Supplementary Figure Legends:

Supplementary Figure S1. MI-2 causes a dose- and time-dependent apoptotic induction selectively in primary CLL cells with minimal toxicity to normal B cells. (A) MEC1 cell line was incubated with increasing concentration of MI-2 (0-1 μM) for 48h, and cell viability was quantified using MTS assay. Data are expressed as percentage relative to the corresponding untreated control. (B) Time-dependent cell death shown as percent decrease in CLL cells viability (CD19+/Annexin-V-/ViViD-; N=18). Comparison is cell death at 24h vs. 48h incubation time with either 2.5 or 5 μM MI-2. Shown is the median (± IQR) relative to time-matched untreated control. (C) Percent increase in apoptosis (measured as an increase in Annexin-V staining above the baseline of untreated control) of CD5+/CD19+ CLL cells of 5 individual patients, after 48h incubation with 0.5, 1, and 2 μM of MI-2, in the presence or absence of 100 μM of the pan-caspase inhibitor z-VAD-fmk. Error bars represent SEM. (D) Normal donor PBMCs (N=5) were incubated with 0-10 μM of MI-2 for 24h, then viability of normal B cells was measured by gating on CD19+/Annexin-V-/ViViD- events, and compared to untreated control. Error bars represent SEM. (E) Summary of difference in sensitivity to MI-2 between CLL (CD19+, N=5) and normal donor B cells (CD19+, N=5) following a 24h exposure to 2.5 and 5 μM. Viability measured by gating on CD19+/Annexin-V-/ViViD- events, and compared to untreated control. Error bars represent SEM. NS, non-significant; IQR, interquartile range; SEM, standard error of mean; **, $P<0.01$; ***, $P<0.001$; ****, $P<0.0001$.

Supplementary Figure S2. Sensitivity to MI-2 is independent of clinical or biological features classically associated with poor outcomes in CLL. (A) PBMCs of 5 patients with CLL were incubated for 48h with 0, 0.5, 2, and 4 μM of MI-2 in the presence or absence of NLC. Shown is the percent change in viability of CD19 gated CLL cells compared to its own control (either with or without NLC). (B) Purified CLL cells (CD19 selection) (N=4) were incubated for 48h with 0, 0.5, 2, and 4 μM of MI-2 in the presence or absence of 5 μg/ml of anti-IgM. Shown is the percent change in viability of CLL cells compared to its own control (either with or without anti-IgM) measured by MTS. (C-D) PBMCs collected from patients with CLL were incubated with 0, 2.5 or 5μM of MI-2 for 24h, and cell viability was quantified using MTS assay. Data are expressed as % decrease in viability relative to the corresponding untreated control. Samples were sub-grouped by (C) *IGHV* mutational status (unmutated, N=9; mutated, N=10), (D) presence (N=7) or absence (N=10) of 17p deletion, (E) previously treated (N=4) vs. treatment naïve (N=15), and (F) CD38+

(N=8) vs. CD38- (N=10). Subgroups were compared using unpaired Student *t* test. Error bars represent SEM.

NLC, nurse-like cells; NS, non-significant; SEM, standard error of mean.

Supplementary Figure S3. Changes in absolute lymphocyte count of patients being treated with ibrutinib. (A) Squares represent the median ALC ± interquartile range of patients who have residual disease above 10,000 cells/μL after 12 months of ibrutinib treatment. Circles represent the median ALC ± Interquartile range of patients who have ALC below 10,000 cells/μL after 12 months of ibrutinib treatment. Symbols in red represent ALCs above 10,000 cells/μL, used in Figure 6a-b. (B) A breakdown of Figure 6E showing responses to MI-2 in CLL samples with acquired ibrutinib resistance. Red lines represent samples with BTK mutations, blue lines represent samples with PLCγ2 mutations, purple lines represent samples with both BTK and PLCγ2 mutations, and black lines represent patients with no known resistance mutations.