Background: Loss of INI1/SMARCB1 protein expression in tumor cells is characteristic of ES and impairs activity of the SWI/SNF chromatin remodeling complex inducing oncogenic dependence on EZH2. Tazemetostat, a potent, selective, orally available EZH2 inhibitor has shown clinical activity in INI1-negative tumors including durable oncoytic dependence on EZH2. SMARCB1 was the most commonly altered gene (3/19 cases each). Additionally, the median mutation burden for ES cases was 25.8 mutations/MB suggesting a greater genetic complexity than other predominantly INI1-negative tumors (e.g. AT/RT and MRT). Interim WES analysis on 19 ES cases established that SMARCB1 was the most affected gene. SNVs were performed on tumor and matched normal samples at 30-200X and 10-50X, respectively.

Results: Interim WES analysis on 19 ES cases established that SMARCB1 was the most frequently-altered gene (16/19 cases). Review of 325 cancer specific genes, including all SWI/SNF complex members demonstrated that CTNNA1, LRP1B, and NOTCH1 were detected. Updated genetic characterization data on N = 43 ES cases, including analyses of DNA methylation data from N = 35). WGS and WES were performed on tumor and matched normal samples at 20-30X and 10-50X, respectively.

Conclusions: Alterations of SMARCB1 were the predominant genetic event observed in ES and is the underlying molecular mechanism leading to loss of INI1 protein expression. Notably, multiple genetic mechanisms leading to protein INI1 loss were detected. Updated genetic characterization data on N = 43 ES cases, including analyses to explore potential genetic associations with clinical outcome will be presented.