Supplementary Figures and Tables.

**Supplementary Table , tab 1**

List of compounds used in the chemical inhibitor screen.

**Supplementary table ,tab 2**

SPIA pathway analysis performed highlighting significantly upregulated/downregulated pathways between BAP1 mutant and BAP1 wild type lines.

**Supplementary table, tab 3.**

GEO data analysis of 40 BAP1wt vs 11 BAP1mt mesothelioma tumours showing fold change in mRNA expression.

**Supplementary figure S1.**  Cell viability of selected mesothelioma cell lines (NCI-H28, MPP-89, H2810, MSTO-211H and H2795), and the FGFR-dependent lung cancer cell line (NCI-H1581) after 72 hours of treatment with FGFR-inhibitor NVP-BGJ398 at a concentration of 300nM, and AZD4547 at 500nM

**Supplementary figure S2 Primary Mesothelioma cell line drug screen**

Figure showing cell viability of 11 primary mesothelioma cell lines (columns) after treatment with a fixed dose of 48 different small molecule inhibitors (rows), depicted in a color scale (green=100% cell viability, red=0% cell viability).

**Supplementary figure S3. BAP1 status does not fully correlate with protein expression.**

**A** Western Blot showing BAP1 protein expression in several MPM cell lines, both *BAP1* wild type (black) and mutant lines (red). Beta tubulin represents the protein loading control.

**B,** List of somatic mutations in *BAP1* seen in MPM cell lines.

**Supplementary figure S4. Activation of other RTK pathways in MPM**

**A,** Western Blotshowing BAP1 protein expression in several MPM cell lines as well as activation of IGF1R, MET and FGFR.

**B,** Phospho RTK array panel showing baseline RTK activation of *BAP1* mutant (highlighted in red) versus wild type mesotheliomas.

**Supplementary figure S5. FGF9 activates FGFR3 and modulates MPM growth kinetics.**

**A**, Western blot of pFGFR in serum starved H2052 MPM cell line at baseline and with the addition of 50ng/ml of recombinant FGF9 ligand after 1 hour. **B**, Light microscopy of H2052 cell line under serum starved conditions, and with the addition of FGF9 ligand at varying concentrations. **C** ,comparative viability of H2052 by syto 60 assay at baseline and following the addition of 50ng/ml and 200ng/ml FGF9 ligand.

**Supplementary figure S6. BAP1 modulation and FGFR pathway activation by gene expression.**

**A,** Gene expression analysis of H226 cell line (BAP1 null) transfected with wild type BAP1 construct vs BAP1 inactive (c91a) construct. SPIA pathway analysis of C91A vs wild type cell line revealed the KEGG “bladder cancer” pathway is significantly activated in C91A cell line- arrow. **B** Bladder cancer pathway showing overexpressed genes in C91A line in red .

**Supplementary figure S7. Xenograft tumours immunohistochemistry**. Showing Immunohistochemistry for Caspase 3 and ki67 in MPM xenograft tumours during vehicle control or AZD4547 treated conditions.

**Supplementary figure S8**. **Combination drug screen of PI3Kinase inhibitor plus drug library in MPM cell lines**.

**A**, Bar chart showing recurrent synergistic events in combination screen of PI3K inhibitor AZD6482 plus 95 small molecule inhibitors across 15 MPM cell lines. Most recurrent synergistic events seen with IGF1R inhibitor BMS-536924 (n=7 cell lines) and FGFR inhibitor PD-173074 (n=6 cell lines).

**B** Validation of synergy between IGF1R inhibitor and PI3K inhibitor AZD6482 in NCI-H28 (FGFRi resistant cell line). Dose-response kinetics of BMS-536924 alone (blue) or with fixed dose (2uM) of AZD6482 (red).

**C** Immunoblot of NCI-H28 FGFRi resistant cell lines treated with combination of IGF1R inhibitor BMS-536924 and PI3K inhibitor AZD6482 showing loss of pAKT with combination treatment.

**D**. Cell Titre blue quantification of 2 week clonogenic survival assay of 5 MPM cell lines with IGF1R inhibitor BMS-536924 alone and in combination with PI3K inhibitor AZD6482.