

SUPPLEMENTARY FIGURE AND TABLE LEGENDS

Supplementary Figure 1. Mutation rates by cohort. Panel A shows that the mutation rate for responders was higher than non-responders ($P = 0.0003$). Likewise, Panel B shows that the mutation rate for *ERCC2* mutant tumors was higher than in *ERCC2* wild-type (WT) tumors ($P = 0.01$).

Supplementary Figure 2. *ERCC2* mutations. Integrated Genomics Viewer (IGV) screenshots of the nine *ERCC2* mutations observed are shown. In each row of screenshots, the top track shows the tumor reads and the bottom track visualizes the germline reads. Additional information about chromosome coordinates, allele changes, cDNA change, and protein change are provided for each variant. Further information about each variant is available in **Supplementary Table 2**.

Supplementary Figure 3. *ERCC2* mutation status and overall survival. Kaplan-Meier curve comparing overall survival between *ERCC2* mutant and *ERCC2* wild-type bladder cancer cases from TCGA. No difference in overall survival was observed ($P = 0.77$; Log-Rank Sum Test).

Supplementary Figure 4. *ERCC2* mutations occur in highly conserved regions. Alignment of *ERCC2* sequences from representative organisms. Conserved amino acid positions are shaded and locations of mutations identified in responders are highlighted in red. The extreme C-terminal portions of the sequences are not shown.

Supplementary Table 1. Treatment information and sequencing metrics for all patients The treatment information and raw sequencing metrics, including mean target coverage, for each case is listed here. In addition, the mutation rate

data referred to in the Results and represented in **Supplementary Figure 1** is listed here by synonymous rate, non-synonymous rate, and total number of mutations per patient. *Cases that were included in the TCGA effort (UC-0296 and UC-0234). (dd = dose dense, GC = gemcitabine/cisplatin, MVAC = methotrexate, vinblastine, doxorubicin, cisplatin). Unavailable cases for Fluidigm Validation (due to inadequate remaining DNA or technical failure) are also denoted (n = 15).

Supplementary Table 2. All alterations in responders and non-responders.

All somatic mutations and short insertion/deletions are listed, with additional annotations regarding genomic coordinates, protein change, allelic fractions, and validation status (if available).

Supplementary Table 3. Significantly altered genes in the combined cohort.

MutSigCV ranked list of significantly mutated genes across the entire cohort (n = 50 patients). Entries are sorted by q values. Entries with significant q values that failed manual review in Integrated Genomics Viewer (IGV) were marked as “Blacklist” in the Notes column and excluded from the final results (see Methods).

Supplementary Table 4. Significantly altered genes in clinical subsets.

MutSigCV ranked lists for significantly mutated genes in the non-responders only (n = 25), the responders only (n = 25), and the *ERCC2^{WT}* responders only (n = 16).

Supplementary Table 5. Damaging scores for alterations. This table shows the damaging scores (Methods) for nonsynonymous alterations (missense, nonsense, splice site, frame shift) studied in this cohort. The damaging score was derived as follows: missense mutations were scored using the Polyphen2

score(41) for the amino acid substitution. Nonsense mutations, splice site mutations, and short insertion/deletions were automatically assigned a damaging score of 1. “Unavailable” damaging scores are those that are missense mutations without a PolyPhen2 score.

Supplementary Table 6. Selective alteration enrichment. This table shows the results of applying Fisher's Exact Test to a tabulated set of predicted damaging somatically altered genes in responders compared to non-responders. A Benjamini-Hochberg/FDR q-value is reported for genes with the minimum number of events necessary to be considered for a theoretically significant p-value of ≤ 0.01 ($n = 6$). The results are sorted by p-value (lowest to highest).