**Supplemental Figure 1: Validation of MCL-1 siRNA.** SKBR3 cells were treated with a panel of different MCL-1 siRNA (all 20nMol) for 24hrs and the effect on MCL-1 expression and apoptosis determined by western blot and flow cytometry respectively. Responses were compared to the parental line or SKBR3 cells treated with BCL-XL siRNA or scrambled siRNA (Sc; both 20nMol; a). SKBR3 overexpressing MCL-1 or the Vector alone (Vct Ctrl) were treated with MCL-1 siRNA that targets the 5’UTR (# 5; 20nMol) or the CDS (#2; 20nMol) and apoptosis determined by flow cytometric evaluation of the sub-G0/G1 content of DNA cell cycle histograms. Responses were compared to untreated cells or cells treated with Sc siRNA (20nMol; b). BCL-2 (c) or BCL-XL(d) were overexpressed in SKBR3 cells and the expression of BCL-2 family members determined by western blot and compared to the parental cell line or SKBR3 cells transfected with the empty vectors pEF (c) or pLOC (d)

**Supplemental Figure 2: The susceptibility of breast cancer cell lines to MCL-1 siRNA according to genotype and expression of BCL-2 family members.** Susceptibility of breast cancer cell lines to MCL-1 siRNA (20nMol; see Supplemental Table 1) was segregated according to genotype (a), *MCL-1* copy number (see Supplemental Table 1; b), correlated with *BCL-2*, *BCL-XL* or *MCL-1* gene expression (see Supplemental Table 1; c), or *MCL-1* copy number (d).

**Supplemental Figure 3: MCL-1 dependency dictates cellular response to the CDK9 inhibitor flavopiridol and correlates with kinetics of death resulting from MCL-1 siRNA treatment.** SKBR3 or HCC-1806 cells were treated with flavopiridol (0, 100, 300 or 500nM) for 4, 8 or 24hrs and the effect on MCL-1 expression and PARP cleavage determined by western blot or apoptosis by flow cytometric evaluation of the sub-G0/G1 DNA content of cell cycle histograms determined (a). Additionally SKBR3 cells were treated with scrambled (Sc) or MCL-1 siRNA (#5; both 20nMol) for the indicated times and the degree of MCL-1 silencing and caspase-3 processing determined by western blot (b), or apoptosis by flow cytometric evaluation of the sub-G0/G1 DNA content of cell cycle histograms (c). Response compared to untreated SKBR3 cells was determined.

**Supplemental Figure 4: *BCL-XL* but not *BCL-2* gene silencing sensitize HCC-1806 cells to A-1210477-induced apoptosis.** HCC-1806 cells were pre-treated with scrambled (Sc), BCL-2 or BCL-XL siRNA (all 20nMol) for 24hrs prior to treatment with A-1210477 for a further 24hrs. The expression of MCL-1, BCL-2, BCL-XL, β-actin and PARP protein were determined by western blot and apoptosis determined by flow cytometry.

**Supplemental Figure 5: Flavopiridol synergizes with navitoclax in breast cancer cell lines *in vitro*.** A panel of breast cancer cell lines were co-treated with flavopiridol (0, 100, 300, & 500nM) and navitoclax (0-10µM) for 72hrs in 10% FBS. The effect on cell viability was determined with CellTIterGlo™ and synergy determined by Bliss analysis.

**Supplemental Table 1: Viability of breast cancer cell lines treated with PBS, scrambled siRNA (Sc; 20nMol) or MCL-1 siRNA (20nMol) for 72hrs compared to non-treated cells with associated genomic information.** Data are presented as the mean of at least three independent experiments

**Supplemental Table 2: Navitoclax *EC50*s in breast cancer cell lines in the presence or absence of MCL-1 siRNA.** Breast cancer cell lines were co-treated for 72hrs with navitoclax alone or in the presence of scrambled siRNA (Sc; 20nMol) or MCL-1 siRNA (20nMol) and viability determined with CellTiterGlo™. *EC50*s were determined from the resulting sigmoidal dose-response curves. Data are presented as the mean of at least three independent experiments.