Supplementary Figure S1: Relative expression of *ATP2A* genes in OAW42-R cell line and assessment of si-SERCA2 efficacy and selectivity

A *ATP2A1*, *-2A2* and *-2A3* mRNA expression were assessed by RT-qPCR in OAW42-R cell line at basal level. Relative *ATP2A1*, *-2A3* mRNA expression were normalized to that of *ATP2A2*. **B** Cells were transfected with 20 nM of si-CT or si-SERCA2 for 24, 48 and 72 h. SERCA2 protein expression was assessed by western blot and its quantification was realised using Image J software. Relative protein expression was normalized to that of SERCA2 upon si-CT transfection at each time of treatment. **C** Effects of 72h-transfection with 20 nM si-SERCA2 were evaluated on mRNA expression. Relative mRNA expression upon si-SERCA2 transfection were normalized to si-CT transfection for each gene (N=3 for all experiments).

Supplementary Figure S2: SERCA2 targeting strategies/ABT-737 combinations induce apoptosis through MOMP that is counteracted by BAK and BAK silencing.

A Pro-apoptotic BAK and BAX protein expression were assessed by western blot after both combinations. Cells were transfected 72 h with 10 nM si-BAX + 10 nM si-BAK + 10 nM si-SERCA2 and then treated 24 h with 5 µM ABT-737 or transfected 24 h with 10 nM si-BAX + 10 nM si-BAK and then treated 24 h with 0.5 µM thapsigargin + 5 µM ABT-737. Effects of these treatments were investigated on **B** cell morphology by optical microscopy (scale bar = 200 µM), on **C** cell viability assessed by the Trypan blue exclusion test (histograms represent the percentage of viable cells normalized to that of control condition (100%)) and apoptosis triggering was assessed **D** by the observation CASPASE 3 cleavage by western blot (N=3 for all experiments). Results were considered statistically different if *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Supplementary Figure S3: SERCA2 targeting strategies/ABT-737 combinations lead to ATF4 transcription up-regulation that is efficiently inhibited by ATF4 silencing

After 72h-transfection with 20 nM si-SERCA2, cells were transfected 24 h with 20 nM si-ATF4 followed by a 24h-treatment with 5 µM ABT-737 (left column) or transfected with 20 nM si-

ATF4 followed by a 24h-treatment with 0.5 µM thapsigargin + 5 µM ABT-737 (right column). *ATF4* mRNA expression was analysed by RT-qPCR (N=3).

Supplementary Figure S4: Silencing CHOP does not counteract Noxa induction upon TG/ABT-737 treatment

OAW42-R cells were transfected 24 h with 20 nM si-CHOP then treated 24 h with 0.5 µM thapsigargin + 5 µM ABT-737. Treatment effects were analysed **A** on cell proliferation by the Trypan blue exclusion test (histograms represent the percentage of viable cells in the treated conditions normalized to that of control condition (100%)), and **B** on CHOP and Noxa expression using western blot analysis (N=2).