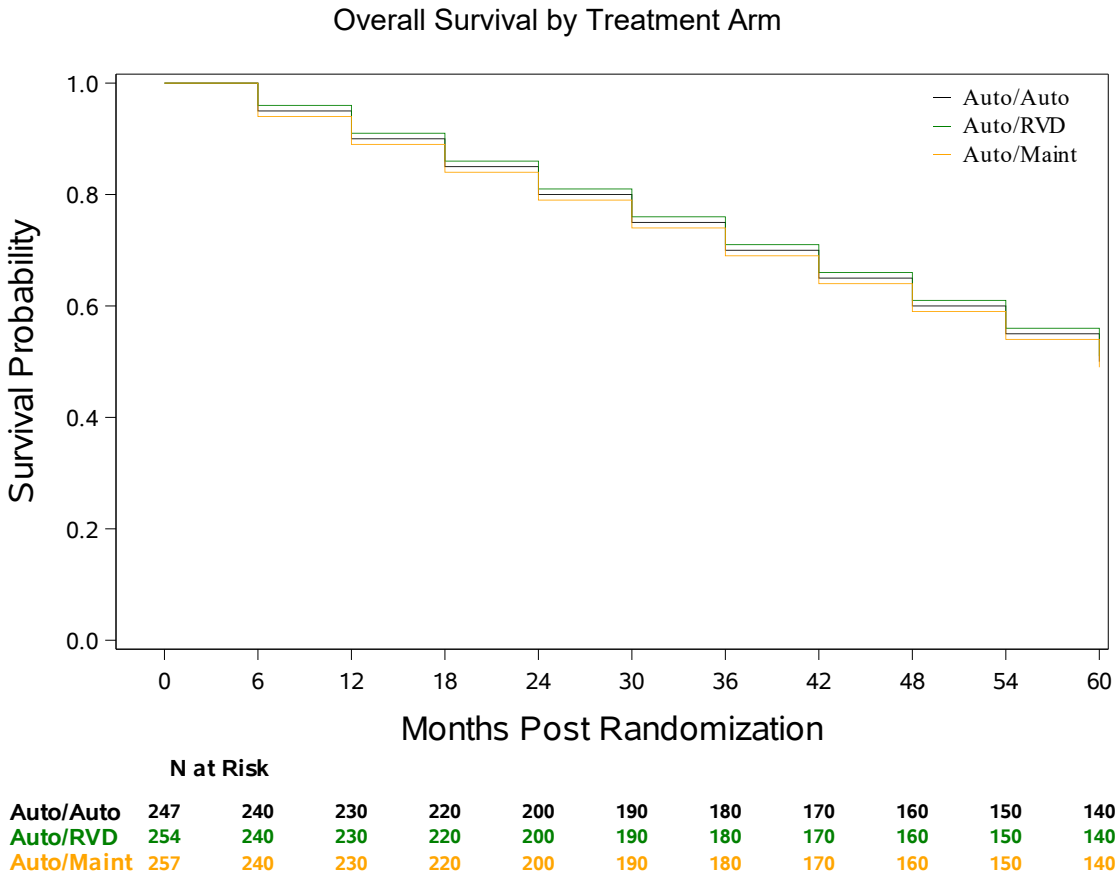
- *Treatment group*
- *Randomized risk strata*
- *Any of the factors in column 2 of the table in Section 3.1 that have a test for treatment group differences that is significant at the 0.1 level. ERC-adjudicated baseline disease response will be tested using 2 categorizations (CR or better, VGPR or better). If both are significant at the 0.1 level, the one that is more significant will be used in the model.*
- *No interactions*
- *Permanent discontinuation of lenalidomide as a time varying covariate.*

Model building and testing:

- *Analysis population is 0702 participants who initiated lenalidomide*
- *Time to PFS is calculated from start time of lenalidomide*
- *Proc phreg in SAS, no model selection procedure*

Exhibit 07LT-5: Overall Survival

Figure template for illustration only



Kaplan Meier Estimates and 98.3% Confidence Intervals

	Auto/Auto	Auto/RVD	Auto/Maint
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

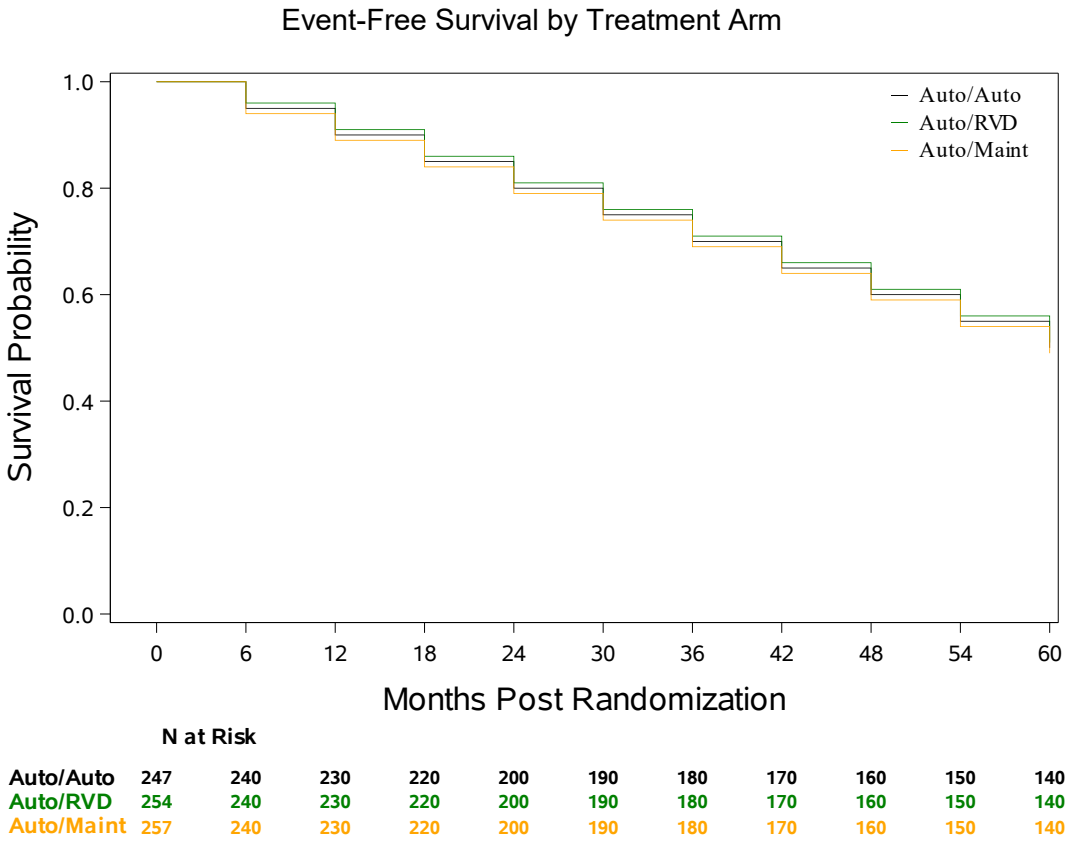
Stratified Log-Rank Test for Treatment Group Differences

Treatment Group Comparison	p-value[1]
Auto/Auto vs Auto/RVD	0.XX
Auto/Auto vs Auto/Maint	0.XX
Auto/RVD vs Auto/Maint	0.XX

[1]Significance level is 0.05/3 for each pairwise comparison.

Exhibit 07LT-6: Event-Free Survival

Figure template for illustration only



Kaplan Meier Estimates and 98.3% Confidence Intervals

	Auto/Auto	Auto/RVD	Auto/Maint
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

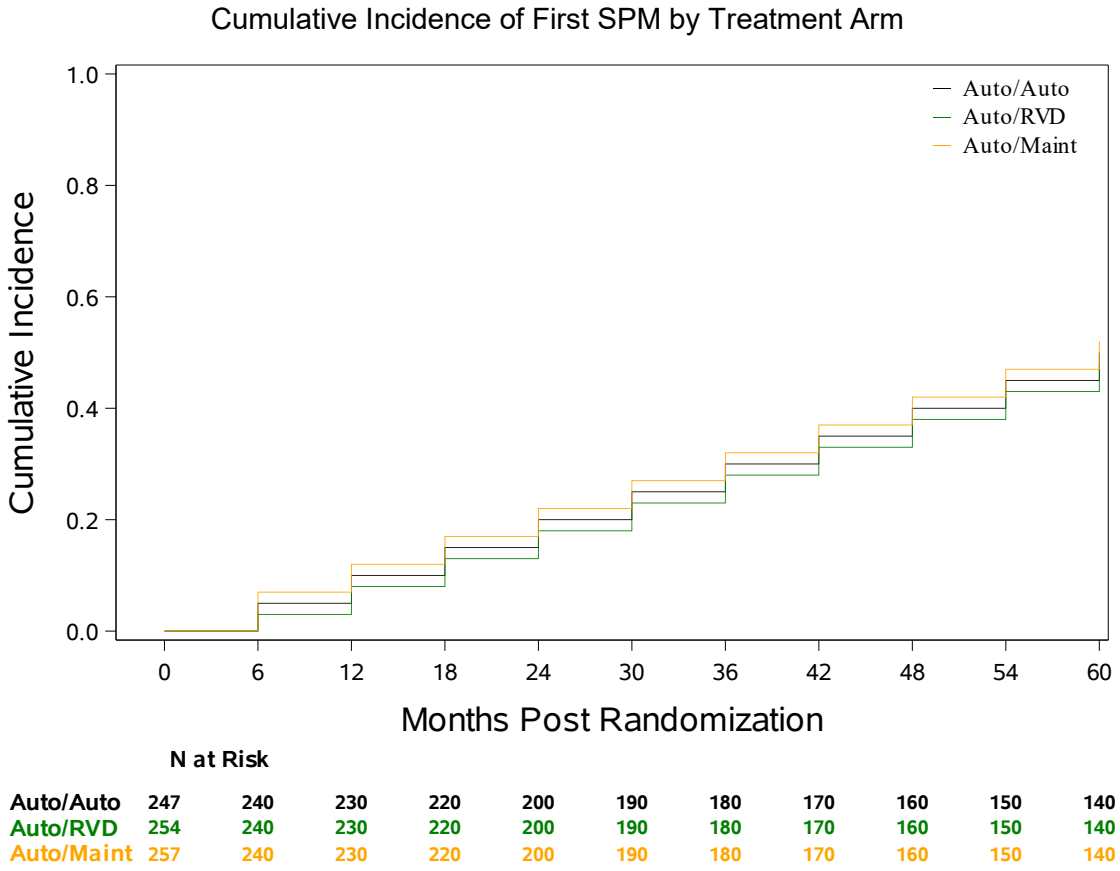
Stratified Log-Rank Test for Treatment Group Differences

			First Event[3]			
Comparison	N	Total Number with an Event	PRG or NPT	SPM	DTH	p-value[1]
Auto/Auto to Auto/RVD	247 254	XXX XXX	XXX XXX	XXX XXX	XXX XXX	0.XX
Auto/Auto to Auto/Maintenance	247 257	XXX XXX	XXX XXX	XXX XXX	XXX XXX	0.XX
Auto/RVD to Auto/Maintenance	254 257	XXX XXX	XXX XXX	XXX XXX	XXX XXX	0.XX

[1]Significance level is 0.05/3 for each pairwise comparison.

Exhibit 07LT-7: Cumulative Incidence of First SPM

Figure template for illustration only



Cumulative Incidence Estimates and 98.3% Confidence Intervals

	Auto/Auto	**Auto/RVD**	**Auto/Maint**
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Stratified Gray's Test for Treatment Group Differences

Treatment Group Comparison	**p-value[1]**
Auto/Auto vs Auto/RVD	0.XX
Auto/Auto vs Auto/Maint	0.XX
Auto/RVD vs Auto/Maint	0.XX

[1]Significance level is 0.05/3 for each pairwise comparison.

Exhibit 07LT-8: SPM Histologic Type

	Auto/Auto		Auto/RVD		Auto/Maint		Total	
	N	%	N	%	N	%	N	%
All[1]	XXX	100.0	XXX	100.0	XXX	100.0	XXX	100.0
Hematologic SPM	XXX	XX.X	XXX	XX.X	XXX	XX.X	XXX	XX.X
High-Level Group Term 1	XXX		XXX		XXX		XXX	
High-Level Group Term 2	XXX		XXX		XXX		XXX	
(etc.)	XXX		XXX		XXX		XXX	
Solid Tumor SPM	XXX	XX.X	XXX	XX.X	XXX	XX.X	XXX	XX.X
High-Level Group Term 1	XXX		XXX		XXX		XXX	
High-Level Group Term 2	XXX		XXX		XXX		XXX	
(etc.)	XXX		XXX		XXX		XXX	

[1]More than one SPM may be reported per participant. SPM reporting on BMT CTN 0702 and 07LT is not required after progression. Supplemental data is provided by the CIBMTR.

Exhibit 07LT-9A: Unexpected Grades 3-5 Adverse Events in Participants Initiating Lenalidomide on BMT CTN 07LT[1]

		Auto/Auto N %	Auto/RVD N %	Auto/Maint N %	Total
All Unexpected Grades 3-5 Adverse Events		XX 100.0	XX 100.0	XX 100.0	XX 100.0
System Organ Class (SOC)	**Preferred Term**				
SOC1	ALL	XX XX.X	XX XX.X	XX XX.X	XX XX.X
	PT1	(just N)	(just N)	(just N)	(just N)
	PT2	(just N)	(just N)	(just N)	(just N)
SOC2	ALL	XX XX.X	XX XX.X	XX XX.X	XX XX.X
	PT1	(just N)	(just N)	(just N)	(just N)
	PT2	(just N)	(just N)	(just N)	(just N)
(etc.)	(etc.)				
Severity					
Grade 3		XX XX.X	XX XX.X	XX XX.X	XX XX.X
Grade 4		XX XX.X	XX XX.X	XX XX.X	XX XX.X
Grade 5		XX XX.X	XX XX.X	XX XX.X	XX XX.X

[1] *The reporting requirements differ for participants taking lenalidomide.*

Exhibit 07LT-9B: Unexpected Grades 3-5 Adverse Events in Participants Enrolled on BMT CTN 07LT Who Did Not Initiate Lenalidomide

		Auto/Auto N %	Auto/RVD N %	Auto/Maint N %	Total
All Unexpected Grades 3-5 Adverse Events		XX 100.0	XX 100.0	XX 100.0	XX 100.0
System Organ Class (SOC)	**Preferred Term**				
SOC1	ALL	XX XX.X	XX XX.X	XX XX.X	XX XX.X
	PT1	(just N)	(just N)	(just N)	(just N)
	PT2	(just N)	(just N)	(just N)	(just N)
SOC2	ALL	XX XX.X	XX XX.X	XX XX.X	XX XX.X
	PT1	(just N)	(just N)	(just N)	(just N)
	PT2	(just N)	(just N)	(just N)	(just N)
(etc.)	(etc.)				
Severity					
Grade 3		XX XX.X	XX XX.X	XX XX.X	XX XX.X
Grade 4		XX XX.X	XX XX.X	XX XX.X	XX XX.X
Grade 5		XX XX.X	XX XX.X	XX XX.X	XX XX.X

Exhibit 07LT-10: Health Quality of Life: FACT-BMT for BMT CTN 07LT English/Spanish-Speaking Participants

Note: The analysis is limited to questionnaires for BMT 07LT-enrolled participants who have not died or progressed. The interpretation of results is limited. Questionnaires not completed within the analysis target window are excluded.

		Treatment Arm											
		Auto/Auto (N=XXX)				Auto/RVD (N=XXX)				Auto/Maint (N=XXX)			
		N	Median	Mean	StdErr	N	Median	Mean	StdErr	N	Median	Mean	StdErr
FACT BMT Concerns (10 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												
FACT-G Total (27 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												
FACT-BMT Total (37 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												
FACT-BMT Trial Outcome Index (24 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												

Figures may also be provided.

Exhibit 07LT-11: Health Quality of Life: SF-36 for BMT CTN 07LT English/Spanish-Speaking Participants

Note: The analysis is limited to questionnaires for BMT CTN 07LT-enrolled participants who have not died or progressed. The interpretation of results is limited. Questionnaires not completed within the analysis target window are excluded.

		Treatment Arm											
		Auto/Auto (N=XXX)				Auto/RVD (N=XXX)				Auto/Maint (N=XXX)			
		N	Median	Mean	StdErr	N	Median	Mean	StdErr	N	Median	Mean	StdErr
Physical Well-Being (7 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												
Social / Family Well-Being (7 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												
Emotional Well-Being (6 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												
Functional Well-Being (7 Items)	**Baseline**												
	R1Y												
	R2Y												
	R3Y												
	R4Y												
	R5Y												

Figures may also be provided.

Supplemental Exhibit 07LT-1: Enrollment

A table will be provided showing actual yearly accrual for each 07LT participating center from 07LT study initiation to accrual closure.

A table will be provided showing time to last contact summarized separately for participants enrolled on BMT CTN 07LT, and for participants not enrolled on BMT CTN 07LT.

Supplemental Exhibit 07LT-2: Significant Protocol Deviations

A table listing significant protocol deviations/violations will be provided separately for those who continued lenalidomide maintenance therapy on 07LT and those who did not, by treatment group for participants enrolled on 07LT.

Supplemental Exhibit 07LT-3: Permanent Discontinuation of Lenalidomide

A table will be provided to describe the reasons for permanent discontinuation of lenalidomide maintenance therapy for BMT CTN 0702-enrolled participants who initiated therapy on BMT CTN 07LT. For particpants who have confirmed they continued on commercial lenalidomide, discontinuation data will be based on discontinuation of commercial lenalidomide.

Supplemental Exhibit 07LT-4: Primary Cause of Death

A table summarizing the primary cause of death by treatment group will be provided; the table will be separated into adjudicated deaths and unadjudicated deaths. Primary cause of death is adjudicated by the BMT CTN 0702 Endpoint Review Committee (ERC) for most participants who died within 38 months of enrollment on 0702. For deaths where cause is not adjudicated by the ERC, if the participant progressed prior to death without a secondary malignancy, cause of death will be reported as progression; if the person progressed prior to death and also reported an SPM, cause of death will be reported as progression/SPM; if the person did not progress prior to death but reported an SPM, cause of death will be reported as SPM; if the person did not progress prior to death and did not report an SPM, site-reported cause of death will be reported.

	Treatment Arm						**Total**	
	Auto/Auto		**Auto/RVD**		**Auto/Maint**			
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Enrolled	247	100.0	254	100.0	257	100.0	758	100.0
Total deaths								
Deaths adjudicated by BMT CTN 0702 ERC								
Deaths not adjudicated by BMT CTN 0702 ERC								
ERC-Adjudicated Deaths								

	Treatment Arm						Total	
	Auto/Auto		Auto/RVD		Auto/Maint			
	N	%	N	%	N	%	N	%
Primary Cause of Death								
Disease Recurrence or Persistence								
Secondary Malignancy								
[Reason 3]								
[Reason 4]								
Deaths with Cause Not Adjudicated								
Primary Cause of Death								
Disease Recurrence or Persistence								
Secondary Malignancy								
Disease recurrence or persistence/secondary malignancy								
[Reason 4]								
[Reason 5]								

Supplemental Exhibit 07LT-5A: Multivariate Cox Regression Analysis of Overall Survival – 0702 baseline factors

Maximum Likelihood Estimates and Hazard Ratios

	Hazard Ratio			
Covariate	Point Estimate	Confidence limit	Confidence limit	Model Parameter Estimate p-value
Auto/Auto treatment arm vs Auto/Maintenance arm[1]				
Auto/Auto treatment arm vs Auto/RVD arm[1]				
Auto/RVD treatment arm vs Auto/Maintenance arm[1]				
Risk strata—High risk vs Risk strata—Standard risk				
(other adjustment factor as needed)				
(other adjustment factor as needed)				
(other adjustment factor as needed)				

[1]P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Notes for this secondary analysis:

Model covariates:

- *Treatment group*
- *Randomized risk strata*
- *Any of the factors in column 2 of the table in Section 3.1 that have a test for treatment group differences that is significant at the 0.1 level. ERC-adjudicated baseline disease response will be tested using 2 categorizations (CR or better, VGPR or better). If both are significant at the 0.1 level, the one that is more significant will be used in the model.*
- *No interactions will be included.*

Model building and testing:

- *Analysis population is 0702 participants*
- *Time to OS is calculated from randomization*
- *proc phreg in SAS, no model selection procedures*

Supplemental Exhibit 07LT-5B: Multivariate Cox Regression Analysis of Overall Survival from Initiation of Lenalidomide

Maximum Likelihood Estimates and Hazard Ratios

	Hazard Ratio			
Covariate	Point Estimate	Lower Confidence Limit	Upper Confidence Limit	Model Parameter Estimate p-value
Auto/Auto treatment arm vs Auto/Maintenance arm[1]				
Auto/Auto treatment arm vs Auto/RVD arm[1]				
Auto/RVD treatment arm vs Auto/Maintenance arm[1]				
Risk strata—High risk vs Risk strata—Standard risk				
Permanent discontinuation of lenalidomide (time-dependent)				
(other adjustment factor as needed)				
(other adjustment factor as needed)				
(other adjustment factor as needed)				

[1] P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Notes for this secondary analysis:

Model covariates:

- *Treatment group*
- *Randomized risk strata*
- *Any of the factors in column 2 of the table in Section 3.1 that have a test for treatment group differences that is significant at the 0.1 level. ERC-adjudicated baseline disease response will be tested using 2 categorizations (CR or better, VGPR or better). If both are significant at the 0.1 level, the one that is more significant will be used in the model.*
- *No interactions*
- *Permanent discontinuation of lenalidomide as a time varying covariate.*

Model building and testing:

- *Analysis population is 0702 participants who initiated lenalidomide*
- *Time to PFS is calculated from start time of lenalidomide*
- *Proc phreg in SAS, no model selection procedure*

Supplemental Exhibit 07LT-6A: Multivariate Cox Regression Analysis of Event-free Survival – 0702 baseline factors

Maximum Likelihood Estimates and Hazard Ratios

	Cox model Parameter		Hazard Ratio		
Covariate	Estimate	p-value	Point Estimate	Confidence limit	Confidence limit
Auto/Auto treatment arm vs Auto/Maintenance arm[1]					
Auto/Auto treatment arm vs Auto/RVD arm[1]					
Auto/RVD treatment arm vs Auto/Maintenance arm[1]					
Risk strata—High risk vs Risk strata—Standard risk					
(other adjustment factor as needed)					
(other adjustment factor as needed)					
(other adjustment factor as needed)					

[1]P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Notes for this secondary analysis:

Model covariates:

- *Treatment group*
- *Randomized risk strata*
- *Any of the factors in column 2 of the table in Section 3.1 that have a test for treatment group differences that is significant at the 0.1 level. ERC-adjudicated baseline disease response will be tested using 2 categorizations (CR or better, VGPR or better). If both are significant at the 0.1 level, the one that is more significant will be used in the model.*
- *No interactions will be included.*

Model building and testing:

- *Analysis population is 0702 participants*
- *Time to EFS is calculated from randomization*
- *proc phreg in SAS, no model selection procedures*

Supplemental Exhibit 07LT-6B: Cause-specific Multivariate Cox Regression Analysis of the Components of Event-free Survival

Maximum Likelihood Estimates and Hazard Ratios: Event=Progression, Censoring Events=SPM, Death

	Cox model Parameter		Hazard Ratio		
Covariate	Estimate	p-value	Point Estimate	Confidence limit	Confidence limit
Auto/Auto treatment arm vs Auto/Maintenance arm[1]					
Auto/Auto treatment arm vs Auto/RVD arm[1]					
Auto/RVD treatment arm vs Auto/Maintenance arm[1]					
Risk strata—High risk vs Risk strata—Standard risk					
Permanent discontinuation of lenalidomide					
(other adjustment factor as needed)					
(other adjustment factor as needed)					
(other adjustment factor as needed)					

[1] P-values are compared to the 0.05/3 significance level.

Maximum Likelihood Estimates and Hazard Ratios: Event=SPM, Censoring Events=Progression, Death

	Cox model Parameter		Hazard Ratio		
Covariate	Estimate	p-value	Point Estimate	Confidence limit	Confidence limit
Auto/Auto treatment arm vs Auto/Maintenance arm[1]					
Auto/Auto treatment arm vs Auto/RVD arm[1]					
Auto/RVD treatment arm vs Auto/Maintenance arm[1]					
Risk strata—High risk vs Risk strata—Standard risk					
Permanent discontinuation of lenalidomide					
(other adjustment factor as needed)					
(other adjustment factor as needed)					
(other adjustment factor as needed)					

[1] P-values are compared to the 0.05/3 significance level.

Maximum Likelihood Estimates and Hazard Ratios: Event=Death, Censoring Events=Progression, SPM

	Cox model Parameter		Hazard Ratio		
Covariate	Estimate	p-value	Point Estimate	Confidence limit	Confidence limit
Auto/Auto treatment arm vs Auto/Maintenance arm[1]					
Auto/Auto treatment arm vs Auto/RVD arm[1]					
Auto/RVD treatment arm vs Auto/Maintenance arm[1]					
Risk strata—High risk vs Risk strata—Standard risk					
Permanent discontinuation of lenalidomide					
(other adjustment factor as needed)					
(other adjustment factor as needed)					
(other adjustment factor as needed)					

[1] P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Supplemental Exhibit 07LT-6C: Multivariate Cox Regression Analysis of Event-free Survival from Initiation of Lenalidomide

Maximum Likelihood Estimates and Hazard Ratios

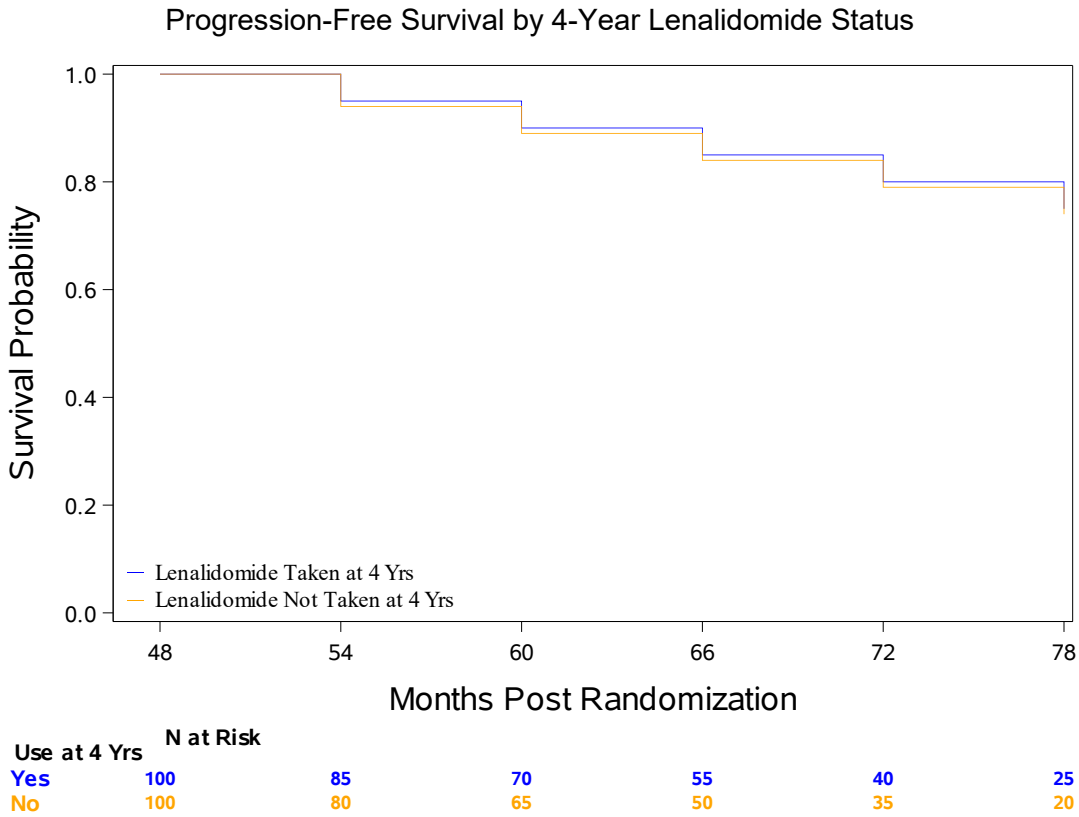
	Cox model Parameter		Hazard Ratio		
Covariate	Estimate	p-value	Point Estimate	Confidence limit	Confidence limit
Auto/Auto treatment arm vs Auto/Maintenance arm[1]					
Auto/Auto treatment arm vs Auto/RVD arm[1]					
Auto/RVD treatment arm vs Auto/Maintenance arm[1]					
Risk strata—High risk vs Risk strata—Standard risk					
Permanent discontinuation of lenalidomide					
(other adjustment factor as needed)					
(other adjustment factor as needed)					
(other adjustment factor as needed)					

[1] P-values are compared to the 0.05/3 significance level.

Figure: A forest plot for the hazard ratios and confidence intervals may also be provided.

Supplemental Exhibit 07LT-6: Landmark Analysis of PFS

Figure template for illustration only



Kaplan Meier Estimates and 95% Confidence Intervals

	Lenalidomide taken at 4 years post randomization	**Lenalidomide not taken at 4 years post randomization**
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

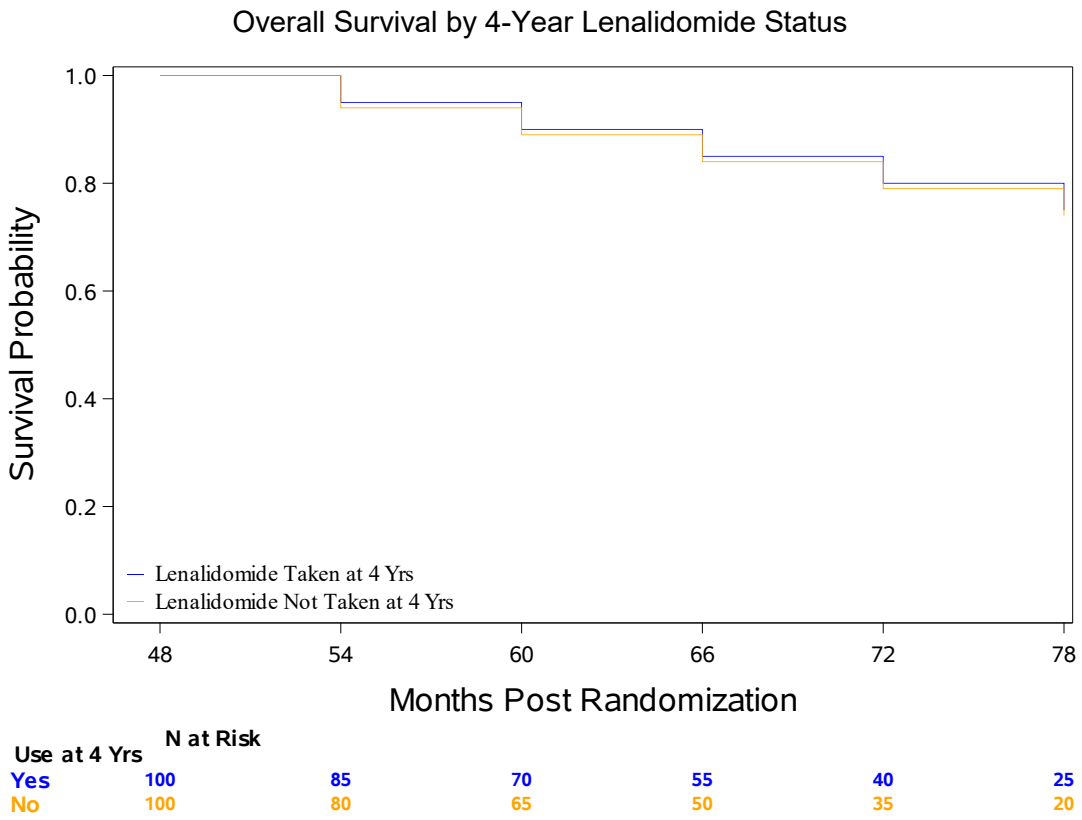
Log-Rank Test for Group Differences

Comparison	**N**	**Total Number with an Event**	**p-value[1]**
Lenalidomide use at 4 years			
Yes	xxx	XXX	
No	xxx	XXX	0.XX

[1]Significance level is 0.05.

Supplemental Exhibit 07LT-7: Landmark Analysis of OS

Figure template for illustration only



Kaplan Meier Estimates and 95% Confidence Intervals

	Lenalidomide taken at 4 years post randomization	Lenalidomide not taken at 4 years post randomization
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

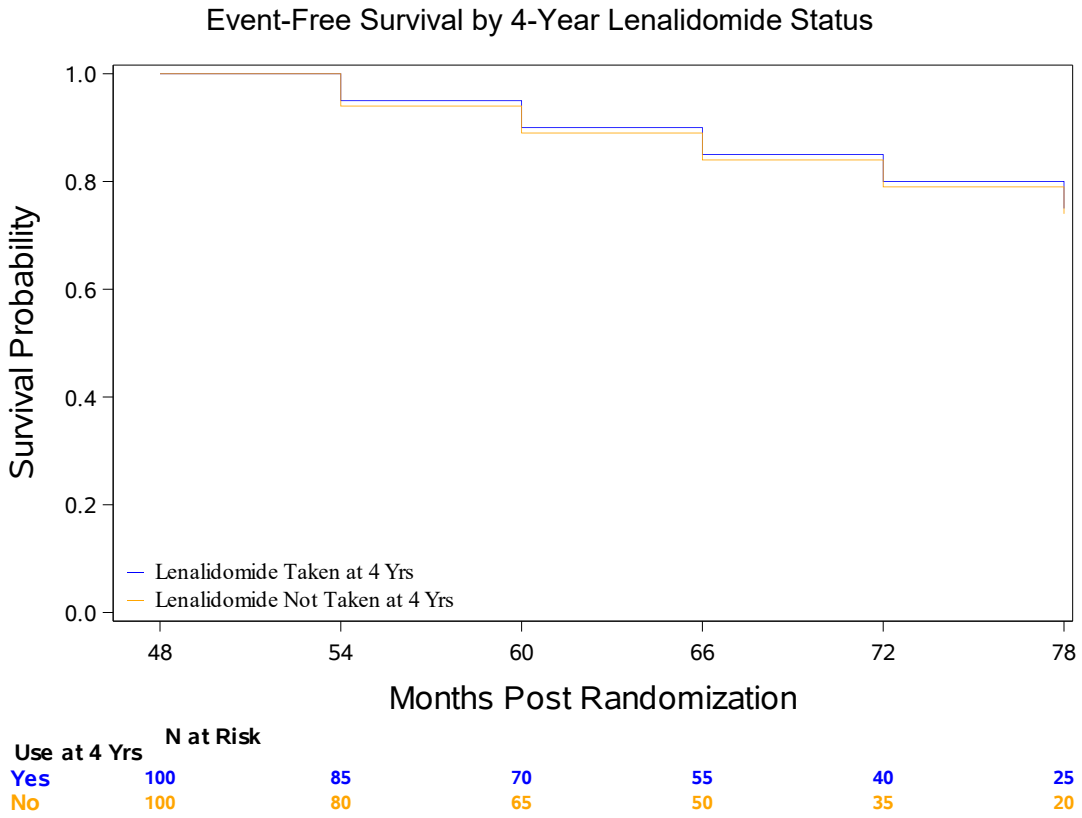
Log-Rank Test for Group Differences

Comparison	N	Total Number with an Event	p-value[1]
Lenalidomide use at 4 years			
Yes	xxx	XXX	
No	xxx	XXX	0.XX

[1]Significance level is 0.05.

Supplemental Exhibit 07LT-8: Landmark Analysis of EFS

Figure template for illustration only



Kaplan Meier Estimates and 95% Confidence Intervals

	Lenalidomide taken at 4 years post randomization	**Lenalidomide not taken at 4 years post randomization**
5-year Estimates:	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)

Log-Rank Test for Group Differences

			First Event			
Comparison	**N**	**Total Number with an Event**	**PRG or NPT**	**SPM**	**DTH**	**p-value[1]**
Lenalidomide use at 4 years						
Yes	xxx	XXX	XXX	XXX	XXX	
No	xxx	XXX	XXX	XXX	XXX	0.XX

[1]Significance level is 0.05.