Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1770-81.

Appendix

Table of Contents

Supplement to McCarthy PL, Owzar K, Hofmeister CC et al, Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma

Contents

Acknowledgements

In addition to the authors, the following investigators/institutions participated in the CALGB 100104 study:

CALGB: Dana Farber Cancer Inst, Boston, MA - J Koreth; Illinois Onc Res Assoc, Peoria IL - P Gomez; Memorial Sloan Kettering Cancer Ctr; NY, NY; Mt Sinai School of Med, NY, NY; North Shore Univ Hosp, Lake Success, NY - RL Bayer; Roswell Park Cancer Inst, Buffalo, NY; Upstate Med Univ, Syracuse, NY - SL Graziano; Ohio State Univ Med Ctr, Columbus, OH - DM Benson; Univ California San Diego, San Diego, CA - E Ball; Univ California San Francisco, CA - LE Damon, JL Wolf; Univ Chicago, Chicago, IL - TM Zimmerman; Univ Illinois Chicago, IL - DJ Peace; Univ Minnesota, Minneapolis, MN - NS Majhail, ED Warlick; Univ Nebraska, Medical Center, Omaha, NE - RG Bociek, EA Faber, JM Vose; Univ North Carolina Chapel Hill, NC; BMT Group Georgia, Atlanta GA; Virginia Commonwealth Univ, Richmond, VA - J McCarty; Univ of Vermont, Burlington VT - BW Grant; Wake Forest Univ School Medicine, Winston-Salem, NC; Walter Reed Army Med Ctr, Washington, DC - DC Van Echo; Washington Univ School Medicine, St Louis MO - C. Abboud, A. Fishback Cashen, J. DiPersio; Weill Med College Cornell Univ, NY, NY - TB Shore; Western Pennyslvania Hosp, Pittsburgh, PA - J Lister, JM Rossetti; ECOG: Cancer Inst of New Jersey, New Brunswick, NY - M Gharibo; Case Western Metro Health Med Ctr, Cleveland OH - HM Lazarus; Columbia Presbyterian; Rocky Mountain Cancer Center/St Lukes Hsp, Denver CO - RM Jotte, JV Matous; Univ of Florida Gainesville, FL - JW Hsu, B Wirk; Fox Chase Cancer Ctr, Philadelphia, PA - R Emmons; Geisinger Med Ctr, Danville, PA - SS Khan; Indiana Univ Medical Ctr, Indianapolis, IL- R Abonour; Jewish Hospital, Cincinnati, OH - E Broun, S Hettinger; Marshfield Clinic, Marshfield, WI - A Onitilo, A Bseiso; Med College Georgia, Augusta, GA - C Ustun, AP Jillella; Univ Miami, Miami, FL - M Goodman; Univ Pennsylvania, Philadelphia, PA; Hillman Cancer Center, Pittsburgh, PA - MY Mapara, A Mounzer; Mayo Clinic, Scottsdale, NY - JR Mikhael, CB Reeder; Univ Hospital Cleveland, Cleveland, OH - TL Kindwall-Keller; Vanderbilt Univ, Nashville, TN - KA Kassim; Med College of Wisconsin, SP Ritch; Univ of Wisconsin, Madison WI; BMT-CTN: City of Hope, Duarte CA - F Sahebi; LDS Hosp, Salt Lake City, UT - C Ford; MD Anderson, Houston, TX - R Champlin, Y Neito, N Shah; Oregon Health Sciences Univ, Portland OR; Univ of Mississippi Med Ctr, Jackson, MI.

The authors wish to thank the patients who participated in this study and the treating clinical research teams who cared for the patients. We thank the CALGB Central Office and Statistical Center for providing the infrastructure for this study. The authors acknowledge the careful reading of and comments on this manuscript by Dr. George Chen, Dr. Theresa Hahn, Dr. Hong Liu, Dr. Daniel Sargent, Ms. Sherry Breaux, Ms. Yali Zhang and Mrs. Jane McCarthy as well as the secretarial support of Ms. Jennifer Kapinos. We acknowledge the helpful discussion of Dr. Boris Freidlin, Dr. Richard Little and Dr. Howard Streicher at the time of and after the study un-blinding. The Information Technology support of the database by Mr. Kevin Dixon, Mr. Adil Khan, Mr. Brian Smith and Mr. Josh Yoder is gratefully acknowledged by the authors. The lenalidomide and placebo drugs utilized in this study were provided by Celgene Corporation and distributed by Cancer Therapy Evaluation Program (CTEP) within the Division of Cancer Treatment and Diagnosis (DCTD).

The research for CALGB 100104 was supported, in part, by grants from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B (Monica M. Bertagnolli, M.D., Chair) and to the CALGB Statistical Center (Daniel J. Sargent, Ph.D., CA33601). Participation of some centers was made possible through the Blood and Marrow Transplant Network (BMT-CTN) supported in part by grant #U01HL069294 from the National Heart, Lung, and Blood Institute and the National Cancer Institute; and the Eastern Cooperative Oncology Group (ECOG) supported by CA21115.

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

Supplemental Methods, Patient Staging and Testing, Lenalidomide Dosing and Observations, Anticoagulation Guidelines, Statistical Methods, Auditing and Compliance

Disease Staging, Testing post-Randomization, Dosing

Patients were initially staged by Durie-Salmon (DS) criteria[1]. Stage 1: all of the following: hemoglobin value >10g/dL, serum calcium value normal or <10.5mg/dL, bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only, low M-component production rates (IgG value <5g/dL; IgA value <3g/dL). urine light chain M-component on electrophoresis <4g/24h; Stage II: Fitting neither Stage I nor Stage III; Stage III: one or more of the following: hemoglobin value <8.5g/dL, serum calcium value >12mg/dL, advanced lytic bone lesions (scale 3), high M-component production rates, (IgG value >7g/dL IgA value >5g/dL), Bence Jones protein >12g/24h. The international staging system was also used for staging at registration based on serum albumin and β-2 microglobulin levels[2]. Stage I: Serum β-2 microglobulin level < 3.5 mg/L and serum albumin $\geq$ 3.5 g/dL; Stage I: not I or III; Stage III: serum β-2 microglobulin level $\geq$ 5.5 mg/L. Staging included bone marrow, blood and urine testing as well as skeletal survey. Patients have been and continue to be screened by blood and urine testing every 3 months for 4 years then every 6 months in year five then once a year for 10 years from study entry. Bone marrow tests have been and will be obtained at 3 and 12 months after day 0 then yearly until 5 years post autologous transplant. Skeletal surveys have been and will be obtained yearly for 5 years. Response/progression evaluation was defined initially according to European Blood and Marrow Transplant (EBMT) criteria[3]. The EBMT criteria for response and progression are as follows:

Response Criteria

Complete Response (CR)

Complete response requires **all** of the following:

- Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.

- <5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.

- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

- Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial Response (PR)

Partial response requires **all** of the following:

- ≥50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.

- Reduction in 24 hour urinary light chain excretion either by ≥90% or to <200 mg, maintained for a minimum of 6 weeks.

- For patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.

- ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as Minimal Response (MR), provided the remaining criteria satisfy the requirements for MR.

Minimal Response (MR)

Minimal response requires **all** of the following:

- 25-49% reduction in the level of serum monoclonal paraprotein maintained for a minimum of 6 weeks.

- 50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hours, maintained for a minimum of 6 weeks.

- For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if a biopsy was performed, maintained for a minimum of 6 weeks.

- 25-49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

- No increase in the size or the number of lytic bone lesions (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

No Change (NC)

No change is defined as neither meeting the criteria for minimal response or progressive disease.

Progressive Disease (PD)

Progressive disease (for patients not in CR) requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL and confirmed by at least one repeated investigation.

- >25% increase in the 24 hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hour and confirmed by at least one repeated investigation.

- >25% increase in plasma cells in a bone marrow aspirate or trephine biopsy, which must also be an absolute increase of at least 10%.

- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

- Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response).

- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L) not attributable to any other cause.

Relapsed Disease

Relapsed disease (for patients who were in CR) requires at least one of the following:

- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.

- ≥5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.

- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).

- Development of hypercalcemia (corrected serum calcium > 11.5 g/dL or 2.8 mmol/L) not attributable to any other cause.

The study was modified to include the International Myeloma Working Group (IMWG) criteria[4] with regard to progression. In particular progression from CR was changed to the same criteria as progression from PR or VGPR so as not to "penalize" relapse from CR. Thus, patients with relapsed disease (recurrence of disease after attaining a CR) continued on treatment if they did not fulfill criteria for progressive disease.

The following section describes the lenalidomide dosing. Patients were scheduled to be re-staged between day 90-100 post-autologous hematopoietic cell transplant (AHCT) and those with SD or better were scheduled to start therapy between day 100 to 120 post-AHCT. All patients started on 2 pills (10 mg of lenalidomide) daily.

Hematologic Dose Modifications

Months 1-3

If on 2 capsules per day, the absolute neutrophil count (ANC) is <500/µL or the platelet count is <30,000/µL, then the study drug will be held for 8 weeks. Study drug may be re-instituted at 1 capsule per day if ANC is ≥500/µL or the platelet count is ≥30,000/µL. If, however, after an 8 week treatment delay, the ANC remains <500/µL or the platelet count <30,000/µL, the patient will be removed from protocol therapy.

If on 1 capsule per day, the ANC is <500/µL or the platelet count is <30,000/µL, then the study drug will be held for 8 weeks. If ANC ≥500/µL or the platelet count is ≥30,000/µL, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the ANC remains <500/µL or the platelet count <30,000/µL, the patient will be removed from protocol therapy.

If on 1 capsule per day for 21 of 28 days, the ANC is <500/µL or the platelet count is <30,000/µL, then the patient will be removed from protocol therapy.

Beyond Month 3

If on 3 capsules per day, the ANC is <500/µL or the platelet count is <30,000/µL, then the study drug will be held for 8 weeks. Study drug may be re-instituted at 2 capsules per day if ANC is ≥500/µL or platelet count is ≥30,000/µL. If, however, after an 8 week treatment delay, the ANC remains <500/µL or platelet count <30,000/µL, the patient will be removed from protocol therapy.

If on 2 capsules per day, the ANC is <500/µL or the platelet count is <30,000/µL, then the study drug will be held for 8 weeks. If ANC is ≥500/µL or the platelet count is ≥30,000/µL, then study

drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the ANC remains <500/μL or the platelet count <30,000/μL, the patient will be removed from protocol therapy.

If on 1 capsule per day, the ANC is <500/μL or the platelet count is <30,000/μL, then the study drug will be held for 8 weeks. If ANC ≥500/μL or the platelet count is ≥30,000/μL, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the ANC remains <500/μL or the platelet count <30,000/μL, the patient will be removed from protocol therapy.

If on 1 capsule per day for 21 of 28 days, the ANC is <500/μL or the platelet count is <30,000/μL, then the patient will be removed from protocol therapy.

Dose Escalation Beyond Month 3

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 by one level (i.e., one capsule every day to two capsules every day, etc.). Hematologic parameters must remain at these threshold values for one month before another dose escalation may occur. Maximum study drug dose will be 3 capsules per day.

If for any reason, a patient is not able to be dose escalated, dose escalation should be attempted by the time of the next re-staging. If at next restaging, the patient has not recurred or progressed, and the patient is not able to be dose escalated, patient may continue on treatment at current dose level.

If for any reason the drug is held for a non-grade 3 hematologic toxicity, the drug will be held until the toxicity resolves and the drug started at one dose level lower. The drug should be re-escalated to the original dose within 4 weeks. The drug should be escalated as per the criteria listed above

Anti-Coagulation Guidelines

Patients at high risk of deep venous thrombosis (DVT)/pulmonary embolism (PE) were required to receive some form of anti-coagulation for DVT prophylaxis, originally with aspirin, warfarin or heparin compounds. The protocol was later amended to specify: "Prophylactic aspirin or low molecular weight heparin are to be given for patients with a high risk of developing DVT/PE or arterial thromboses during maintenance therapy unless contraindicated. Warfarin also may be used. High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, use of oral contraceptives, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease also are considered to be at high risk." This was later modified to state that "patients receiving epoetin during maintenance therapy may be at an increased risk of developing DVT/PE and must receive prophylaxis with aspirin or low molecular weight heparin unless contraindicated. Coumadin (Warfarin) also may be used."

Statistical Considerations

The primary endpoint of the study protocol is time to progression defined as time of documented progressive disease or death due to any cause after AHCT. The primary statistical hypothesis was that the time to progression distribution in the lenalidomide arm was stochastically larger than the placebo arm. The clinical study was designed so as to have, at the one-sided level of 0.05, a power of 0.9 for the two-sample log-rank test to detect a hazard ratio of 1.4. For the design, in addition to the assumption of proportional hazards, it was assumed that the time to progression distribution for the placebo and treatment arms were exponential with medians of 24 and 33.6 months respectively. The proposed plan was to randomize 462 patients over a period of 33 months allowing for 30 months of follow-up after completion of accrual. To account for pre-randomization drop-out, it was planned to register 544 patients. The censoring law was assumed to be uniform over the intervals 30 to 63 months. Under these assumptions, 309 events were expected to have been realized by the end of the follow-up period.

Overall survival was a secondary endpoint of the study protocol. Per protocol, the reference date for the time to progression and overall survival endpoints was the date of AHCT for multiple myeloma (MM).

The study was monitored by the CALGB Data and Safety Monitoring Board (DSMB) on a semiannual basis in June and November of each year per CALGB policy. Per protocol, the first interim analysis was to be presented after at least 20% of the expected events had been realized. A group sequential design was employed to monitor time to progression for superiority[5,6]. The bounds were truncated by the 1-0.005 quantile of a standard normal distribution. Time to progression was also to be monitored for futility at each interim analysis to test the specific hypothesis that the hazard ratio is at least 1.4 as a fixed one-sided level of 0.005. A randomized permuted block procedure using three stratification factors (β-2M elevation, prior thalidomide induction therapy and prior lenalidomide induction therapy) was employed.

The study was opened on 12/15/2004. Accrual to the study did not begin until 04/2005. Given that the observed accrual rate had differed considerably from that assumed in the original design, an amendment to the statistical considerations was necessitated so as to comply with an NCI CTEP policy regarding accrual. It is noted that the study team had not carried out any interim analyses when this amendment was drafted and consequently approved. Furthermore, the time to progression distribution assumptions in the amendment and the targeted number of events (309) were identical to those of the original design. Only the assumed distribution of the administrative censoring mechanism had been revised.

The first interim analysis was submitted for the 06/2009 DSMB meeting. This analysis was based on 74 (24 treatment/50 placebo) progressive disease events among 375 (188 treatment/187 placebo) randomized patients. The standardized test statistic was 3.94. The observed statistic exceeded the superiority bound for the first look of 2.57. The numbers of observed deaths on the lenalidomide and

placebo arms were 8 and 10 respectively. The corresponding p-value for the log-rank test for the overall survival analysis was 0.42. Given the strong evidence in favor of the study hypothesis but relative low maturity of the outcome data, at the request of the DSMB an updated analysis was submitted in 09/2009. This analysis was based on 87 (29 treatment/58 placebo) events among 418 (210 treatment/208 placebo) patients. The marginal (unadjusted) standardized test statistic was 3.85. The numbers of observed deaths on the treatment and placebo arms were 11 and 17 respectively. The corresponding p-value for the log-rank test was less than 0.2. An additional sensitivity analysis, to empirically assess the potential impact of missing data on the observed time to progression signal, was conducted in 10/2009 and presented to the DSMB at the 11/2009 meeting. The DSMB released the study data to the CALGB 100104 study team on 12/17/2009. Each DSMB report included interim analysis results for time to progression, overall survival and adverse events. The DSMB reports, including analysis results, summaries and recommendations, were drafted and presented by the statistical team. The clinical team members, including the study chair and data coordinators, were blinded with respect to these analyses and results.

An additional non-protocol endpoint considered was event-free survival (EFS). The definition of the latter considered any second primary malignancy (excluding cutaneous basal cell and squamous cell carcinomas) reported post randomization, along with progressive disease or death, as events. Note that for this endpoint, the time to event is based on the date of the first event (progressive disease, death or second primary malignancy). For patients not reported as experiencing a second primary malignancy and reported as dead, it was assumed that the death was not secondary to a second primary malignancy. For patients for whom progressive disease was the first event, it was assumed that no second primary malignancy event had occurred between randomization and the date of the progressive disease. Two

study-wide requests regarding cancer screening were sent out to the study sites in 2011 and over 500 reports were returned regarding second primary malignancy and cancer screening.

The marginal survival distributions for time to progression, overall survival and EFS are estimated using Kaplan-Meier estimators[7]. Discrepancies among time-to-event distributions are tested using the Cox score (log-rank) test[8]. The corresponding effect size is quantified on the basis of the hazard ratio under the framework of a univariable proportional hazard model[8]. To estimate and compare cause-specific hazard (progression, death and second primary malignancy), marginal estimators of the corresponding cumulative incidence profiles[9] and the log-rank test proposed by Gray are used[10]. To test whether there is an interaction between a baseline co-variable and randomization arm, a two-way multiplicative Cox model is employed. A forest plot is used to provide a graphical presentation of the absolute and relative effect sizes. For this plot, the effect size is presented as the log hazard ratio (i.e., the regression coefficient from the Cox model). The radii of the circles are proportional the inverse of the square of the standard error. It is noted that all hazard ratios discussed in the text and illustrated in the forest plot have been quantified within the context of univariable Cox model without accounting for other additive or multiplicative effects. For all of time to event analyses, standard asymptotics is employed to characterize the sampling distributions for the statistics and estimators. As a descriptive analysis, the discrepancies between the toxicity profiles of the two arms were assessed using Fisher's exact test[11].

For the progressive disease events, patients for whom no event had been realized were censored at the last documented clinical assessment date at which they were found to be in remission. For the overall survival endpoint, patients who are alive are censored at the last date of follow-up. Some patients withdrew consent to further follow-up. For these patients, only follow-up information provided on or before the date of withdrawal of consent was used.

For the analyses, an intent-to- treat (ITT) approach is employed whereas any patient randomized to the study is included in the analyses and classified according to the randomization assignment and the stratification factor provided at the time of randomization. While the events have been reviewed and adjudicated by the study team, the baseline stratification factors have not. For the efficacy analyses, the results are presented based on the follow-up data submitted on or before the un-blinding date of December 2009 and based on all available follow-up data. The first set of analyses is intended to report the results before any bias introduced by un-blinding and cross-over. The latter set of analyses is intended to present the long-term results. The study team is planning to amalgamate the requisite data to more carefully assess the potential effect of cross-over by accounting for potential time dependency in the future. For the descriptive AE analyses, patients without submission of AE forms are assumed to have not experienced any treatment-related adverse events. The AE summaries are presented on the basis of the AE forms submitted after randomization on or before the un-blinding date.

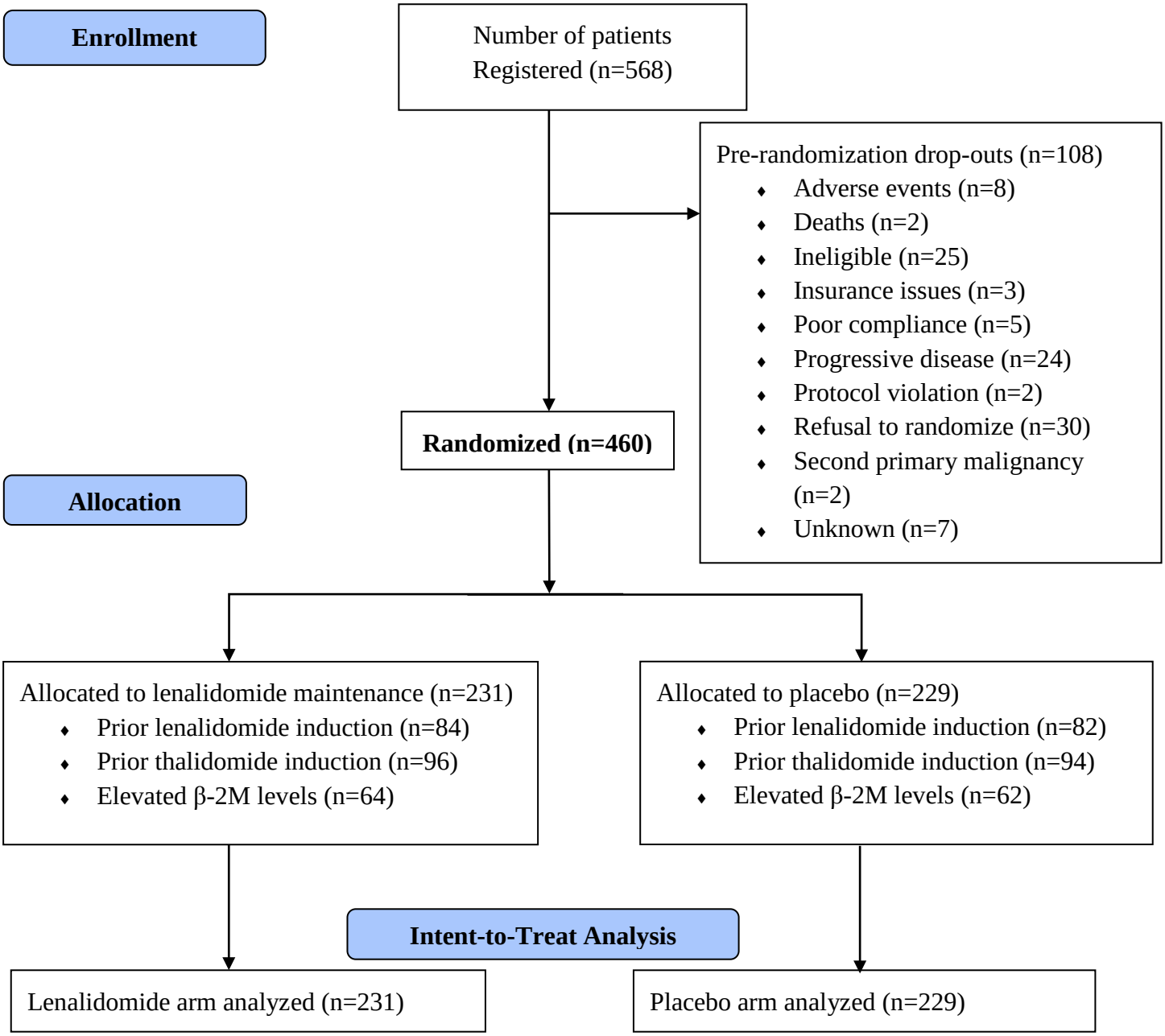
In addition to the two interim analyses presented to the DSMB, analyses for three abstracts and meeting presentations and the final analysis presented in this paper have been conducted. One abstract for meeting presentation consisted of demographic information without time to progression/overall survival analysis. While the progressive disease and second primary malignancy events are subject to interval censoring, in the analyses, they have been right censored to the date of clinical assessment. The statistical analyses are carried out using the R statistical environment (version 2.13.2) along with the survival (version 2.36-9) and cmprsk (version 2.2-2) extension packages.

CALGB Central Office Protocol Auditing and Compliance

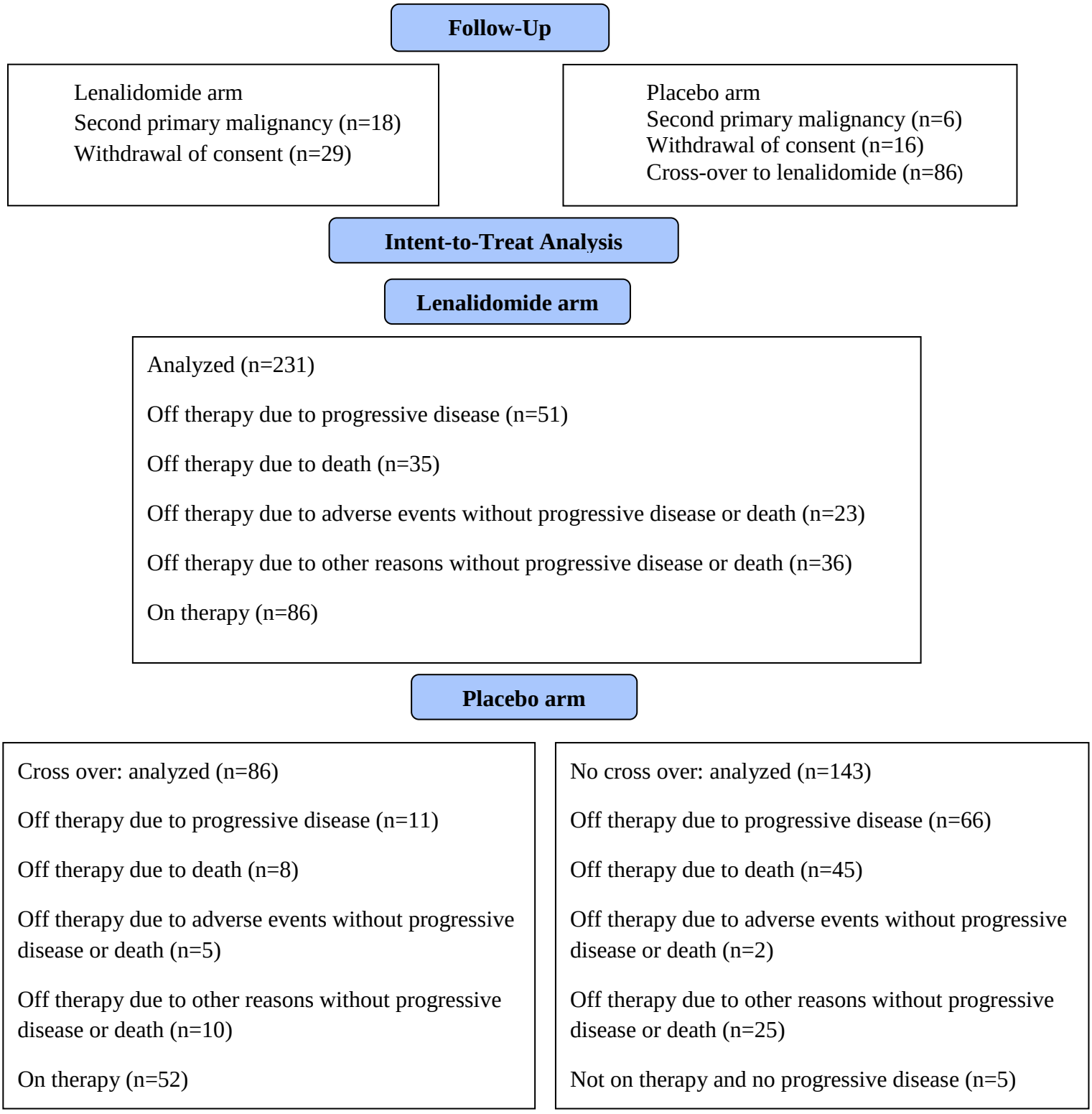
As part of the CALGB quality assurance program, Audit Committee members visit all participating institutions at least once every three years to review source documents. Auditors verify compliance with

federal regulations and protocol requirements, including eligibility, treatment, AEs, response, and outcome in a sample of protocols at each institution. On-site review of medical records was performed for a subgroup of 38 (7%) of the 568 patients in this study.

S1a: CALGB 100104 CONSORT Flow Diagram

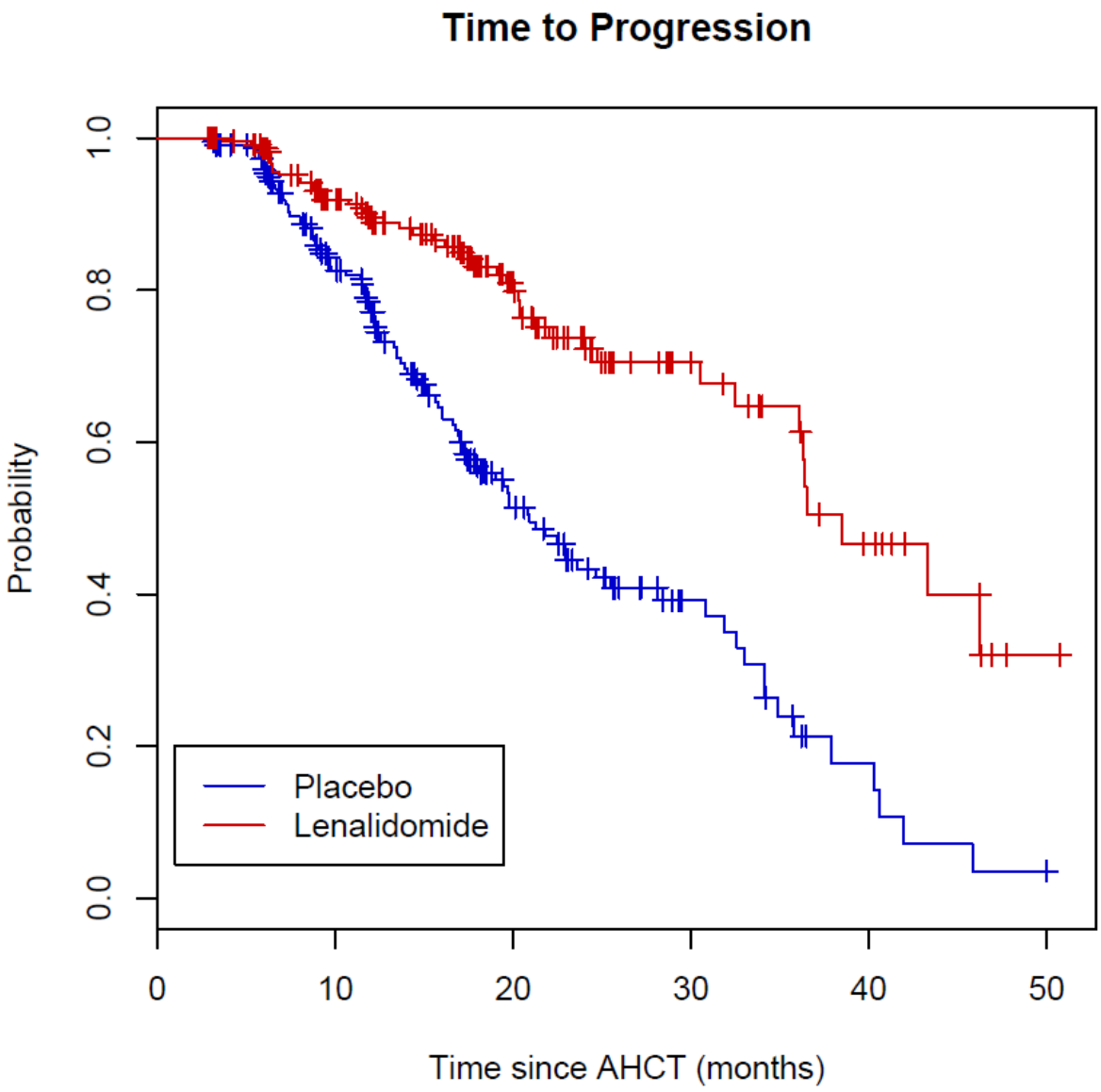


S1b: CALGB 100104 CONSORT Flow Diagram



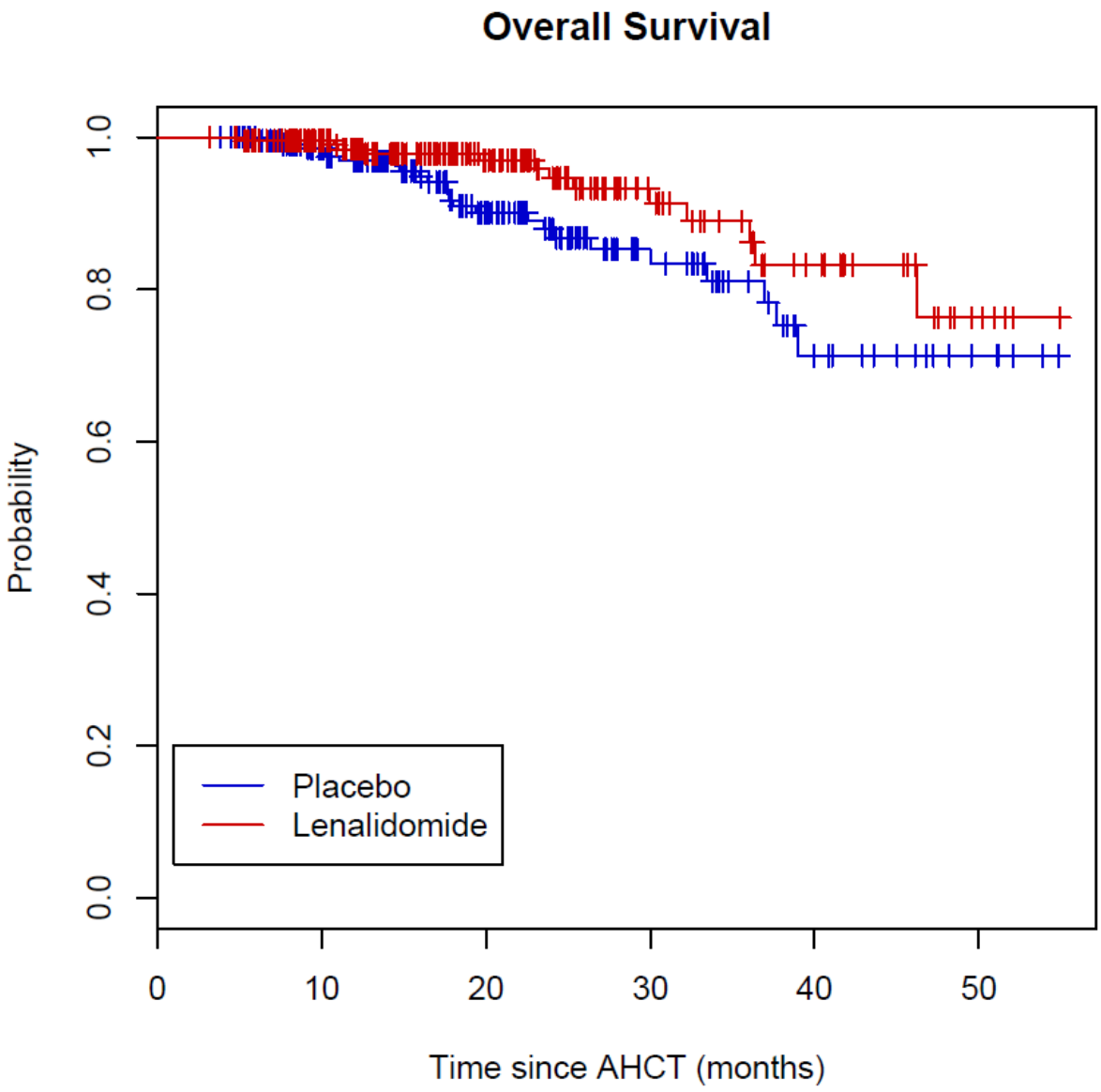
The lenalidomide and thalidomide stratification numbers in the Consort flow diagram reflect the stratification as reported by the centers at registration whereas the numbers reported in Table 1 are based on the information abstracted from the data report forms.

S2a: Time to Progression at Study Un-blinding (December 2009)



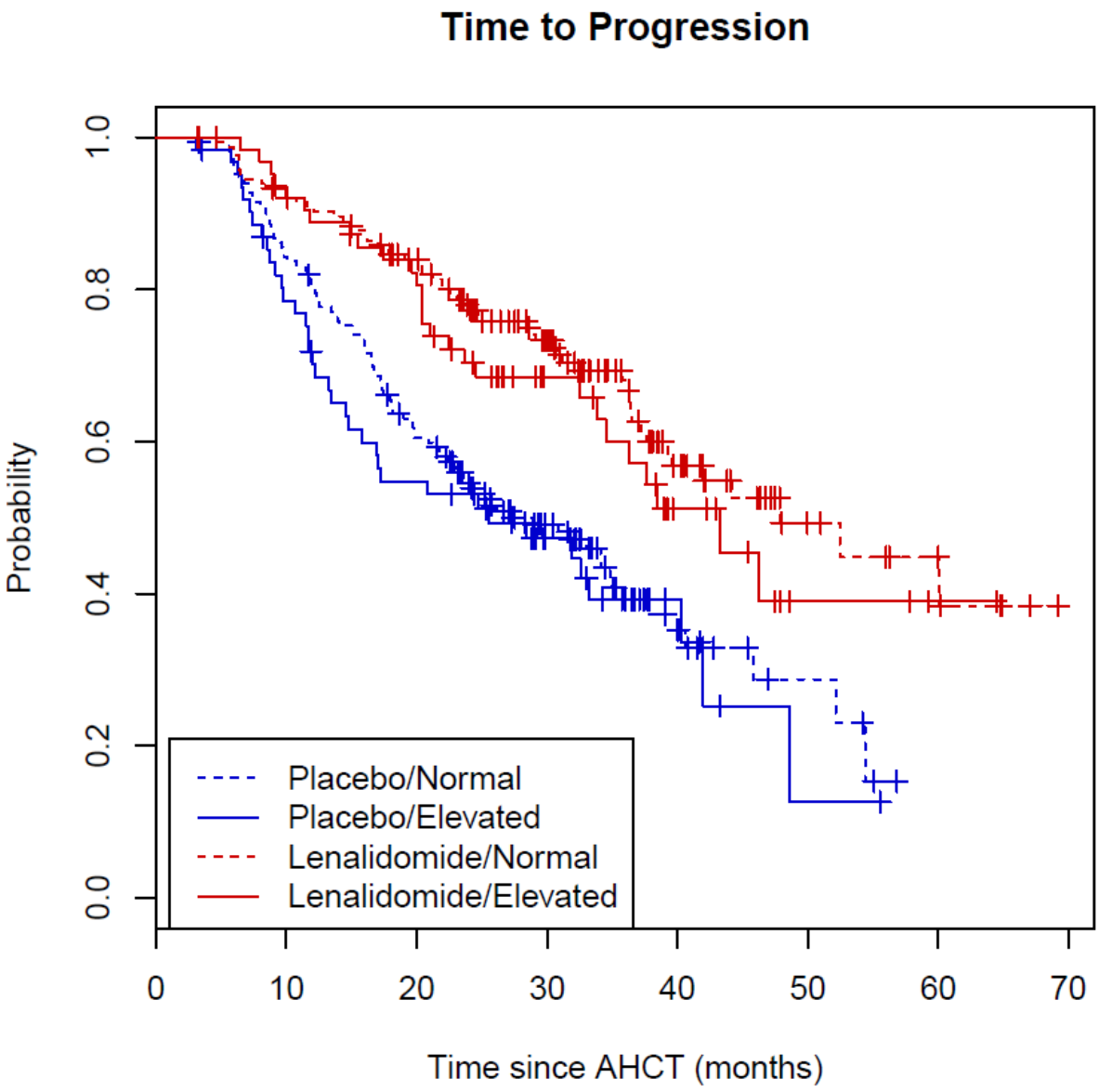
AHCT: Autologous Hematopoietic Cell Transplant; (Two sided p<0.001)

S2b: Overall Survival at Study Un-Blinding (December 2009)



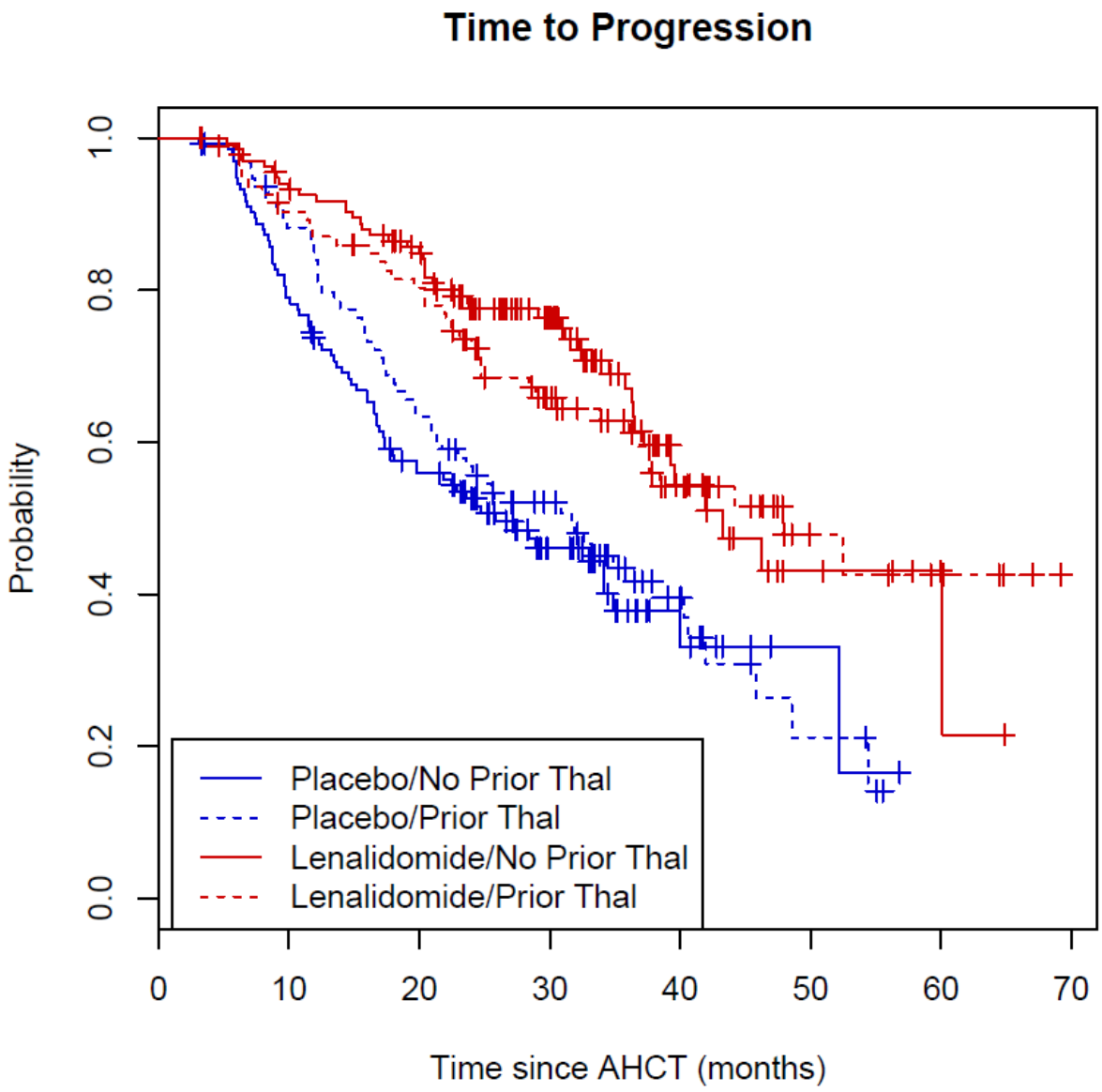
AHCT: Autologous Hematopoietic Cell Transplant (Two sided p<0.053)

S2c: Time to Progression Stratified by High and Normal β-2M at Registration, Later Analysis



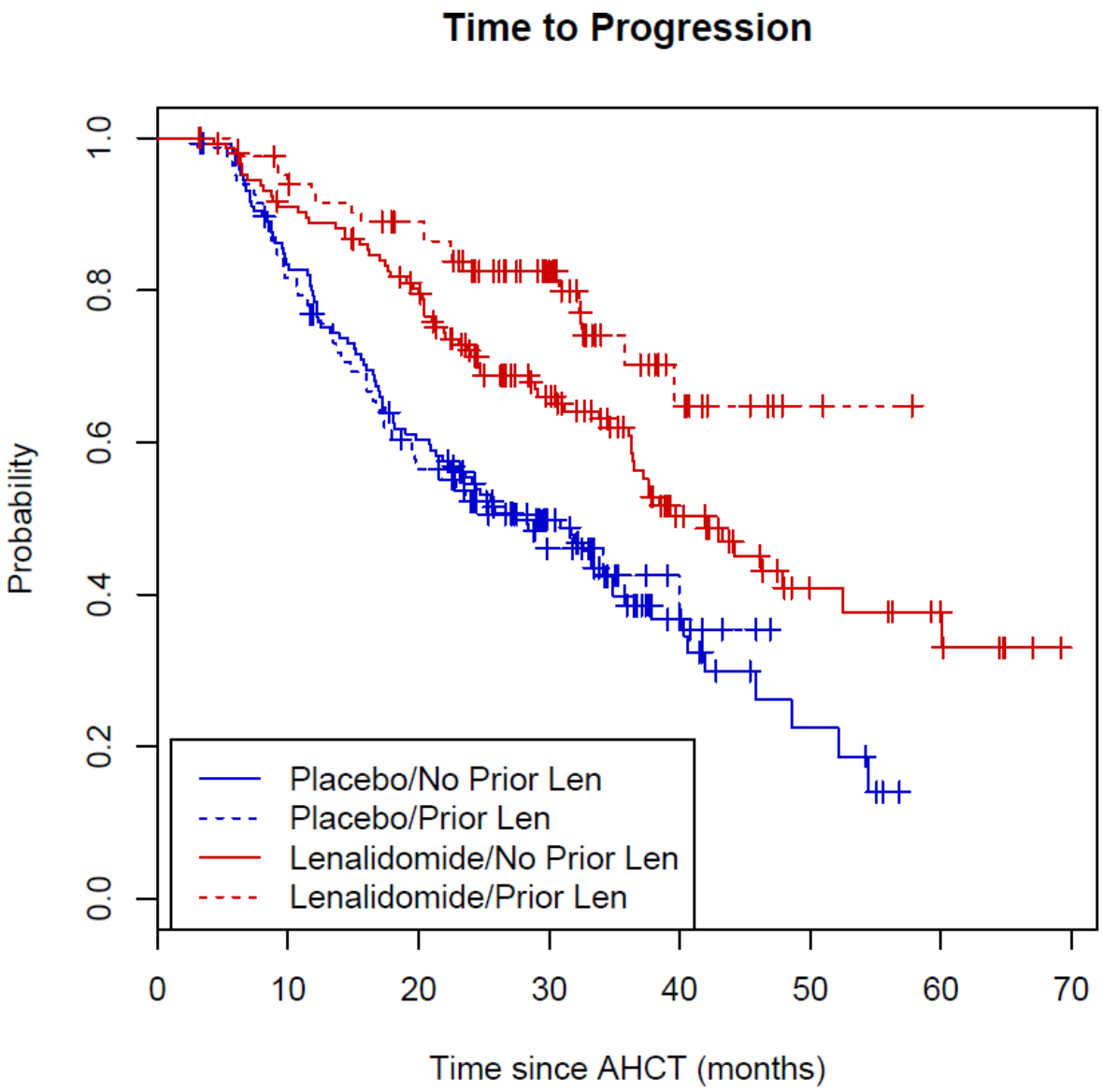
Autologous Hematopoietic Cell Transplant, AHCT; For patients with a normal β-2M level, the median time to progression is 48 months for lenalidomide and 27 months for placebo arm patients. For patients with an elevated β-2M level, the corresponding medians are 43 and 26 months respectively.

S2d: Time to progression stratified by Prior Thalidomide Exposure during Induction, Later Analysis



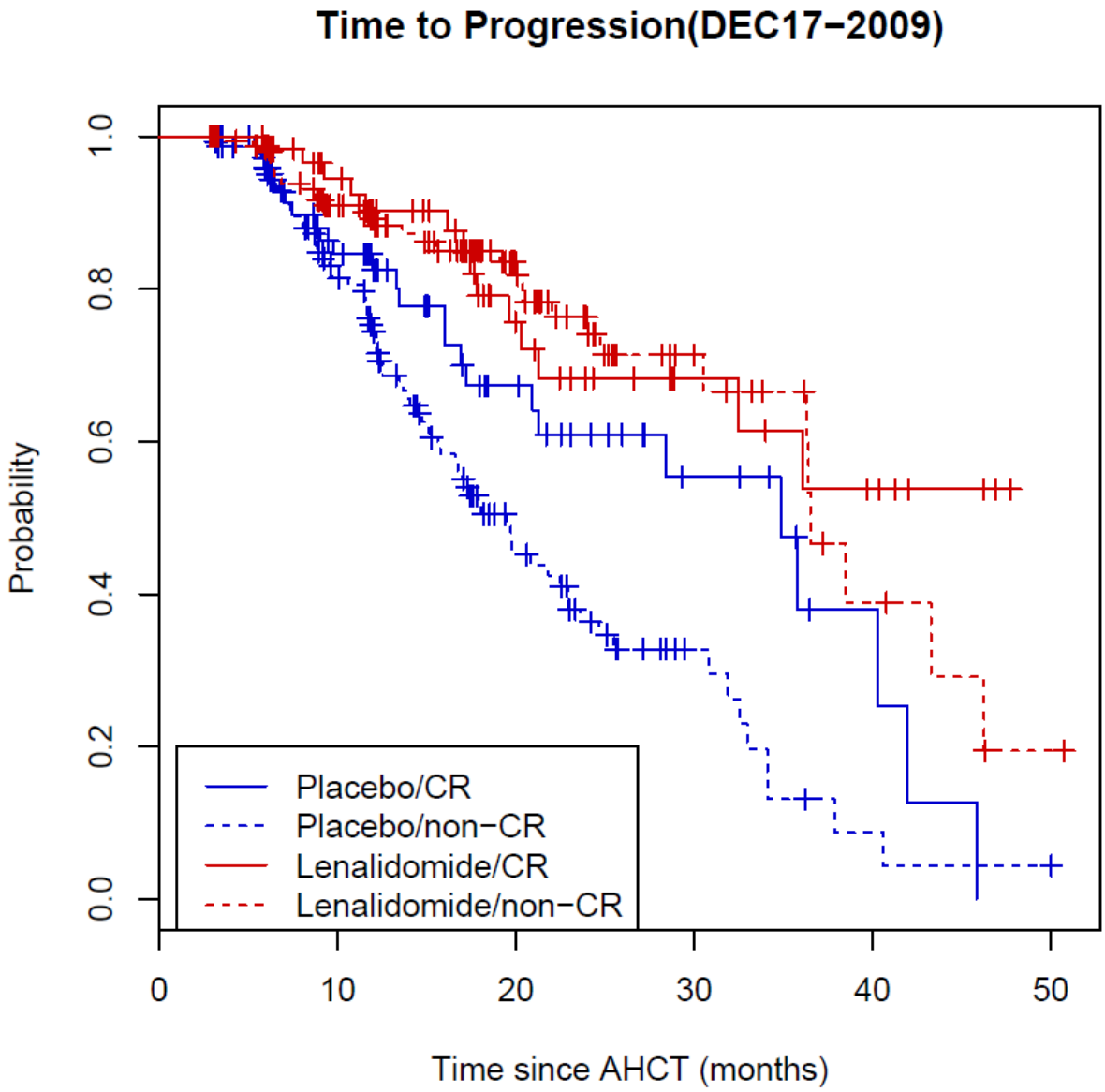
Autologous Hematopoietic Cell Transplant, AHCT; For patients stratified by prior thalidomide induction therapy, the median time to progression is 48 months for lenalidomide and 32 months for placebo arm patients. For patients not receiving prior thalidomide therapy, the corresponding medians are 43 months and 26 months respectively.

S2e: Time to Progression Stratified by Prior Lenalidomide Exposure during Induction, Later Analysis



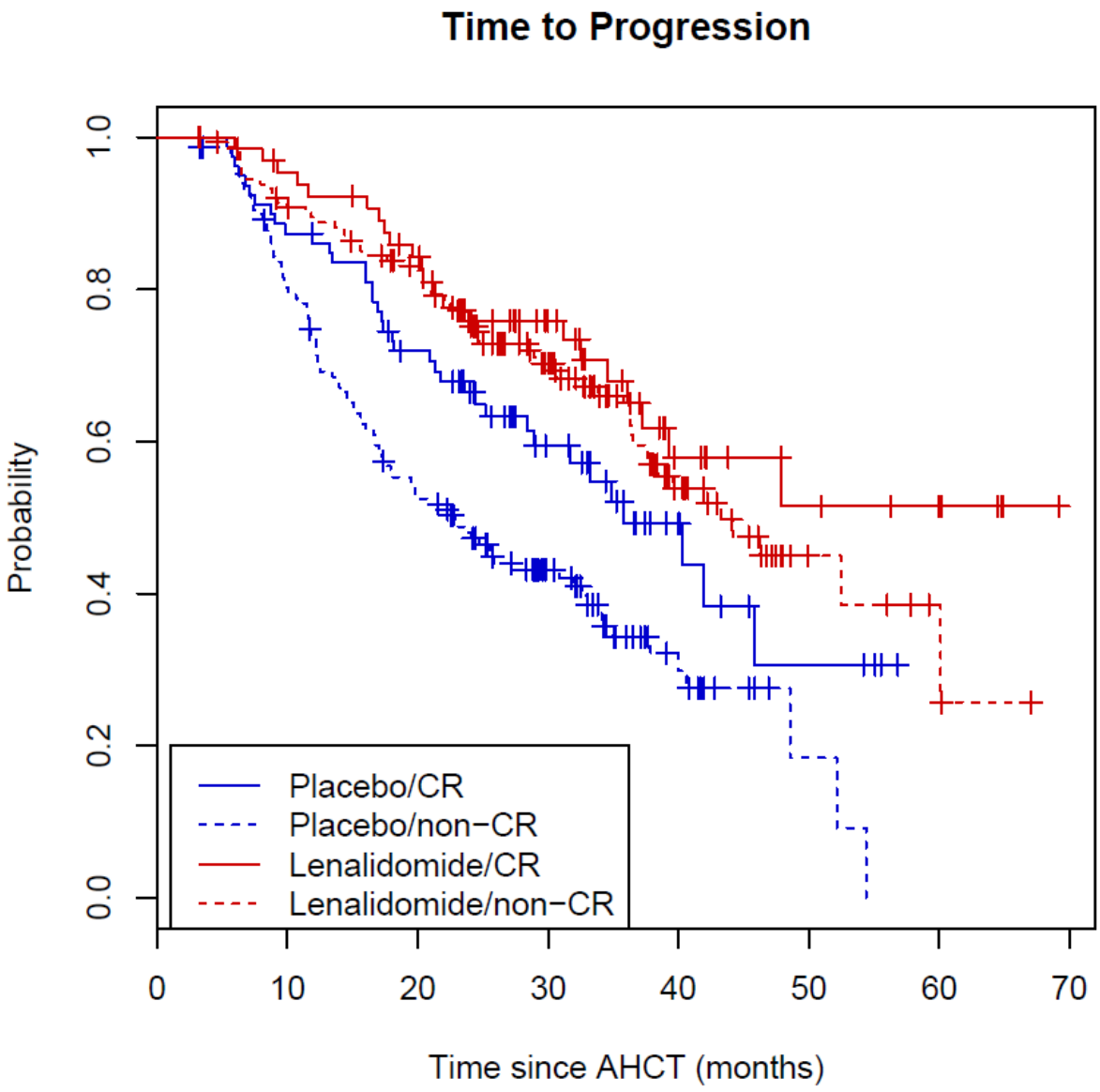
AHCT: Autologous Hematopoietic Cell Transplant; For patients stratified by prior lenalidomide induction therapy, the median time to progression for the lenalidomide arm has not been reached and is 28 months for placebo arm patients. For patients not receiving prior lenalidomide therapy, the corresponding medians are 42 months and 27 months respectively.

S2f: Time to Progression by Response at Randomization at Study Un-Blinding



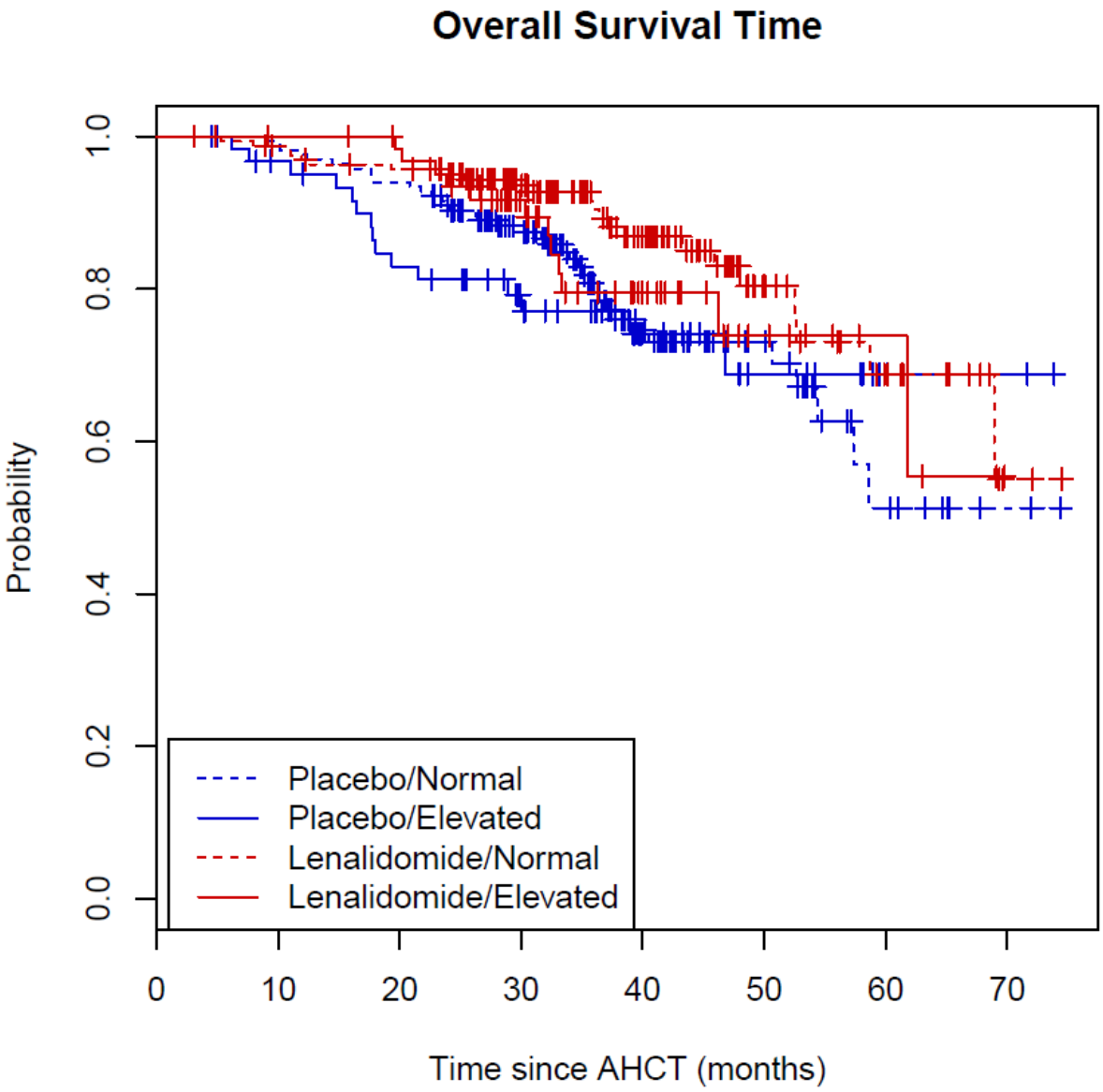
AHCT: Autologous Hematopoietic Cell Transplant; CR; Complete Remission; For patients in CR at study un-blinding, the median time to progression for lenalidomide arm patients had not been reached and for placebo arm patients was 35 months. For patients whose response was less than a CR, the corresponding medians were 37 months and 20 months respectively.

S2g: Time to Progression by Response at Randomization, Later Analysis



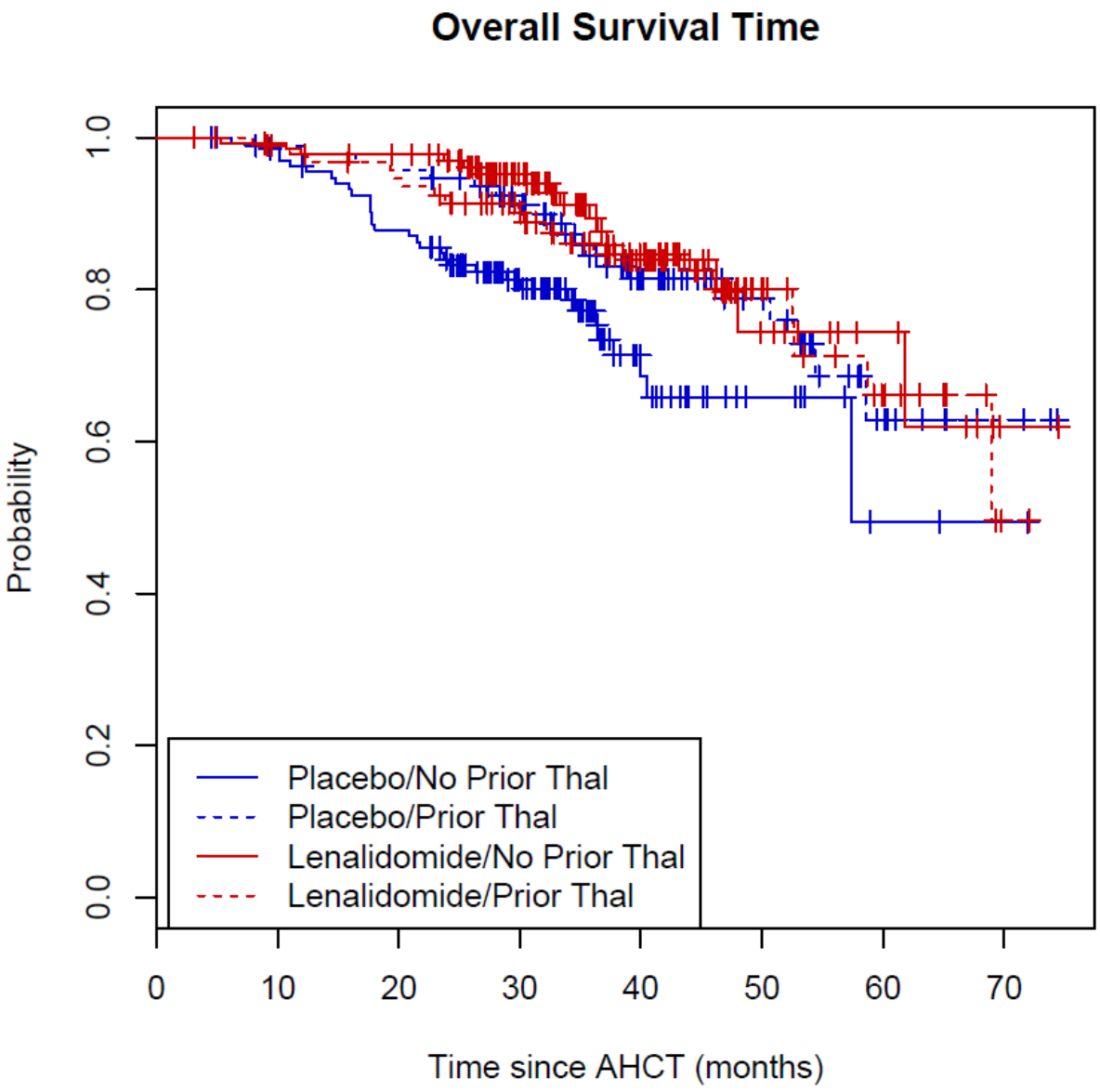
AHCT: Autologous Hematopoietic Cell Transplant; CR; Complete Remission; For patients in CR, the median time to progression for lenalidomide arm patients has not been reached and for the placebo arm patients is 36 months. For patients whose response was less than a CR, the corresponding medians are 43 months and 23 months respectively.

S2h: Overall Survival Stratified by High and Low β-2M at Registration, Later Analysis



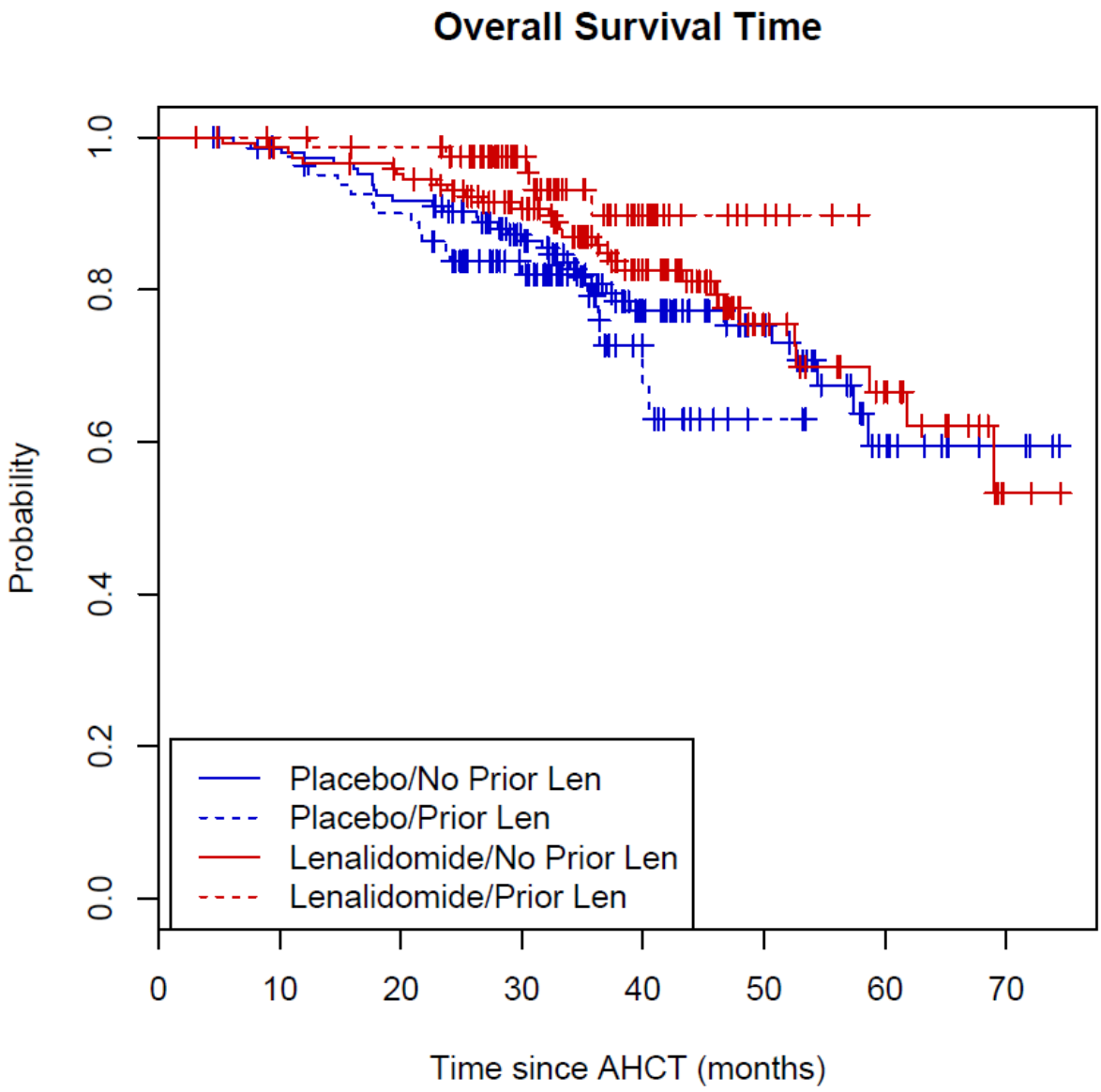
AHCT: Autologous Hematopoietic Cell Transplant. There is no difference in overall survival when stratified by β-2M level and the median overall survival for all arms has not been reached.

S2i: Overall Survival stratified by prior Thalidomide Exposure during Induction, Later Analysis



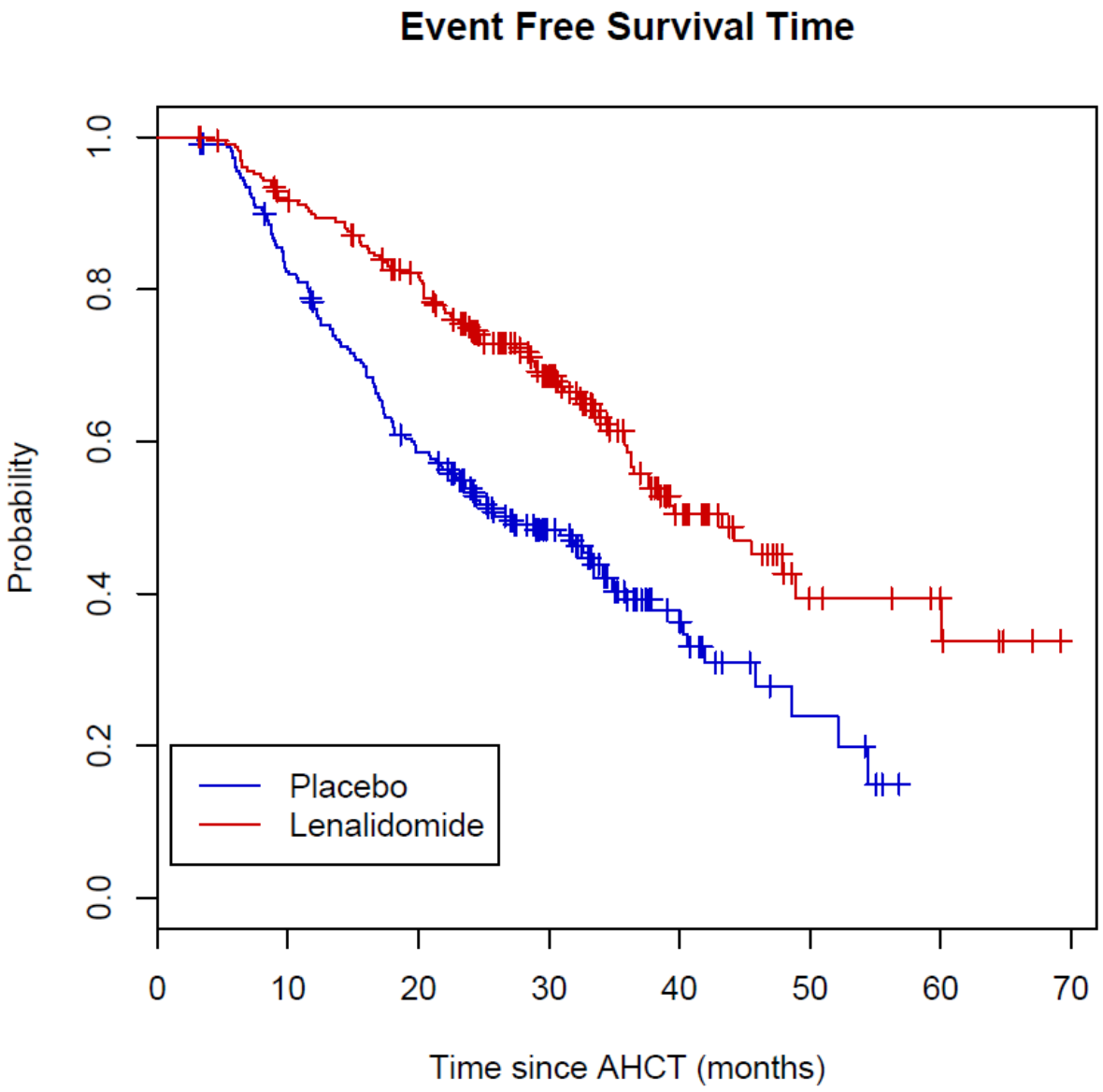
AHCT: Autologous Hematopoietic Cell Transplant. There is no difference in overall survival when stratified by prior thalidomide therapy during induction. The median overall survival for the lenalidomide arm patients with prior thalidomide induction therapy is 69 months and for the patients with no prior thalidomide induction therapy, has not been reached. The median overall survival for the placebo arm patients with prior thalidomide induction therapy has not been reached and for no prior thalidomide induction therapy is 57 months.

S2j: Overall Survival stratified by prior Lenalidomide Exposure during Induction, Later Analysis



AHCT: Autologous Hematopoietic Cell Transplant. The median overall survivals for all stratifications have not been reached. For patients stratified by prior lenalidomide induction and receiving lenalidomide maintenance, 5/84 (6%) have died compared to 19/82 (23%) on the placebo arm. For patients not receiving lenalidomide induction and receiving lenalidomide maintenance, 30/147 (20%) have died compared to 34/147 (23%) on the placebo arm.

S2k: Event Free Survival, Later Analysis



AHCT: Autologous Hematopoietic Cell Transplant; (two-sided p<0.001)

Supplemental Tables

Table S1: Non Hematologic Adverse Events (5 or more per arm) after Randomization. All Grade 5 Adverse Events are listed. The percentages are rounded to the nearest whole number.

Type	**Arm**	**Grade 3**		**Grade 4**		**Grade 5**		**Total**	**P-Value**
		N	***%***	**N**	***%***	*N*	***%***	**N**	
Fatigue	Len	13	*6*	0	*0*	0	*0*	231	0.2526
	Placebo	7	*3*	0	*0*	0	*0*	229	
Febrile Neutropenia	Len	12	*5*	1	*0*	0	*0*	231	0.0192
	Placebo	2	*1*	1	*1*	0	*0*	229	
Infection with Normal ANC or Gr 1/2 neutropenia	Len	12	*5*	0	*0*	1	*0*	231	0.0192
	Placebo	3	*1*	0	*0*	0	*0*	229	
Infection, clinical or microbiological documentation	Len	12	*5*	2	*1*	0	*0*	231	0.1075
	Placebo	6	*3*	0	*0*	0	*0*	229	
Diarrhea	Len	11	*5*	0	*0*	0	*0*	231	0.1125
	Placebo	4	*2*	0	*0*	0	*0*	229	
Rash/desquamation	Len	9	*4*	0	*0*	0	*0*	231	0.0623
	Placebo	2	*1*	0	*0*	0	*0*	229	
Hypokalemia	Len	5	*2*	0	*0*	0	*0*	231	0.7242
	Placebo	3	*1*	0	*0*	0	*0*	229	
Pain	Len	5	*2*	0	*0*	0	*0*	231	0.7714
	Placebo	7	*3*	0	*0*	0	*0*	229	
Pneumonitis/pulmonary infiltrates	Len	6	*2*	0	*0*	0	*0*	231	0.1222
	Placebo	1	*0*	1	*0*	0	*0*	229	
Cardiac Arrhythmia	Len	1	*0*	0	*0*	0	*0*	231	0.6225
	Placebo	1	*0*	0	*0*	1	*0*	229	
Death not associated with CTCAE term	Len	0	*0*	0	*0*	1	*0*	231	1.00
	Placebo	0	*0*	0	*0*	0	*0*	229	
SUMMARY									
Max Non-Hematologic	**Len**	**73**	***32***	**8**	***3***	**2**	***1***	**231**	**<0.001**
	Placebo	**37**	***16***	**6**	***3***	**1**	***0***	**229**	

The highest grades of Hematologic AE are given at the un-blinding date of Dec, 2009 and patients with multiple AEs are listed once by highest AE Abbreviations: AE: Adverse Events; ANC: Absolute Neutrophil Count; CTCAE: Common Terminology Criteria for Adverse Events; Gr: Grade; Len: Lenalidomide; Max: Maximum. Lenalidomide AE deaths were due to Atypical Meningitis (the patient was off lenalidomide due to second primary malignancy) (n=1); Cardiac (Myocardial infarction) (n=1). The placebo AE death was due to Infection (Influenza) (n=1).

Table S2: All Adverse Events After Randomization

		Grade of Adverse Event						
	ARM	**3**		**4**		**5**		**Total**
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Hematologic Adverse Events								
Blood/Bone Marrow								
Blood/Bone Marrow - Other	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Hemoglobin	A	9	*(4%)*	2	*(1%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Hemolysis (e.g. immune hemolytic anemia)	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Leukocytes (total WBC)	A	24	*(10%)*	3	*(1%)*	0	*(0%)*	231
	B	7	*(3%)*	1	*(0%)*	0	*(0%)*	229
Lymphopenia	A	15	*(6%)*	1	*(0%)*	0	*(0%)*	231
	B	3	*(1%)*	1	*(0%)*	0	*(0%)*	229
Neutrophils/granulocytes (ANC/AGC)	A	74	*(32%)*	30	*(13%)*	0	*(0%)*	231
	B	27	*(12%)*	7	*(3%)*	0	*(0%)*	229
Platelets	A	21	*(9%)*	11	*(5%)*	0	*(0%)*	231
	B	3	*(1%)*	8	*(3%)*	0	*(0%)*	229
SUMMARY								
Maximum Hematologic AE	**A**	**74**	***(32%)***	**36**	***(16%)***	**0**	***(0%)***	**231**
	B	**27**	***(12%)***	**12**	***(5%)***	**0**	***(0%)***	**229**
Non-Hematologic Adverse Events								
Allergy/Immunology								
Allergy/Immunology – Other	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Cardiac Arrhythmia								
Conduction abnormality/atrioventricular	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	1	*(0%)*	229
Cardiac General								
Cardiac ischemia/infarction	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	1	*(0%)*	0	*(0%)*	229
Hypotension	A	0	*(0%)*	1	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Restrictive cardiomyopathy	A	0	*(0%)*	1	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Coagulation								
INR	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229

		Grade of Adverse Event						
	ARM	3		4		5		Total
		n	(%)	n	(%)	n	(%)	
Constitutional Symptoms								
Constitutional Symptoms - Other	A	0	(0%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Fatigue (asthenia, lethargy, malaise)	A	13	(6%)	0	(0%)	0	(0%)	231
	B	7	(3%)	0	(0%)	0	(0%)	229
Fever (in the absence of neutropenia)	A	1	(0%)	0	(0%)	0	(0%)	231
	B	0	(0%)	0	(0%)	0	(0%)	229
Weight loss	A	1	(0%)	0	(0%)	0	(0%)	231
	B	0	(0%)	0	(0%)	0	(0%)	229
Death								
Death not associated with CTCAE term	A	0	(0%)	0	(0%)	1	(0%)	231
	B	0	(0%)	0	(0%)	0	(0%)	229
Dermatology/Skin								
Pruritus/itching	A	1	(0%)	0	(0%)	0	(0%)	231
	B	0	(0%)	0	(0%)	0	(0%)	229
Rash/desquamation	A	9	(4%)	0	(0%)	0	(0%)	231
	B	2	(1%)	0	(0%)	0	(0%)	229
Gastrointestinal								
Anorexia	A	1	(0%)	0	(0%)	0	(0%)	231
	B	0	(0%)	0	(0%)	0	(0%)	229
Dehydration	A	0	(0%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Dental: periodontal disease	A	0	(0%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Diarrhea	A	11	(5%)	0	(0%)	0	(0%)	231
	B	4	(2%)	0	(0%)	0	(0%)	229
Distension/bloating, abdominal	A	0	(0%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Mucositis/stomatitis (functional/symptomatic)	A	1	(0%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Nausea	A	4	(2%)	0	(0%)	0	(0%)	231
	B	0	(0%)	0	(0%)	0	(0%)	229
Obstruction GI	A	0	(0%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Vomiting	A	2	(1%)	0	(0%)	0	(0%)	231
	B	1	(0%)	0	(0%)	0	(0%)	229
Hepatobiliary/Pancreas								

		Grade of Adverse Event						
	ARM	**3**		**4**		**5**		**Total**
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Cholecystitis	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Infection								
Febrile neutropenia (fever of unknown origin)	A	12	*(5%)*	1	*(0%)*	0	*(0%)*	231
	B	2	*(1%)*	1	*(0%)*	0	*(0%)*	229
Infection (documented)	A	12	*(5%)*	2	*(1%)*	0	*(0%)*	231
	B	6	*(3%)*	0	*(0%)*	0	*(0%)*	229
Infection - Other	A	2	*(1%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Infection with normal ANC	A	12	*(5%)*	0	*(0%)*	1	*(0%)*	231
	B	3	*(1%)*	0	*(0%)*	0	*(0%)*	229
Infection with unknown ANC	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Infection without neutropenia	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Opportunistic infection	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Metabolic/Laboratory								
ALT, SGPTs	A	4	*(2%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
AST, SGOT	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Alkaline phosphatase	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Bilirubin (hyperbilirubinemia)	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
CPK (creatine phosphokinase)	A	0	*(0%)*	1	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Creatinine	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	2	*(1%)*	0	*(0%)*	229
GGT (gamma-Glutamyl transpeptidase)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Glucose serum-high (hyperglycemia)	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*	229
Phosphate serum-low (hypophosphatemia)	A	2	*(1%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Potassium serum-high (hyperkalemia)	A	2	*(1%)*	0	*(0%)*	0	*(0%)*	231

		Grade of Adverse Event						
	ARM	**3**		**4**		**5**		**Total**
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Potassium serum-low (hypokalemia)	A	5	*(2%)*	0	*(0%)*	0	*(0%)*	231
	B	3	*(1%)*	0	*(0%)*	0	*(0%)*	229
Sodium serum-low (hyponatremia)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	1	*(0%)*	0	*(0%)*	229
Uric acid serum-high (hyperuricemia)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Neurology								
CNS cerebrovascular ischemia	A	0	*(0%)*	1	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Dizziness	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Mood alteration	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Neurology – Other	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Neuropathy: motor	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Neuropathy: sensory	A	4	*(2%)*	0	*(0%)*	0	*(0%)*	231
	B	3	*(1%)*	0	*(0%)*	0	*(0%)*	229
Syncope (fainting)	A	2	*(1%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Pain								
Pain	A	5	*(2%)*	0	*(0%)*	0	*(0%)*	231
	B	7	*(3%)*	0	*(0%)*	0	*(0%)*	229
Pulmonary/Upper Respiratory								
Cough	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Dyspnea (shortness of breath)	A	1	*(0%)*	2	*(1%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Hypoxia	A	2	*(1%)*	1	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Pneumonitis/pulmonary infiltrates	A	6	*(3%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	1	*(0%)*	0	*(0%)*	229
Renal/Genitourinary								
Renal failure	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229

		Grade of Adverse Event						
	ARM	**3**		**4**		**5**		**Total**
		n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Renal/Genitourinary – Other	A	1	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Secondary Malignancy								
Secondary Malignancy - possibly related to cancer	A	0	*(0%)*	1	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*	229
Vascular								
Thrombosis/embolism (vascular access-related)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*	231
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*	229
Thrombosis/thrombus/embolism	A	3	*(1%)*	0	*(0%)*	0	*(0%)*	231
	B	0	*(0%)*	1	*(0%)*	0	*(0%)*	229
SUMMARY								
Maximum Non-Hematologic AE	**A**	**73**	***(32%)***	**8**	***(3%)***	**2**	***(1%)***	**231**
	B	**37**	***(16%)***	**6**	***(3%)***	**1**	***(0%)***	**229**
SUMMARY								
Maximum Overall AE	**A**	**94**	***(41%)***	**42**	***(18%)***	**2**	***(1%)***	**231**
	B	**53**	***(23%)***	**15**	***(7%)***	**1**	***(0%)***	**229**

The highest grades of Hematologic AE are given as of February 2012 and patients with multiple AEs are listed once by highest AE Abbreviations: Grade 3: Severe; Grade 4: Life-Threatening; Grade 5: Lethal. A= Lenalidomide, B= Placebo; ANC/AGC: Absolute Neutrophil Count/Absolute Granulocyte Count; CTCAE: Common Terminology Criteria for Adverse Events; INR: International Normalized Ratio of prothrombin; SGPT serum glutamic pyruvic transaminase; SGOT serum glutamic oxaloacetic transaminase.

Supplemental Statistical Consideration References

1. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975, 36: 842–54.
2. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412-20. Erratum, J Clin Oncol. 2005;23:6281]
3. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115-23.
4. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.
5. Emerson SS, Fleming TR. Symmetric group sequential designs. Biometrics, 1989. 45: 905-23.
6. Emerson SS. S+SEQTRIAL Technical Overview. Insightful Corporation (2002).
7. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 1958;53:457-81.
8. Cox DR, Oakes D. Analysis of Survival Data: Chapman & Hall; 1984.
9. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data: Wiley Series in Probability and Statistics; 2002:248-66.
10. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics 1988;16:1141-54.
11. Fisher RA. The logic of inductive inference. Journal of the Royal Statistical Society 1935;98:39-54.