Supplementary Table Descriptions:

Supplementary Table S1. Patient characteristics. Patients with CLL grouped based on their age, gender, Rai stage, prior therapy status, CD38 status, FISH (Döhner classification), *IGHV* mutational status, and ZAP70 status.
M, male; F, female; N, no; Y, yes; NEG, negative; POS, positive; NA, not available.

Supplementary Table S2. Characteristics of patients treated with ibrutinib. Patients with ALC above 10,000 cells/μL after 12 months of treatment with ibrutinib (IB-1 to IB-10), and patients who progressed on ibrutinib (PD-1 to PD-10) are grouped as in "Supplementary Table S1", in addition to type of response at time of cell collection, time on treatment, ALC at 12 months, and mutated gene responsible of ibrutinib's resistance.
M, male; F, female; N, no; Y, yes; NEG, negative; POS, positive; FISH, fluorescence in situ hybridization; NA, not available; PR, partial response; PRL, partial response with lymphocytosis; CR, complete response; PD, progressive disease; MO, month; IB, ibrutinib.

Supplementary Table S3. Primers and probes used for digital PCR. List of primer and probe sets used to identify VAF for known ibrutinib resistance mutations.

Supplementary Table S4. List of genes up- or down-regulated genes by MI-2 in CLL. List of 438 genes whose expression changed ≥2-fold at $P<0.05$ (312 down- and 126 up-regulated) following treatment of CD19-selected CLL cells (N=3) with 2 μM of MI-2 for 8h.

Supplementary Table S5. Gene sets identified by GSEA that are affected by MI-2. CLL-relevant gene sets identified by GSEA were selected for FDR ≤0.05 and NES ≥ 1.50, and grouped based on their functional similarities. We included gene sets in which the "leading edge genes" consist of at least 7 genes. NES, normalized enrichment score; FDR, false discovery rate; *, include one functional gene signature previously validated in CLL; ^, include two functional gene signatures previously validated in CLL and multiple myeloma.