and in CLL patients with poor prognostic features including high risk cytogenetic abnormalities and bulky disease. A phase II trial initiated in the relapsed/refractory setting to compare the safety and efficacy of lenalidomide at 25 mg/d with 10 mg/d resulted in 5 cases of tumor lysis syndrome (TLS). Therefore, in an effort to determine a safe dose and schedule the protocol was amended to a stepwise dose-escalation. Herein we present an interim safety data from the amended protocol. Methods. Eligible patients for discontinuation included hematoma (≥0.60 mL/min), received prior therapy or an alkylation agent and failed or progressed within a year of completing a fludarabine-based regimen. Lenalidomide was started at 2.5 mg daily dose. Intra-patient dose escalation to 5 mg/d occurred after 28 days with further dose escalations in 5 mg increments performed every 28 days in 6-patient cohorts, until the median tolerated dose escalation level (MTDEL) was reached or the 25 mg dose level was attained. Patients continued on therapy until disease progression. TLS prophylaxis with 300 mg/d allopurinol and oral hydration were started 3 days before lenalidomide and continued for 3 cycles, with dose monitoring for early signs of TLS (Caio-Bishop grading), particularly at drug initiation and dose escalations. Results. For 30 patients enrolled, median age was 66 years (range 50-76); 23 patients (76.7%) had bulky disease (LAN ≥25 cm), and had failed a median 4 prior therapies (range 2-14); 13 patients (45.3%) were refractory to fludarabine and 6 (20.0%) had failed alemtuzumab. Grade 3-4 adverse events (AEs) were consistent with previous studies of lenalidomide in similar patient populations, and included thrombocytopenia (16.7%) and neutropenia (63.3%), of which 3% were febrile neutropenia. Ten patients (35%) developed tumor flare (3 cases were grade 5) at a median dose of 2.5 mg/d and most commonly during the first cycle. Laboratory TLS occurred in 1 patient at the 2.5 mg/d dose level and resolved without drug interruption. There are 14 patients currently on study and 16 patients discontinued therapy. Reasons for discontinuation included lack of efficacy in 7 patients, of whom 5 did not reach the 10 mg/d dose, and 5 patients developed AEs (at 10 mg/d: 1 AIHA, not attributed to lenalidomide and 1 PE in patient with DVT history and on antithrombotic prophylaxis; at 2.5 mg/d every other day: 2 Grade 4 thrombocytopenia and 1 Grade 3 neutropenia). At last follow up lenalidomide was deemed tolerable up to the 15 mg/d dose level and the MTDEL had not been reached. Further escalation to the 20 mg/d dose level is under investigation and anticipated for presentation.

Conclusions. A preliminary safety analysis of lenalidomide stepwise dose escalation was found to be tolerable with MTDEL not yet reached at the 15 mg/d dose level. Close monitoring and prophylaxis were effective in the prevention, early detection and treatment of TLS in this heavily pretreated patient population with bulky disease.