Study Title	Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma		
METHODS			
Study Design	Double-blind, placebo-controlled, phase 3 trial		
Inclusion Criteria	• Adult patients with relapsed AND/OR refractory multiple myeloma • Measurable levels of disease • ECOG = 0-2 • 1-3 prior therapies • Adequate hematologic/hepatic function, renal function ≤30 mL/min	**Exclusion Criteria**	• Peripheral neuropathy (1 with pain or >2) • Refractory to prior lenalidomide therapy or proteasome inhibitor–based therapy (primary refractory disease eligible)
Treatment	• 1:1 ratio of treatment to control • 28-day cycles, 4 mg of oral ixazomib OR placebo on days 1, 8, and 15 • 25 mg of oral lenalidomide on days 1 through 21 • 10 mg for patients with CrCL ≤60 OR ≤50 mL/40 mg of oral dexamethasone on days 1, 8, 15, 22		
Randomization	Stratified according to: • # of prior therapies (1 vs. 2 or 3) • Previous exposure to proteasome inhibitors (not exposed vs. exposed) • International Staging System disease stage (I or II vs. III)		
Details	• Treatment continued until disease progression/development of unacceptable toxic effects • Thromboprophylaxis was required in all patients (97% ixazomib, 98% placebo) • Dose adjustments for toxic effects permitted		
Assessment	Response to study regimen was performed every cycle until disease progression.		
RESULTS			
Patient Population	• 722 patients at 147 sites in 26 countries • August 28, 2012, to May 27, 2014 • Baseline characteristics were well balanced between the study groups • Cytogenetic analysis available for 76% of patients [19% = high-risk cytogenetic abnormalities, 10% with del(17p)]		
Efficacy	**Treatment Group**	**Control Group**	
Primary End Point: ***Progression-free survival***	• Median: 20.6 months (HR = 0.74; CI – 95%, 0.59 – 0.94, P = 0.01) • Overall rates of response: 78.3% • Complete response + very good partial response =48% • Median time to response: 1.1 months • Median duration of response: 20.5 months	• Median: 14.7 months • Overall rates of response: 71.5 % • Complete response + very good partial response = 39% • Median time to response: 1.9 months • Median duration of response: 15.0 months	
	Median follow-up ~23 months, median overall survival has not been reached, follow-up is ongoing		
Safety	• SAEs: 47% • Death:4% • AE ≥ grade 3 severity: 74% • *Thrombocytopenia: Gr 3:12% , Gr 4: 7%* • Discontinue: 62% (disease progression 34%, AE 17%)	• SAEs: 49% • Death: 6% • AE ≥ grade 3 severity: 69% • Thrombocytopenia: Gr 3:5% , Gr 4: 4% • Discontinue:63% (disease progression 40%, AE 14%)	
CONCLUSIONS	Significantly longer (35%) progression-free survival by adding ixazomib (median duration ~6 months); additional toxic effects were limited. Overall survival benefit not yet shown. No adverse effect on QoL. May improve prognosis for patients with high-risk cytogenetic features (usually associated with poor prognosis) by lengthening the progression-free survival similar to those with standard-risk cytogenetic features. Responses were rapid and durable, and deepened with increasing duration of treatment. An increased focus on continuous therapy requires regimens that have acceptable side-effect profiles, that allow QoL to be maintained, and that are easy to administer. Almost half the patients had received treatment for at least 18 cycles at the 23-month analysis. All-oral ixazomib regimen was as simple and convenient for patients to follow as the placebo regimen.		

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