Supplementary Methods:

Primer sequence for site directed mutagenesis of cysteine 481 to serine on BTK gene:
(5' - GAG TAC ATG GCC AAT GGC TCC CTC CTG AAC TAC CTG AGG CCT CAG GTA GTT CAG GAG GGA GCC ATT GGC CAT GTA CTC-3').
CD 19+ B cells from patients with CLL (n=12) were incubated with or without 1µM IPI-145 for 24-72 hours. Viability was determined by annexin/PI flow cytometry. Above shows the time-dependent graph from 1µM treatment. IPI-145 causes significant linear and quadratic cytotoxicity over both time and dose P<0.01.
Viability of CLL cells after IPI-145 treatment was compared based on their known IGHV mutational status. Mutated (n=4) and unmutated (n=6) were graphed side by side. No significant difference of viability was observed.
A. CD $3^+$ T cells (n=4) from healthy volunteers were incubated with or without IPI-145 (1µM) for 48 hours. Viability was determined by annexin/PI flow cytometry. Paired samples are connected by lines.

B. Whole blood from healthy donor (n=4) was incubated with 1µM IPI-145 for 48 hours. Absolute count of live CD$3^+$ T cells were measured by flow cytometry. Paired samples are connected by lines.
A. CD 19+ B cells from patients with CLL (n=3) that relapsed from previous ibrutinib treatment that harbored the BTK C481S mutation were treated with vehicle or 1μM IPI-145 for 24 hours or with 1 μM ibrutinib for 1 hour followed by washout and incubated in media for 24 hours. Viability was determined by annexin/PI flow cytometry.

B. Cells were left untreated or treated with 1 μM IPI-145 for 1 hour or with 1 μM ibrutinib for 30 minutes followed by washout and incubated in media for another 30 minutes. Cell lysates were immunoblotted for pAKT^{S473}, total AKT. The blots are representative of three independent experiments.