**Supplemental Materials and Methods**

**Table 1. Oligonucleotide sequences**

|  |  |
| --- | --- |
| **qPCR Primers** | **Sequence（ 5’— 3’）** |
| PTEN-F | TTTGAAGACCATAACCCACCAC |
| PTEN-R | ATTACACCAGTTCGTCCCTTTC |
| GAPDH-F | GGAGCGAGATCCCTCCAAAAT |
| GAPDH-R | GGCTGTTGTCATACTTCTCATGG |
| **sgRNAs** | **Sequence（ 5’— 3’）** |
| PTEN sgRNA1 | GAACTTGTCTTCCCGTCGTGT |
| PTEN sgRNA2 | GGGCCTCCCACCTTGAACTA |
| **shRNAs** | **Sequence（ 5’— 3’）** |
| MCL-1 shRNA1-F | CCGGGCTTCGGAAACTGGACATCAACTCGAGTTGATGTCCAGTTTCCGAAGCTTTTTG |
| MCL-1 shRNA1-R | AATTCAAAAAGCTTCGGAAACTGGACATCAACTCGAGTTGATGTCCAGTTTCCGAAGC |
| MCL-1 shRNA2-F | CCGGGCTGGAGATTATCTCTCGGTACTCGAGTACCGAGAGATAATCTCCAGCTTTTTG |
| MCL-1 shRNA2-R | AATTCAAAAAGCTGGAGATTATCTCTCGGTACTCGAGTACCGAGAGATAATCTCCAGC |

**Recipe of RIPA buffer:** 50 mM Tris-HCl buffer pH 7.4, 1% NP-40, 150 mM NaCl, and 0.1% SDS. The supplemental protease inhibitors in RIPA buffer were 20 mM sodium fluoride, 0.5% sodium deoxycholate, 1 mM sodium orthovanadate, 2 mM sodium pyrophosphate decahydrate, 25 mM disodium-β-glycerophosphate, 1 mM PMSF, 1 mM benzamidine-HCl, 0.5 μg/ml leupeptin, 2 μg/ml aprotinin, 0.7 μg/ml pepstatin, 10 µM E-64, 10 μM bestatin, and 1 mM AEBSF.

**Immunohistochemistry (IHC) staining of the tissue array.** A tissue microarray containing 139 patient-derived glioma samples in a slide and their clinical information were provided by OUTDO Biotech (Shanghai, China). First, the slides were deparaffinized by xylene and ethanol washes using a Leica Autostainer XL ST5010 and rehydrated with deionized water. Antigens in the samples were retrieved by high-pressure repair in a citric acid buffer. The slides were blocked with peroxidase-blocking reagent for 15 min at room temperature and incubated overnight at 4 °C with the primary antibodies anti-MCL1 (CST, 39224) and anti-PTEN (CST, 9559). Then, the slides were incubated at room temperature for 30 min with the appropriate secondary antibody (Envision+/HRP, Rabbit, DAKO) and subjected to DAB staining. Next, the slides were bathed for 40 seconds in hematoxylin solution and for 2 seconds in 0.25% acid alcohol (1 ml hydrochloric acid in 400 ml of 70% ethanol); the slides were dehydrated in a Leica Autostainer XL ST5010. Finally, the slides were air-dried and mounted with neutral balsam for visualization.

 For evaluation of tissue staining, an intensity score from 0 to 2 was given to each sample with negative to high PTEN staining: 0, negative; 1, middle; 2, high. Because the staining of MCL1 was generally low across samples, an intensity score of 0 or 1 was given to each sample with MCL1 staining; the percentage of MCL1 staining area was also assessed. The product of the intensity score and positive area percentage was calculated, and based on the results, all the samples were categorized as negative (0), weak (<0.5), or positive (>0.5) for MCL1 staining.

**Apoptosis antibody array.** For the apoptosis antibody array, an Apoptosis Array Kit (CST, #ARY009) containing antibodies specific for 37 apoptosis-related proteins was used. Briefly, 1×107 cells were harvested and lysed to obtain 400 μg cell lysates. A total of 250 μL lysates/array was incubated overnight at 4 °C. Then, the arrays were washed with PBS and treated with streptavidin-HRP for 30 min and Chemi Reagent Mix for 1 min. Next, the membranes were exposed on X-ray film for 10 min. The array images were analyzed using a transmission mode scanner and image analysis software.

**Analysis of GDSC drug sensitivity data in pan-cancer and GBM cell lines.** The Genomics of Drug Sensitivity in Cancer (GDSC) database (www.cancerRxgene.org) is the largest public database for information on drug sensitivity in cancer cells and molecular markers of drug response. It contains drug sensitivity from 1000 human cancer cell lines and screened them with more than 100 of compounds. We chose PTEN as a biomarker and analyzed the drug sensitivity data in GDSC2 dataset. The log10 p-values *vs.* IC50 effect sizes from either a collection of pan-cancer cell lines or GBM cell lines were plotted in volcano plots. The p-value was calculated from the ANOVA of a drug-gene interaction on an inverted log10 scale. The effect size is proportional to the difference in mean IC50 between wild-type and mutant cell lines. Numbers less than 0 indicate drug sensitivity, numbers greater than 0 indicate drug resistance. FDR<20% were regarded as statistically significant sensitizing or resistance effects for PTEN.

**Analysis of combination interactions between UMI77 and temozolomide.** To analyze the combination effect of UMI77 and temozolomide, we used an online tool Horizon’s proprietary ChaliceTM software (Currently it is a commercialized software of Horizon) which allows researchers to quantitatively assess the strength of combination interactions and to extract potential data trends and insights from high-throughput combination activity profiling experiments. To accomplish the analysis of UMI-77-temozolomide combination treatment data, the following four steps were performed: select the data source and analytical options, specify data characteristics and execute the query. More details about using the software refer to its online manual (https://horizondiscovery.com/-/media/Files/Horizon/resources/Technical-manuals/hd-technical-manual-chalice-analyzer-viewer.pdf ). Dose matrices is the phenotypic measurements for single agents or fixed ratio combinations as a series of concentrations (doses) or for pairwise combinations. After execute the query the growth inhibition and Loewe excess dose matrices for the combined effect of UMI-77 and temozolomide were generated. Horizon also provides a scalar measure to quantify the synergistic interaction of UMI-77 and temozolomide in a combination termed the Synergy Score. It was calculated from an equation derived from Loewe model for additivity by which the experimentally-observed activity volume at each point in the matrix in excess of a model surface numerically derived from the activity of each agents were integrated.