**Supplementary Figure 1: CP466722 does not affect cell viability.** Normal diploid HFF (dnHFF), HFF(hTERT) and A-T(hTERT) cells were plated in triplicate (40,000cells/plate) before being incubated in the presence of DMSO or 6μM CP466722 for 0-72h. Cell viability was assessed using a Vi-CELL XR cell viability analyzer.

**Supplementary Figure 2: CP466722 inhibits ATM kinase activity in human cells in response to IR-induced DNA damage.** (a) Mcf7, HFF(hTERT), A-T(hTERT) and (b) normal diploid HFF (dnHFF) cells were preincubated with varying concentrations of CP466722, DMSO or 10μM KU55933 (KU) prior to mock-IR (control) or IR (2Gy) followed by incubation at 37$^{o}$C for 30min before harvesting. To determine the effect of CP466722 on ATM kinase activity, ATM-intermolecular autophosphorylation at Serine 1981 and phosphorylation of downstream ATM-targets were monitored by western blotting analysis (representative of several repeat experiments).

**Supplementary Figure 3: CP466722 inhibits ATM kinase activity in MEFs in response to IR-induced DNA damage.** Atm wild type and deficient MEFs (Atm$^{+/+}$, *Arf*$^{-/-}$ and *Atm*$^{-/-}$, *Arf*$^{-/-}$ respectively) were preincubated for 30min with DMSO, 6μM of CP466722 or a 1h preincubation with 10μM KU55933 (KU) prior to mock-IR (control) or IR (5Gy) followed by incubation at 37$^{o}$C for 1h before being harvested. To determine the effect of CP466722 or KU55933 on ATM kinase activity, phosphorylation of downstream ATM targets were monitored by western blotting analysis (representative of several repeat experiments).

**Supplementary Figure 4: CP466722 and KU55933 do not inhibit Abl kinase activity but effect Src autophosphorylation at Tyrosine 416.** (a) Mouse pre-B cells (p185+/*Arf*$^{-/-}$) expressing BCR-Abl were treated with DMSO(Control), CP466722, KU55933 or Imatinib (10μM) for a period of 4h before being harvested. Western blotting analysis was used to detect autophosphorylation of BCR-Abl (Tyr245), Abl (Tyr245) and phosphorylation of CrkL (Tyr207) as a measure of Abl kinase activity and autophosphorylation of Src (Tyr416) was used as a readout of Src kinase activity. (b) To demonstrate that CP466722 and KU55933 were active, mouse pre-B cells (p185+/*Arf*$^{-/-}$) expressing BCR-Abl were preincubated with DMSO, 6μM CP466722 (CP), 10μM KU55933 (KU) or 10μM Imatinib (IM) prior to mock-IR (control) or IR (2Gy) followed by incubation at 37$^{o}$C for 30min before being harvested. The effect of CP466722, KU55933 or Imatinib on ATM kinase activity was determined by monitoring p53 (Ser15) phosphorylation and stabilization of p53.

**Supplementary Figure 5: Transient exposure of A-T fibroblasts to CP466722 does not sensitize cells to IR-induced DNA damage.** A-T(hTERT) fibroblasts were plated in triplicate and incubated for 24h. Cells were preincubated for 30min with DMSO or 6μM CP466722 before being exposed to a range of doses of IR (0-10Gy). Cells were incubated for 4h following irradiation before being re-plated in fresh media in the absence of drug and incubated for a period of 10 days to allow for colony formation. To determine the effect of transient exposure to CP466722 in response to IR the surviving colonies were counted and the data presented on a log axis (represents the mean of three independent experiments +/-SE).