

### **Figure S1**

Whole-cell lysates were prepared from the indicated HNSCC cell lines and immunoblotted for SMG-1 and tubulin. \* - tubulin band is stronger due to residual signal from immunoblotting for additional proteins; loading in this sample is comparable to the other samples.

### **Figure S2**

Upper panel: Images from RPPA analysis, showing expression of ATM and ATR proteins in HPV-positive and negative HNSCCs.

Lower panel: Scatter plots quantifying RPPA.

### **Figure S3**

*E6* real time PCR in SCC61 cells (**A**) and normal human keratinocytes (**B**), transfected with either empty vector or E6/E7 expression construct.

### **Figure S4**

SCC61 cells with stable expression of E6/E7 proteins (SCC61 E6/E7) were compared to cells harboring empty vector (SCC61v), as well as parental SCC61 cell line in terms of *TP53* mRNA (left panel) and protein (right panel) levels. Error bars represent SD.

### **Figure S5**

Relative *SMG-1* expression in cells treated with azacitidine (aza) normalized to untreated controls.

### **Figure S6**

SCC61 cells expressing HPV-16 E6/E7 (SCC61 E6/E7) or empty vector (SCC61v) were treated with azacitidine (aza) and analyzed by qRT-PCR for *TP53* expression. Data was normalized to value obtained for SCC61v cells. Error bars represent SD.

### **Figure S7**

(**A**) Apoptosis induction in JHU012 cells transduced with either empty vector or two different SMG-1 shRNA and treated with Zeozin (Zeo) as determined with Annexin V staining and flow

cytometry. **(B)** SMG-1 and  $\gamma$ H2AX Western Blot analysis of cells used in(A). PCNA was used as a loading control. **(C)** Western Blot with SMG1 and PARP-1 antibodies of SCC25 cells transduced with empty vector and SMG-1 shRNA construct and treated with Zeozin. PCNA was used as a loading control.

### **Figure S8**

Propidium iodide staining and cell cycle analysis of UMSCC47 cells transfected with either empty vector or SMG-1 expressing construct and irradiated with 10Gy **(A)**. **(B)** Western blot with SMG-1 antibody of cells used in A.