Introduction: Lenalidomide is approved for the treatment of del(5q) MDS in US and Japan. In Low to Intermediate-1 (Int-1) risk non-del(5q) MDS, lenalidomide treatment is less effective with a lower response rate (25%) and shorter response duration [Raza et al, Blood, 2008.111,1]. Ezatiostat, a glutathione S-transferase P1-1 (GST P1-1) inhibitor, activates Jun kinase, promoting the growth and maturation of hematopoietic progenitors while inducing apoptosis in malignant cells. Based on the novel mechanism of action, response rates, non-overlapping toxicities, and tolerability observed in a single agent ezatiostat Phase 2 study in MDS, a study of the combination of ezatiostat and lenalidomide was conducted to determine the safety and efficacy of ezatiostat with lenalidomide in non-del(5q) Low to Int-1 risk MDS. Methods: In this multicenter Phase 1 dose-ranging study, ezatiostat was given at a starting dose of 2000 mg in combination with lenalidomide at 10 mg, days 1-21 of a 28-day cycle. In stage 1, 3-6 patients in a standard 3+3 design were treated before escalation to the ezatiostat/lenalidomide 2500/10 mg dose level. Treatment was given until lack of MDS response or unacceptable toxicity. Hematologic improvement-erythroid (HI-E) rates were determined by the MDS International Working Group (IWG; 2006) criteria. Results: Eighteen pts (median age 73 yrs; range 57–82; 72% male), with World Health Organization classifications: 4 refractory anemia (RA), 2 RA with excess blasts-1, 4 refractory cytopenia with multilineage dysplasia (RCMD), 5 RCMD with ring sideroblasts, 2 MDS-unclassified, 1 MDS/myeloproliferative disorder-U were enrolled. Thirteen pts (72%) were Int-1 risk, 5 (28%) Low risk; 4 pts (22%) had abnormal cytogenetics. Twelve RBC transfusion-dependent pts (67%) required a median of 6 units (range 4–10)/8-weeks. Two pts (11%) were platelet transfusion dependent. A total of 67 treatment cycles were given (median 3.5 cycles/pt [range 1–11]) and only 6 cycles (9%) required dose reductions and 8 (12%) dose delays. Two of 6 pts reported DLTs (Grade 3 diarrhea and Grade 3 rash) at 2500/10 mg, with 9 additional pts receiving the recommended combination dose of 2000/10 mg. Eleven of 18 pts were evaluable (4 at 2500/10 mg and 7 at 2000/10 mg), and 3 pts are still on therapy with insufficient treatment duration to be evaluable. The HI-E rate was 43% (3/7, 95% CI, 10%–82%) for pts at the recommended 2000/10 mg dose and 6 pts are continuing therapy at the time of analysis. Three of 8 (38%; 95% CI, 9%–76%) RBC transfusion-dependent evaluable pts achieved transfusion independence including 1 responder who did not respond to prior lenalidomide. In responders, the median increase in hemoglobin level was 3.4 g/dL (from 7.9 g/dL). In 2 of 4 thrombocytopenic pts, a HI-platelet (HI-P) response was observed. A bilineage (HI-E and HI-P) response in 2 of 4 pts with anemia and thrombocytopenia was reported. One RBC and platelet transfusion-dependent pt who had a poor response to prior anti-thymocyte globulin treatment achieved complete RBC and platelet transfusion independence. The combination was generally well tolerated with no unexpected toxicities. Most common treatment-related non-hematologic adverse events (AEs) were Grades 1 and 2 including: fatigue (6%, 28%), swelling (0%, 11%), anorexia (11%, 6%), rash (0%, 6%), skin odor (11%, 6%), nausea (39%, 11%), diarrhea (22%, 17%), vomiting (28%, 17%), upper abdominal pain (5.6%, 5.6%), and constipation (11%, 0%). Grade 3 events were rash (11%), nausea (6%), diarrhea (17%), and vomiting (6%). Most common hematologic-related AEs were Grades 1 and 2 thrombocytopenia (11%, 6%) and neutropenia (0%, 11%). Grade 3-4 AEs were thrombocytopenia (11%, 17%), neutropenia (17%, 11%), anemia (6%, 6%), and febrile neutropenia (11%, 0%). Conclusions: Ezatiostat is the first GST P1-1 inhibitor to cause clinically significant reductions in RBC and platelet transfusions, including RBC and platelet transfusion independence. Since ezatiostat is non-myelosuppressive, it is a good candidate for combination with lenalidomide and in this study, the combination was well tolerated. Interestingly, ezatiostat may also have the potential to enhance lenalidomide’s efficacy. The recommended doses of this combination regimen for future studies is the ezatiostat/lenalidomide 2000/10 mg.