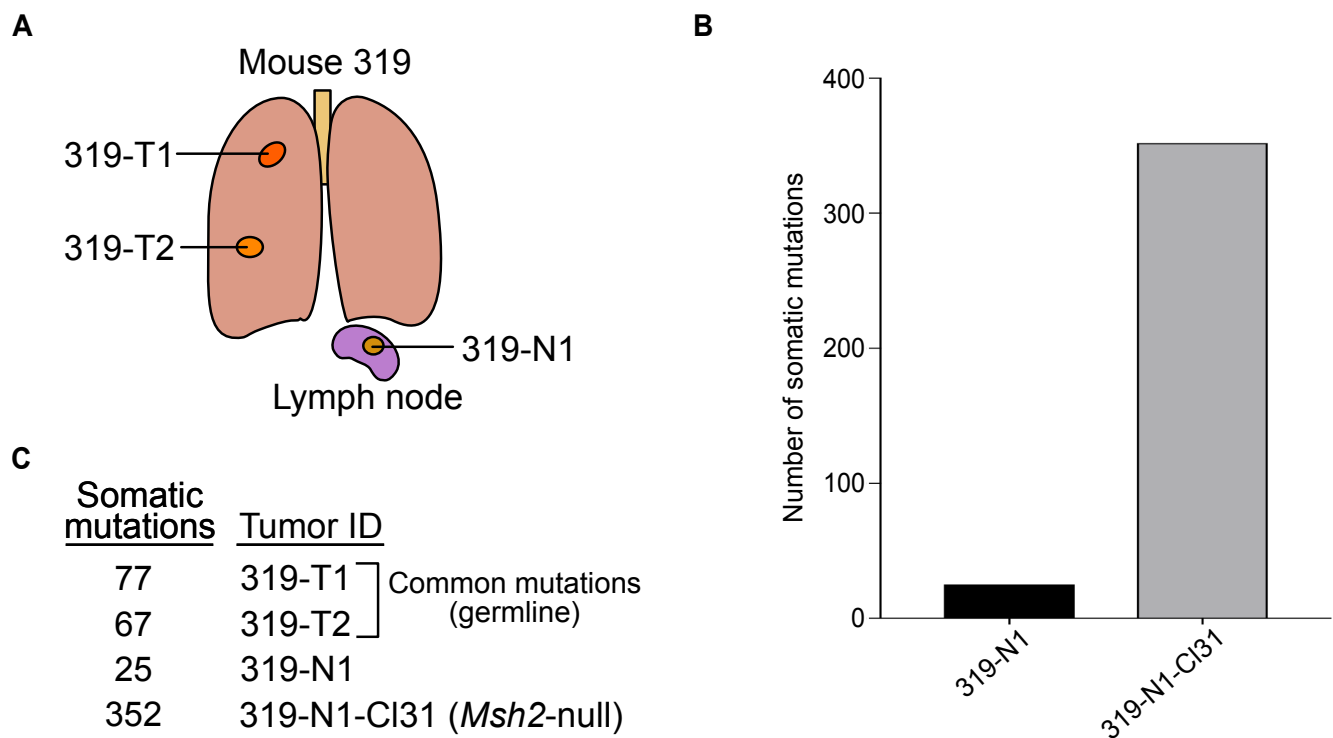
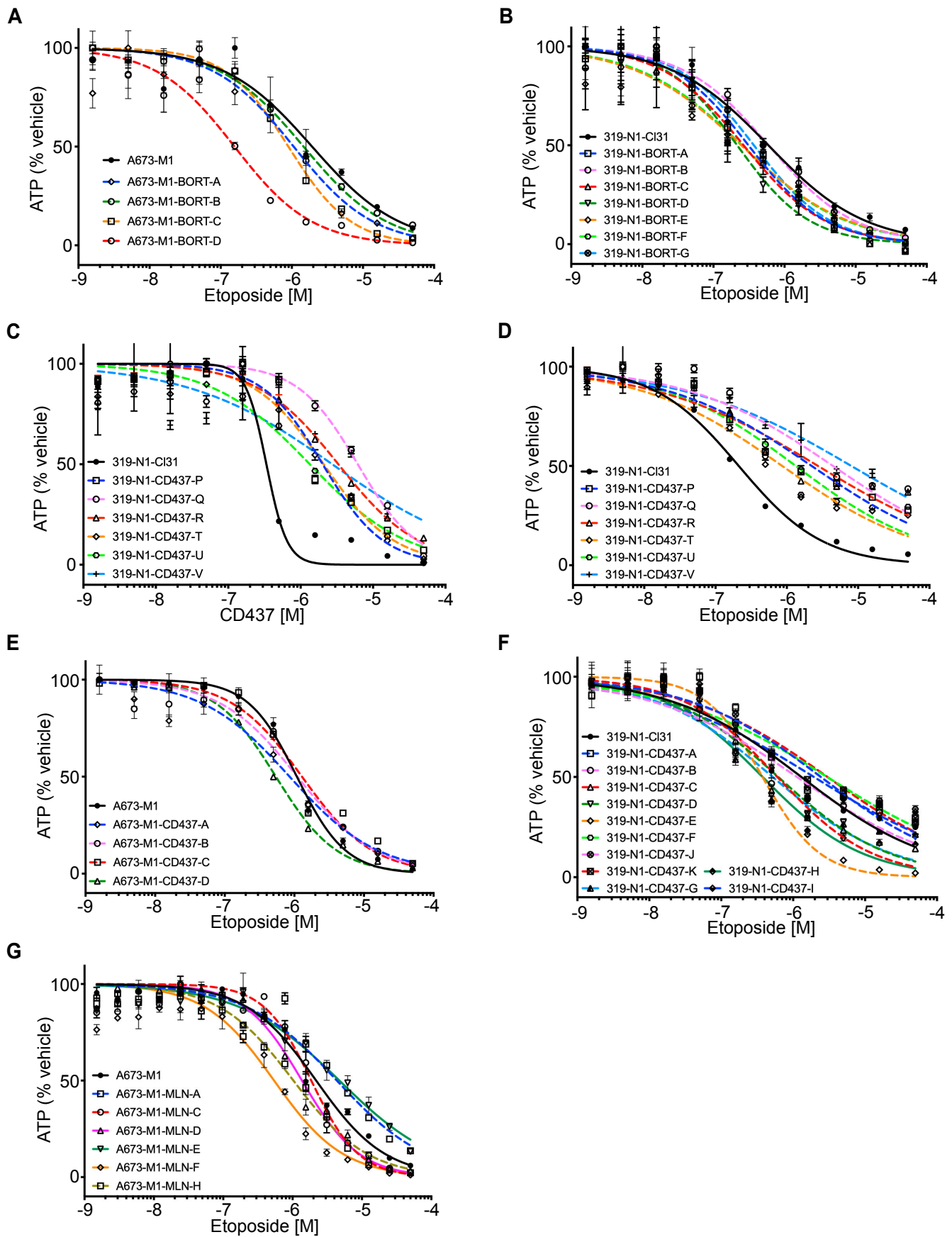


**Figure S1, related to Figure 1.** (A) Msh2 and Actin protein levels are shown for 319-N1 (negative control), 984NA CI38 (Msh2 edited mouse small cell lung cancer cell line, as positive control), and clones 319-N1 CI9 and 319-N1-CI31. (B) Capillary electrophoresis histogram of mBat37 locus for 319-N1 and 319-N1-CI31. The most prominent peak in the histogram determine the allele size is shown in solid blue. (C) Table of microsatellites assessed in 319-N1-CI31 cells. Difference in the dominant allele size between the parental 319-N1 and 319-N1-CI31 MMR deficient cell line is reported. Number of microsatellites affected in relation to the number of microsatellites studied is displayed in the last column. (D) MSH2 locus in dMMR Ewing sarcoma clones, A673-M1 and A673-M8. Number of reads for each allele is represented on the left column. sgRNA sequence is underlined in orange. PAM sequence is underlined in black. (E) Msh2 locus in dMMR murine SCLC clone, 319-N1-CI31. Number of reads for each allele is represented on the left column. sgRNA sequence is underlined in orange. PAM sequence is underlined in black.



**Figure S2, related to Figure 1.** (A) Diagram depicting the origin of each tumor sample used for whole exome sequencing. (B) Number of somatic mutations observed in 319-N1 and 319-N1-CI31 cell lines. Mutations with an allelic fraction (AF) higher or equal to 0.15 are reported. (C) Table of somatic mutations reported for each cell line. Common mutations between 319-T1 and 319-T2 cell lines were used to identify germline variants.



**Figure S3, related to Figure 2, 3 and 4.** (A) Cell Titer Glo assay of etoposide 10-point dose response curve for bortezomib-resistant clones compared to the parental A673 cell line. (B) Etoposide 10-point DRC for bortezomib-resistant clones compared to the mSCLC parental cell line. (C) Cell Titer Glo assay of CD437 10-point DRC for parental cell line and clones P, Q, R, S, T, U and V. (D) Cell Titer Glo assay of etoposide 10-point DRC for P, Q, R, S, T, U and V clones compared to the parental cell line. (E) Cell Titer Glo assay of etoposide 10-point dose response curve for CD437-resistant clones compared to the parental cell line. (F) Etoposide 10-point DRC for CD437-resistant clones compared to the parental cell line. (G) Etoposide 10-point DRC for MLN4924-resistant clones compared to the parental cell line. Data are represented as mean  $\pm$  SD.