Supplemental Text

Supplemental Statistical Methods

If an early stopping rule (ending accrual if 7 of the first 18 patients have grade 4 toxicity) was not invoked, then observing 0 to 7 patients of 45 with grade 4 non-hematologic toxicity would be considered acceptable. This was because an exact two-sided 90% confidence interval on 8/45 is 10.6% to 27.0%, which would thus include 25% and exceed 10%, while up to 7/45 was allowable. Since 21 of the 46 total patients at 25 mg required dose reductions (including 3 from the dose escalation portion), the protocol was amended to use a Simon two-stage min-max design based on clinical response. This amendment allowed enrollment of up to 14 additional patients at a lower dose of lenalidomide (15 mg).

Time to progression (TTP) was determined from the on-study date until the date of progression or last follow-up without progression, while survival was determined from on-study date until the date of death or last follow-up. Patients who did not progress but were removed from treatment for adverse effects, preference, and other reasons had follow-up for TTP censored at that time. The probability of TTP or survival as a function of time was determined by the Kaplan-Meier method. The statistical difference between a pair of Kaplan-Meier curves, or among a set of Kaplan-Meier curves, was determined by the log-rank test. For analyses involving outcomes according to genotype, when data were combined into groups after examining their association with survival or TTP, the subsequent p-values were adjusted by multiplying the unadjusted p-value by two or three as needed to account for the implicit number of tests performed to arrive at the categories identified. The Cox proportional hazards model was used to determine the joint significance of factors associated with TTP or survival.

National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used to assess adverse events. Patients had physical examinations, toxicities and laboratory assessments including PSA at each 3 week visit and weekly complete blood counts (CBCs). Patients had restaging radiographic imaging, consisting of computed tomography (CT) scan and Technetium-99 bone, at 6 weeks and then at 9 week intervals.

Treatment Modifications

Docetaxel was withheld for grade 3 or 4 hematologic toxicities or grade 3 non-hematologic toxicities. For febrile neutropenia or grade 4 neutropenia lasting for ≥5 days the dose of docetaxel was reduced by 25% during the subsequent cycles of treatment. Bevacizumab was withheld for 24 hour if urine protein >2 grams and re-introduced during the next treatment cycle if the urine protein was <2 grams. Bevacizumab was discontinued for grade ≥2 arterial thrombosis, grade ≥3 venous thrombosis, grade ≥2 pulmonary hemorrhage, wound dehiscence, and gastrointestinal perforation or fistula. No dose reduction was allowed for bevacizumab.

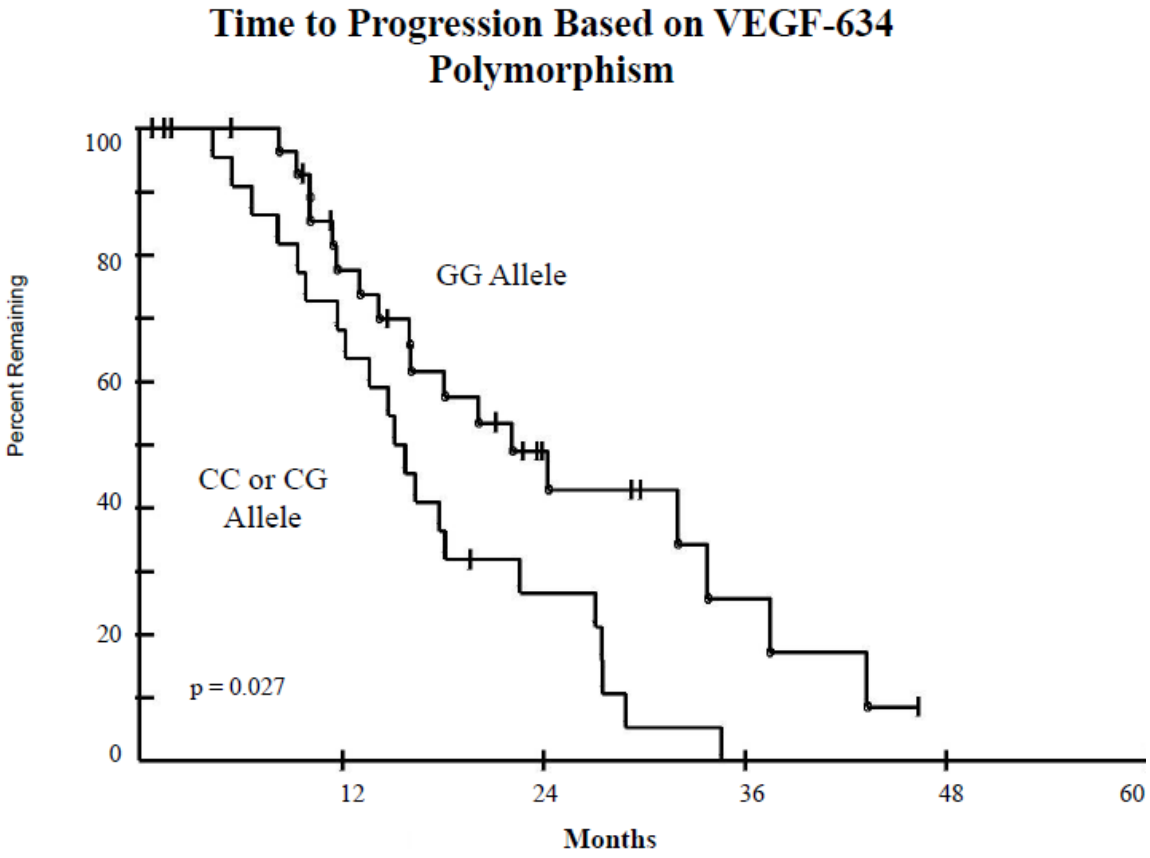
For grade 4 neutropenia lasting for <3 days lenalidomide was withheld until the absolute neutrophil count was ≥1000/µL. If the neutropenia lasted for ≥3 days lenalidomide was re-started with a 5 mg dose reduction. Patients with febrile neutropenia also had lenalidomide reduced by 5 mg. Lenalidomide was interrupted for platelet count <50,000/µL and re-started at a daily dose of 15 mg when the platelet count returned to >50,000/µL. Lenalidomide was withheld for grade ≥3 non-hematologic toxicities and re-initiated at a dose reduced by 5 mg during the subsequent cycles if the toxicity returned to baseline or grade 1. If lenalidomide or bevacizumab were permanently discontinued,

patients were allowed to continue to receive treatment with the remainder of the regimen. Patients were also allowed to continue on study despite transient treatment interruptions or “holidays” due to cumulative toxicity as long as disease and symptoms remained stable.

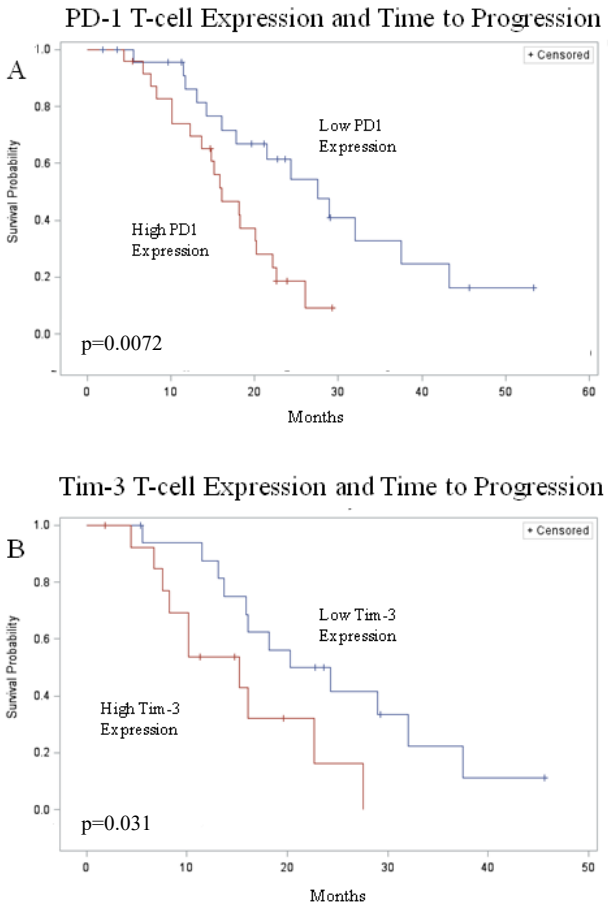
Supplemental Table 1. Comparison of Docetaxel, Anti-Angiogenesis Combination Trials

Treatment	n	50% PSA Declines	Overall Survival
Docetaxel +/- bevacizumab (CALGB 90401) [1]	1050	70%	22.6 months (docetaxel alone: 21.5)
Docetaxel +/- lenalidomide (MAINSAIL) [2]	1059	59%	17.7 months (docetaxel alone: not reached)
Docetaxel +/- aflibercept (VENICE) [3]	1224	69%	22.1 months (docetaxel alone: 21.2)
Docetaxel, thalidomide, bevacizumab [4]	60	90%	28.2 months
Docetaxel, lenalidomide, bevacizumab	63	90%	24.6 months

Supplemental Figure 1.



Supplemental Figure 2



Supplemental Figure 3.