Lenalidomide (Len) plus dexamethasone (Dex) is approved for the treatment of relapsed or refractory multiple myeloma (RRMM). It is possible that single-agent Len may be effective as prolonged treatment regimen in RRMM once patients demonstrate an initial response to Len+Dex induction. Patients with RRMM who responded to first-line Len+Dex in an observational study (NCT01430546) received up to 24 cycles of either Len (25 mg/day) or Len+Dex (25 mg/day and 40 mg/week) as prolonged treatment in a subsequent phase 2 clinical trial (NCT01450215). In the observational study (N = 133), median time to response was 1.7 (range 0.6-9.6) months. A complete response to all treatments received in both studies was observed in 11% of patients; very good partial response and partial response rates were 31% and 38%, respectively. Corresponding response rates in the subgroup of patients who did not enter the phase 2 trial (n = 71) were 3%, 18%, and 39%, respectively. Rates of disease progression at 2 years in the phase 2 trial were 47% versus 31% for Len versus Len+Dex (P = 0.14). After 36 months median follow-up in surviving patients, median time to progression was not reached with Len+Dex and was 24.9 months (95% confidence interval 12.5-not calculable, P < 0.001) with Len. Three-year OS among the total observational study population was 61% (95% CI, 52-69%). The corresponding rate among patients who entered the phase 2 clinical trial was 73% (95% CI, 60-83%) and was significantly lower among those patients who achieved ≥PR but did not proceed into the phase 2 trial (55%; P = 0.01). In the phase 2 trial, OS was 73% in both treatment arms (P = 0.70). Neutropenia and thrombocytopenia were more common with prolonged (phase 2 trial) versus short-term (observational study) Len administration but remained manageable. Prolonged treatment with Len with or without Dex provides sustained, clinically relevant responses and demonstrates an acceptable safety profile.