**Supplementary Figure legends.**

**Figure S1. PARP inhibitors restore sensitivity to temozolomide in MSH6-inactivated, temozolomide resistant glioblastoma cells.** (A-D) Cell viability assay for temozolomide (TMZ) dose response in glioblastoma cells engineered with shNS or shMSH6no.1 lentivirus. Cells were treated with specified concentrations of TMZ, and cell viability was evaluated by Cell Titer Glo on day6. (D) Patient-derived GBM sphere line (MGG4) was engineered with a non-targeting shRNA (shNS) or MSH6-directed shRNA (shMSH6no.1) lentivirus. Immunoblot confirmed MSH6 knockdown, with Actin as a loading control. Cells were treated with temozolomide (TMZ) 10 uM, Veliparib 3 uM or TMZ combination with Veliparib, and cell viability was evaluated by Cell Titer Glo on day 6. \*P<0.0001(student *t*-test) (F,H) Glioblastoma (GBM) cell lines (LN229 and Gli36) were engineered with MSH6-directed shRNA (shMSH6no.2) lentivirus. Immunoblot confirmed MSH6 knockdown, with Actin as a loading control. Cells were treated with specified concentrations of TMZ, and cell viability was evaluated by Cell Titer Glo on day 6. (G,I) shNS and shMSH6no.2 cells were treated with temozolomide (TMZ), Veliparib/Olaparib or TMZ combination with Veliparib/Olaparib, and cell viability was evaluated by Cell Titer Glo on day 6. G: LN229 (TMZ 200 uM, Veliparib 3 uM, Olaparib 1uM) I: Gli36 (TMZ 30 uM, Veliparib 1 uM, Olaparib 0.5 uM) \*P<0.05, \*\*P<0.01, \*\*\*P<0.001, \*\*\*\*P<0.0001 (student *t*-test).

(J) Cell viability assay for Veliparib(left)/Olaparib(right) dose response in LN229shNS and LN229shMSH6no.2. Cell viability was evaluated by Cell Titer Glo on day 6.

**Figure S2. XRCC1 inactivation does not restore the sensitivity to TMZ in MSH6-deficient cells.** (A, B) TMZ dose response in LN229shNS, LN229shMSH6, LN229shXRCC1, LN229shMSH6/XRCC1 (dual knockdown) cells. A, shXRCC1-1; B, shXRCC1-2. Cell viability was evaluated by Cell Titer Glo on day 6. (C) Veliparib (left) or Olaparib (right) dose response in LN229shNS, LN229shMSH6, LN229shXRCC1, and LN229shMSH6/XRCC1 (dual knockdown) cells. Cell viability was evaluated by Cell Titer Glo on day 6. (D,E) MSH6 knockdown (shMSH6no.2) LN229 cells were treated with TMZ (200 uM), APE inhibitor (1 uM, in D), MeOX (3 mM, in E), or TMZ combination with APE inhibitor (D) or MeOX (E). Cell viability was evaluated by Cell Titer Glo on day 6. (F,G) Same experiments as B and C using Gli36shMSH6no.2. TMZ (30 uM), APE inhibitor (1 uM, in F), MeOX (3 mM, in G).