**Supplemental Figure 1.** **The mutational status of the *TP53* constructs**. *TP53*mutations with a variety of EA scores were classified as low or high risk. Primers used to introduce the desired mutations into the wildtype *TP53* sequence (mutated nucleotide is underlined) are indicated (Panel A). Western blot of basal total p53 and p21 expression in UMSSC1 and PCI13 HNSCC isogenic cell lines stably expressing wildtype and mutant p53 constructs (Panel B).

**Supplemental Figure 2. Cellular proliferation is independent of *TP53* status.**Proliferations assays were performed on UMSCC1 and PCI13 HNSCC isogenic cell lines stably expressing either pBabe, wildtype p53, low risk or high risk mutations (Panel A and B). The low and high risk series are a composite of three mutations, F134C, A161S, and Y236C and five mutations, R175H,C176F,H179Y, C238F, G245D, respectively and the results represent two independent experiments.

**Supplemental Figure 3. Comparison of disruptive and truncating p53 classification systems in the training set.** Wildtype p53 had a significantly improved overall survival relative to mutated p53, *p*=0.02,(Panel A). Patients with tumors harboring disruptive mutations (n=118) had a similar overall survival to tumors with nondisruptive mutations (n=84) in the training set, *p=*0.15 (Panel B). Furthermore tumors with truncating mutations (n=69) had similar overall survival to missense mutations (n=125) in the training set, *p=*0.61 (Panel C).

**Supplemental Figure 4. Comparison of disruptive and truncating p53 classification systems in the validation set.** Patients with tumors harboring disruptive mutations (n=32) had similar overall and disease free survival rates and time to distant metastases compared to tumors with nondisruptive mutations (n=37) in the validation set, *p=*0.33, 0.44, and 0.14 respectively (Panels A-C). Furthermore tumors with truncating mutations (n=22) had similar overall and disease free survival compared to missense mutations, *p=*0.33 and 0.69 (n=47) (Panel D&E) but there was decreased time to the development of distant metastases, *p*=0.05, in the validation set (Panel F).

**Supplemental Methods**