

CALGB 100104

A Phase III Randomized, Double-Blind Study of Maintenance Therapy With Lenalidomide (CC 5013) or Placebo Following Autologous Stem Cell Transplantation for Multiple Myeloma

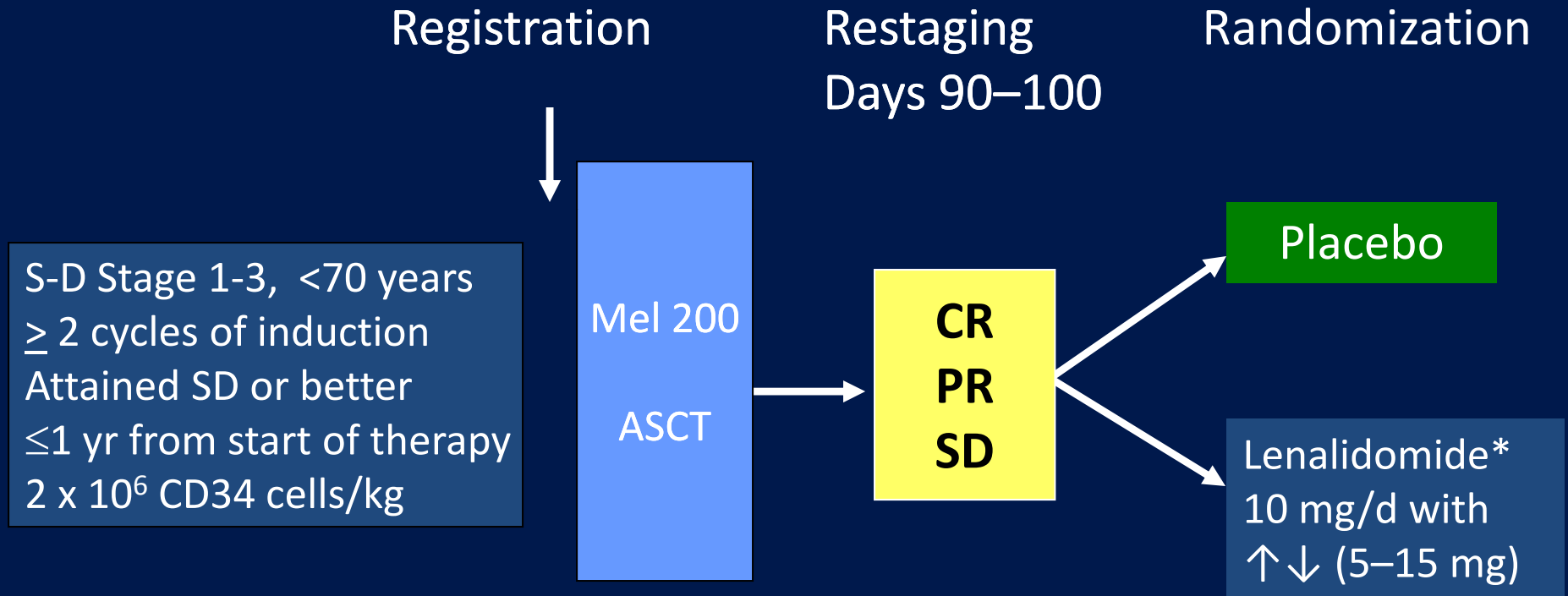


Philip McCarthy, Roswell Park Cancer Institute, representing CALGB, ECOG and BMT CTN

Why Maintenance Therapy?

- Induction therapy followed by autologous stem cell transplant (ASCT) alone will cytoreduce but not cure most Multiple Myeloma patients
- Can maintenance therapy:
 - prevent or delay disease progression?
 - convert partial responses to complete responses?
 - improve overall survival?

CALGB 100104 Schema



*Revlimid® Celgene Corp, Summit, NJ

Stratification based on diagnostic β -2M and thalidomide and lenalidomide use during Induction

Objectives

- **Primary Objective:**

- Determine the efficacy of lenalidomide in prolonging time to progression (TTP) in myeloma patients following ASCT
- Powered to determine a TTP improvement prolongation from 24 months to 33.6 months (9.6 months)

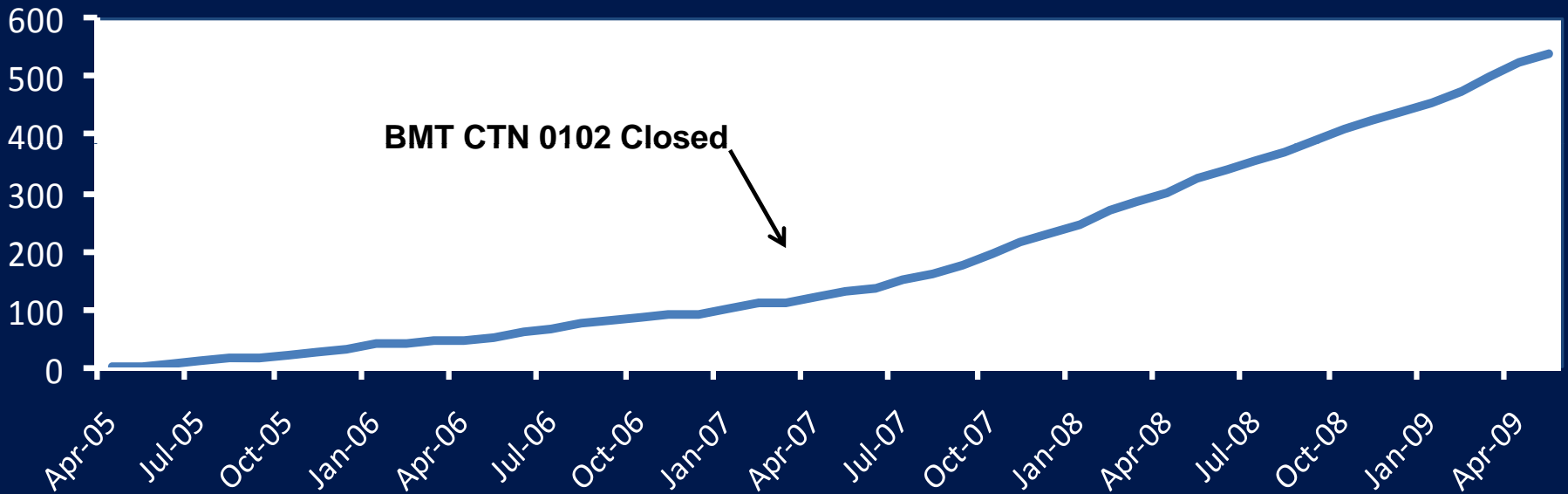
- **Secondary Objectives:**

- CR rate post-ASCT
- PFS and OS
- Feasibility of long-term lenalidomide administration

Accrual

- Target Accrual: Register 538 with a goal of 462 randomized based on 10% drop out rate
- First enrollment in April of 2005
- Accrual increased after BMT CTN 0102 closed in 2007
 - CALGB: n=376; ECOG : n=133; BMT CTN: n=59
- Closed in July of 2009: 568 registered pts from 46 Centers
- Drop out rate before randomization is ~15%
- Patients continued on therapy until progression
- The CALGB DSMB Report in November of 2009 analyzed outcomes for 418 pts: 210 randomized to lenalidomide and 208 to placebo
- The DSMB report results were released in December of 2009

Monthly Accrual



Adverse Events during maintenance for 368 of 418 randomized patients

Max Adv Events	3- Severe		4- Life Threat		5-Lethal		Total
	n	%	n	%	n	%	
Hematologic							
Lenalidomide	61	31	26	13	0	0	194
Placebo	8	5	8	5	0	0	174
Non Hematologic							
Lenalidomide	60	31	6	3	3	2	194
Placebo	33	19	5	3	3	2	174

Hematologic events: $p=0.0001$

Non-hematologic events: $p=0.0096$

Grade 3-5 Adverse Events during maintenance for 368 of 418 randomized patients

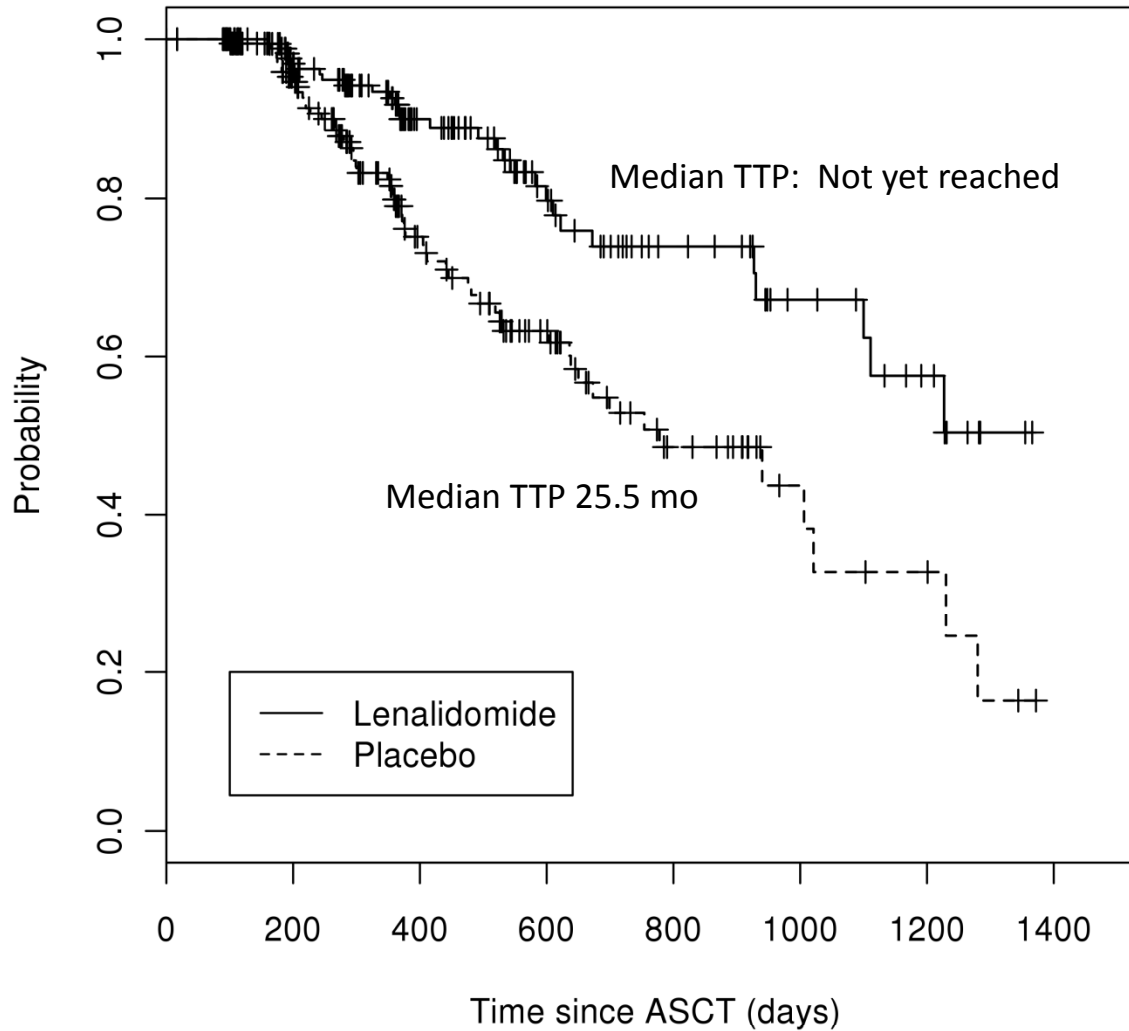
	Lenalidomide n=194		Placebo n=174		P-Value
	N	%	N	%	
Thrombocytopenia	23	12	6	3	=0.01
Neutropenia	83	42	13	7	<0.0001
Anemia	10	6	1	1	=0.0028
Fatigue	11	6	5	3	=0.19
Rash	9	5	3	2	=0.12
Diarrhea	8	4	5	3	=0.52
Febrile neutropenia	11	6	3	2	=0.48
Documented Infection	13	7	3	2	=0.03

13% (28 of 210) on Lenalidomide and 2% on placebo (4 of 208) came off therapy due to AEs and 12% (26 of 210) on Lenalidomide and 7% (14 of 208) on placebo came off therapy for other reasons

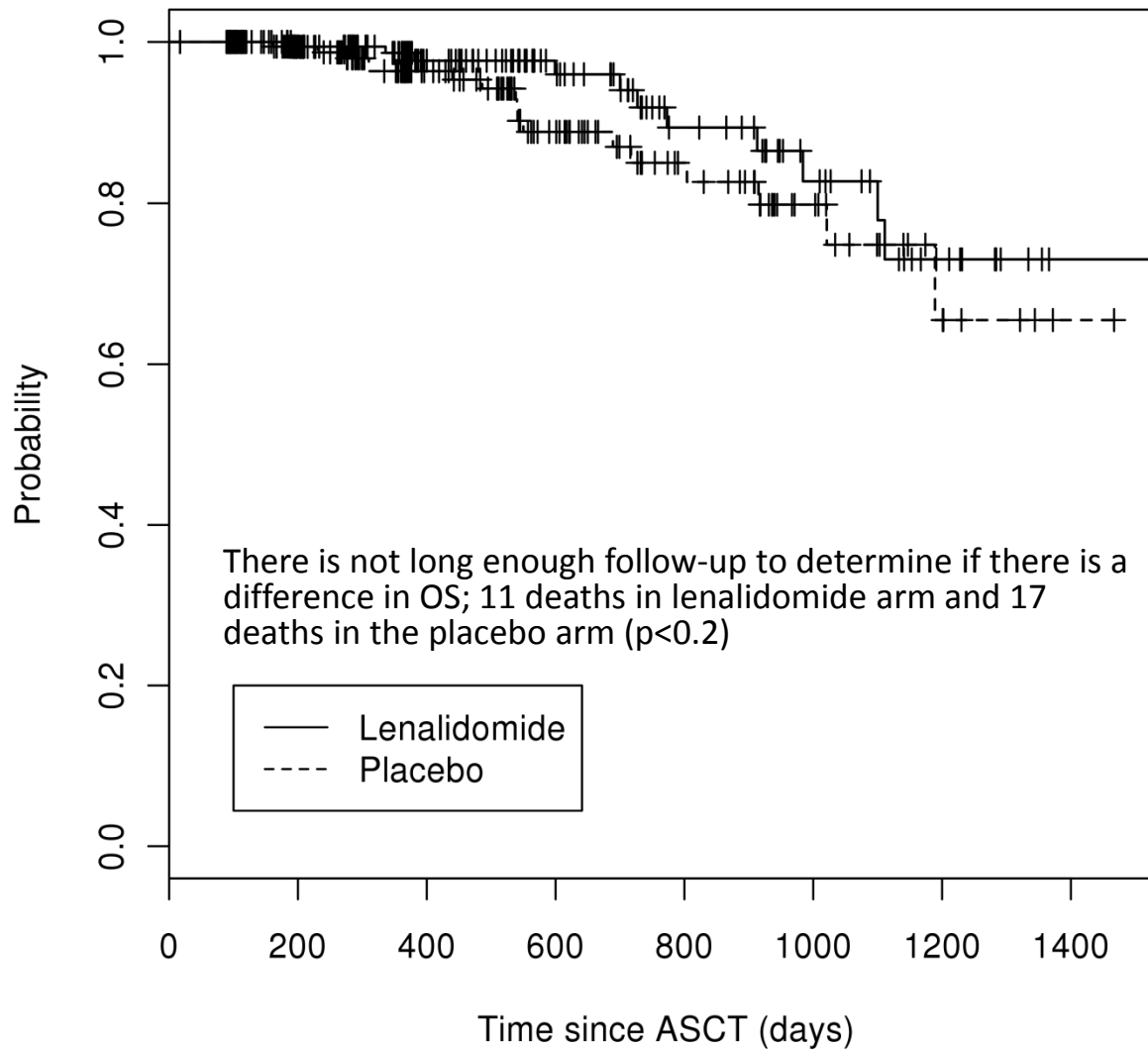
Results

- TTP was defined as disease progression or death due to any cause
- TTP was calculated from day 0 of ASCT
- Of 210 lenalidomide pts, 29 have experienced an event (progression or death)
- Of 208 placebo pts, 58 have experienced an event ($p < 0.0001$)
- Estimated hazard ratio of 0.42, thus a 58% reduction in the risk of disease progression with lenalidomide

Time to Progression



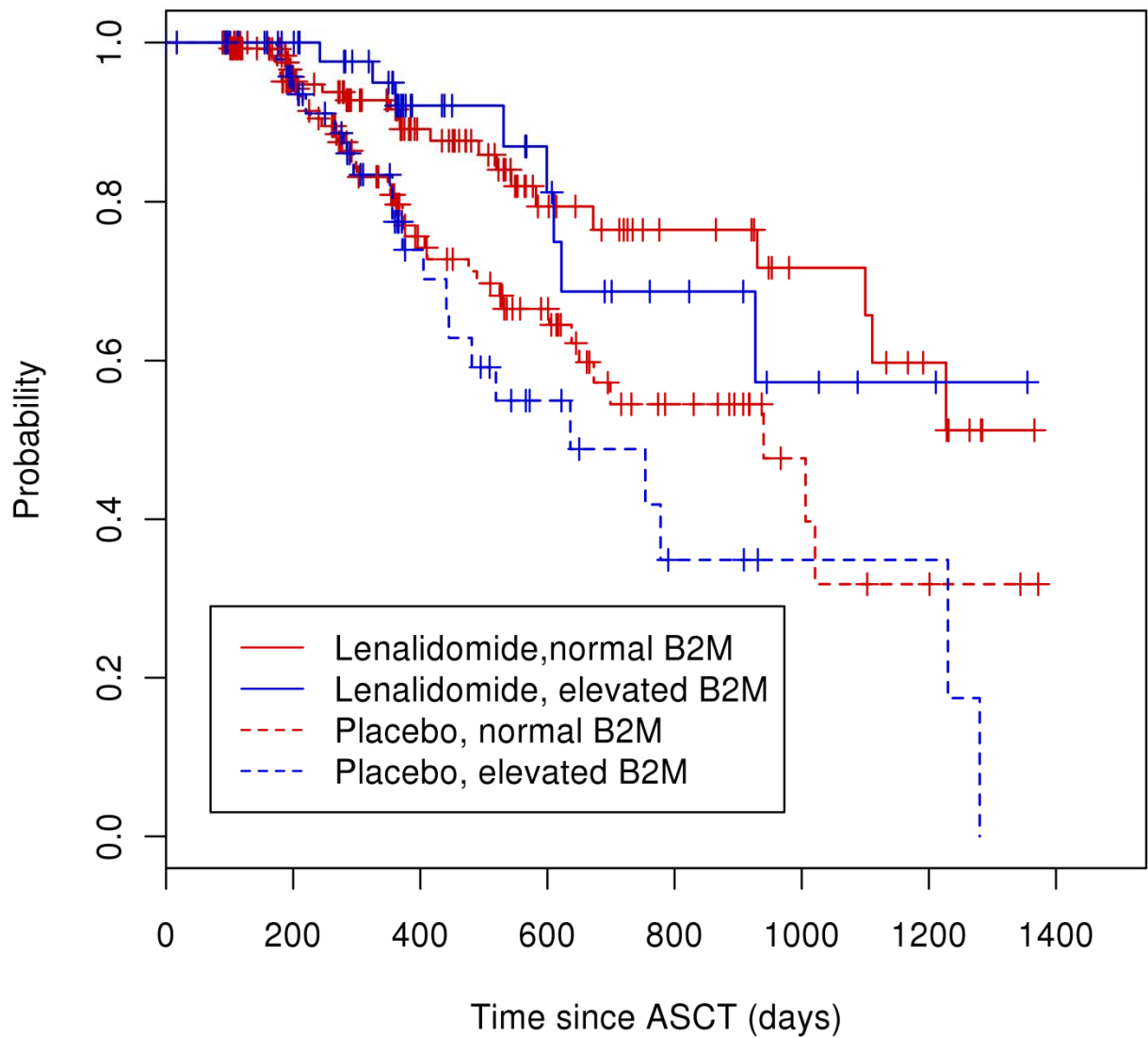
Overall Survival



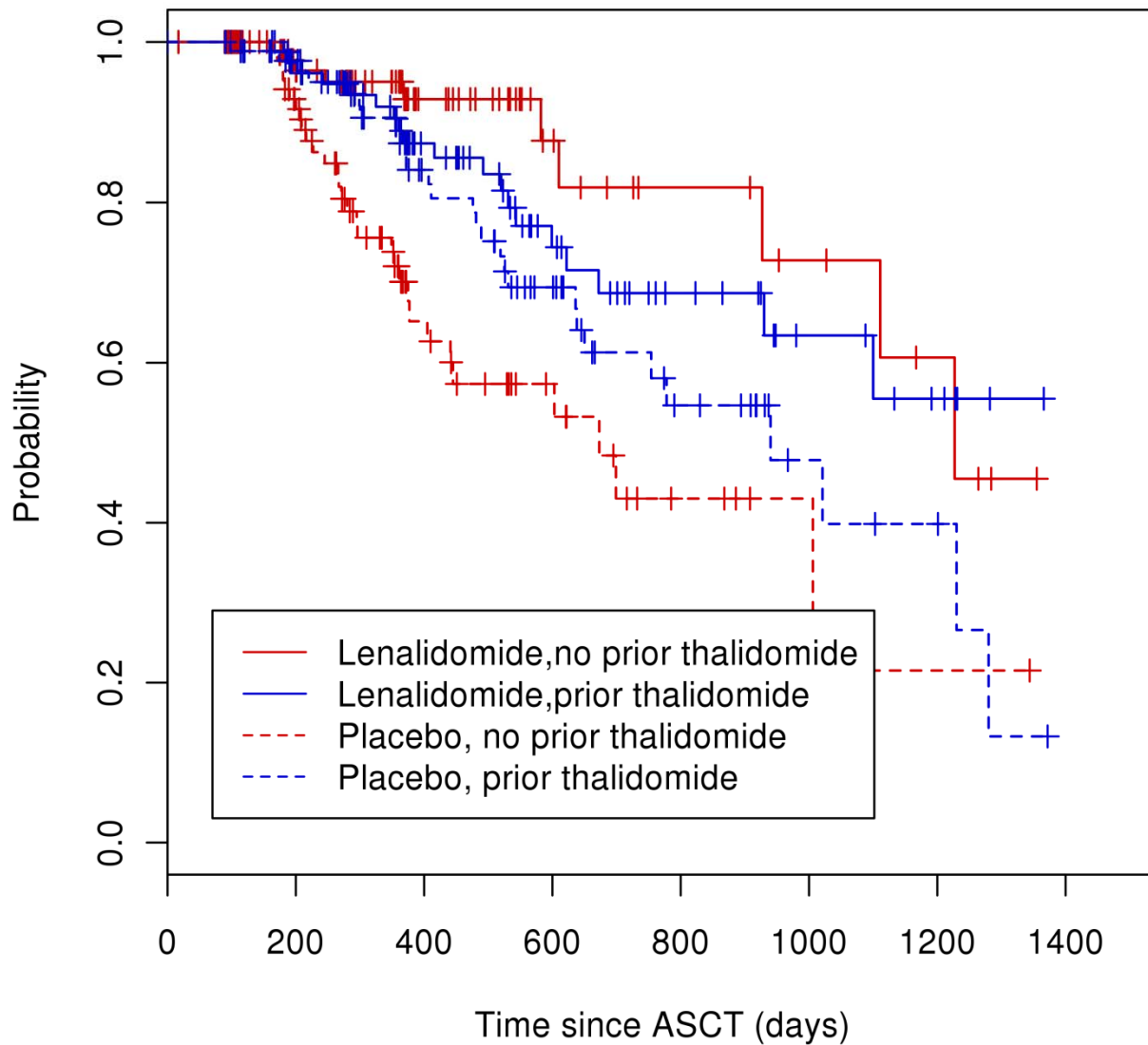
Results

- 28% of the 309 targeted events have occurred
- Stratification by Beta-2 microglobulin and previous thalidomide or lenalidomide exposure during induction demonstrated a benefit between lenalidomide over placebo in each stratification
- The study was un-blinded in December 2009 allowing patients (with physician support) to cross over to open-label lenalidomide
- 77 of 89 eligible placebo patients have started lenalidomide therapy

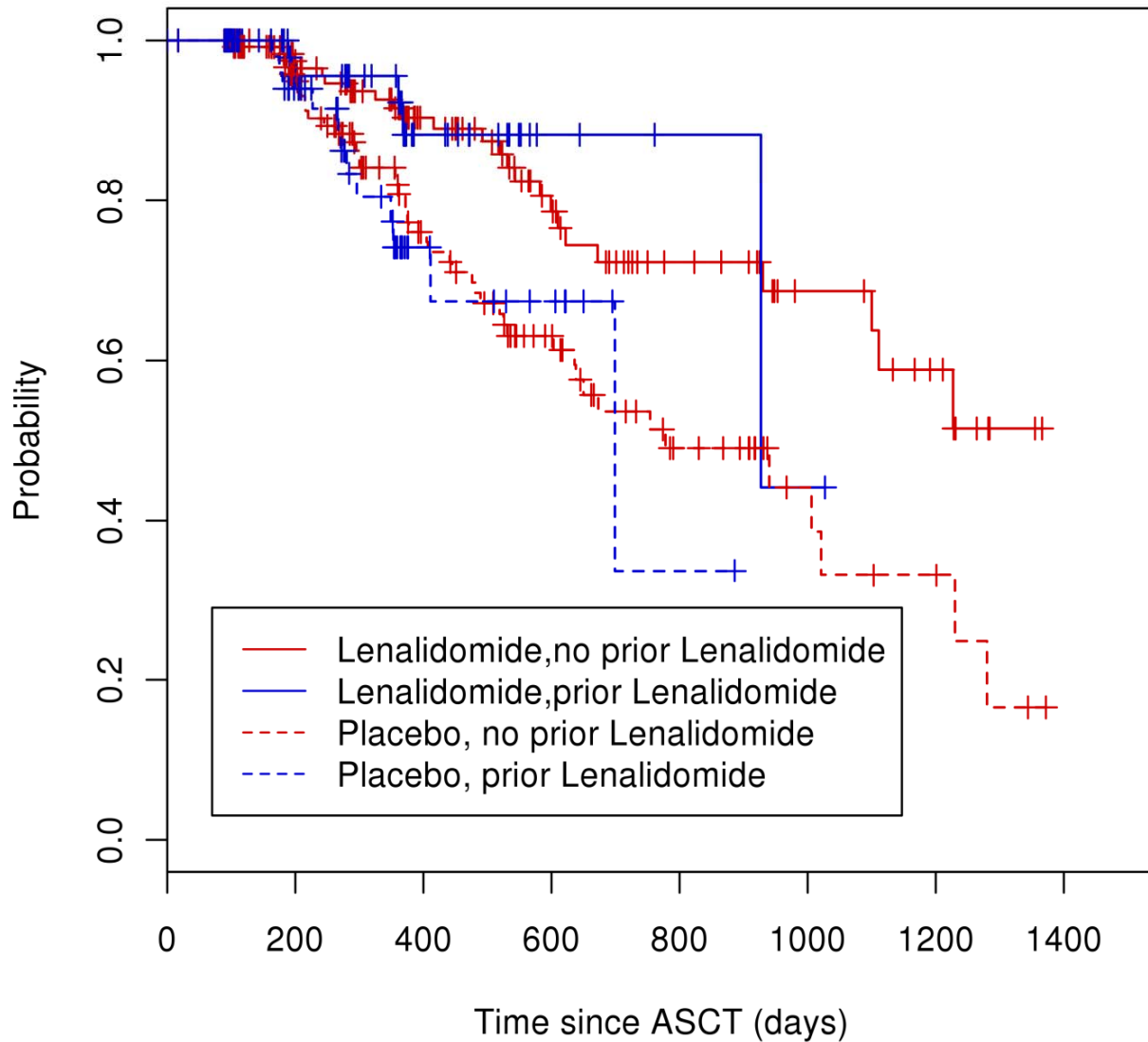
TTP Stratified by Arm and Beta2 Microglobulin elevation



TTP Stratified by Arm and Prior Thalidomide



TTP Stratified by Arm and Prior Lenalidomide



Conclusions

- Maintenance therapy with lenalidomide when compared to placebo will significantly prolong time to disease progression
- Currently, there is no difference in OS at a median follow-up of 1 year post-ASCT
- Lenalidomide prolonged TTP within patient stratification by high and low β 2M, and prior thalidomide or lenalidomide induction therapy
- Lenalidomide maintenance produced some hematologic toxicity, but this was not severe with dropouts due to all AEs at 13%

Participating Centers

- CALGB: Dana Farber Cancer Inst, Illinois Onc Res Assoc, Memorial Sloan Kettering Cancer Ctr, Mt Sinai School of Med, North Shore Univ Hosp, Roswell Park Cancer Inst, State Univ NY, Upstate Med Univ, Ohio State Univ Med Ctr, Univ California San Diego, Univ California San Francisco, Univ Chicago, Univ Illinois Chicago, Univ Minnesota, Univ Nebraska, Univ North Carolina Chapel Hill, BMT Group Georgia, Virginia Commonwealth Univ, Univ of Vermont, Wake Forest Univ School Medicine, Walter Reed Army Med Ctr, Washington Univ School Medicine, Weill Med College Cornell Univ, Western Pennsylvania Hosp
- ECOG: Cancer Inst of New Jersey, Case Western Metro Health Med Ctr, Columbia Presbyterian, St Lukes Hsp, Univ of Florida Gainesville, Fox Chase Cancer Ctr, Geisinger Med Ctr, Indiana Univ Medical Ctr, Jewish Hospital, Marshfield Clinic, Med College Georgia, Univ Miami, Univ Pennsylvania, Univ Pittsburgh, Scottsdale, Univ Hospital Cleveland, Vanderbilt Univ, Med College of Wisconsin, Univ of Wisconsin
- BMT-CTN: City of Hope, LDS Hosp, MD Anderson, Oregon Health Sciences Univ, Univ of Mississippi Med Ctr

CALGB 100104 Cooperative Effort

CALGB: C Linker, K Anderson, K Owzar, R Larson, R Schilsky, M Bertagnolli, V Hars, M Kelly, M Seiler, L Bressler, J Postiglione, S Sutherland, C Hofmeister, H Hassoun, D Hurd, P Richardson, D Weisdorf, R Vij, T Gentile, K van Besien, T Shea, A Bashey, L Isola, S Devine

ECOG: E Stadtmauer, J Wingard, N Callandar

BMT-CTN: S Giralt, M Horowitz, M Pasquini, J Ferrara, J Antin, R Maziarz, A Krishnan, G Somlo, S Carter, N Poland, A Foley, C Gurgol

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Ongoing Statistical Center Analyses

- Evaluating other induction regimens (Bortezomib, other agents)
- Evaluating Detailed AEs
 - relationship to lenalidomide or placebo dose
- Response data
 - prior to ASCT, at randomization, following maintenance
- Ability to Continue Therapy
- Dose modification
- Other patient risk factors e.g. cytogenetics, LDH
- Therapy after progression
- Long term Follow-up

Induction Regimens: Preliminary Results

Regimen	N	%
Thalidomide-based (No Bortez or Len)	152	27
Lenalidomide-based (No Bortez or Thal)	122	22
Bortezomib-based (No Len or Thal)	109	20
Bortezomib+Thalidomide-based (No Len)	68	12
Bortezomib+Dex+Lenalidomide (No Thal)	52	9
Dexamethasone-based (No Bortez, Len or Thal)	23	4
Thalidomide and Lenalidomide treatment	17	3
Bortezomib, Lenalidomide and Thalidomide treatment	3	1
Other	2	1
Missing	6	1
Total	554	100