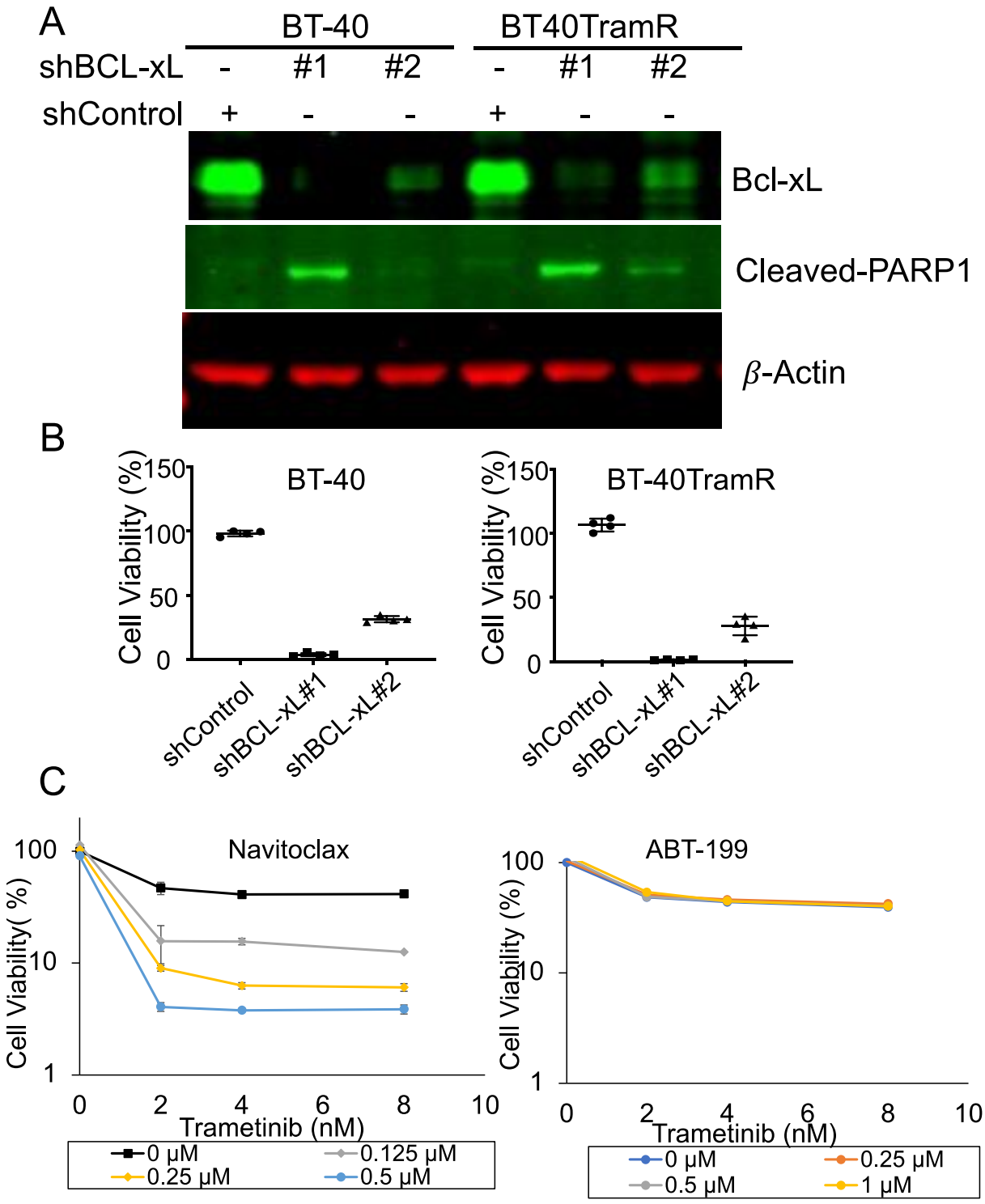

Fig S10. Down-regulation of the apoptotic threshold overcomes the resistance to trametinib.

A. Bcl-xL is essential for the viability of both BT-40 and BT40TramR cells. Bcl-xL Knockdown by shRNA resulted in apoptosis. 10^4 cells infected with lentivirus expressing shControl, and two shRNA's against Bcl-xL were cultured in 24-well plate for 96 Hr, and levels of BCL-xL and cleaved PARP were determined by immunblotting. β-actin was used as a loading control.

B. Knockdown of BCL-xL in BT-40 parental and BT-40TramR (trametinib resistant) cells induces loss of viability.

C. Combining trametinib with panBcl2 inhibitor Navitoclax (*left panel*) but not Bcl2 specific inhibitor ABT-199 (right panel) sensitized BT-40TramR cells to trametinib. Cells were seeded in 96-well plates at $2x10^3$ cells per well and incubated overnight. Trametinib was added at the indicated concentration combined with different concentrations of pan-Bcl2/Bcl-xL inhibitor or Bcl2 specific inhibitor, and cultured for 72 Hr. Cell viability was measured by Alamar Blue staining. Results are expressed as percentage of control cells treated with DMSO (0.1%). The experiments were repeated in triplicate (mean ± SD). The concentration of navitoclax and ABT-199 are indicated in the box under the graphs, respectively.