## Supplemental Figure Legends

**Supplemental Figure 1. Schema of sample selection and sequencing.** Patients were selected based on being treated at UNC Healthcare, having advanced or metastatic urothelial carcinoma, being treated with ICB, and having appropriate tissue available for sequencing (n = 109). One patient did not have response data available, leaving n = 108 patients for tumor sequencing analysis. Of these 108 patients, 103 and 89 patients had sufficient quantity and quality of DNA and RNA, respectively, for targeted exon capture sequencing. Targeted exon sequencing and fusion detection demonstrated n = 13 patients with FGFR3 mutations and n = 4 patients with FGFR3 fusions (all FGFR3-TACC3).

**Supplemental Figure 2. Duration of therapy based on FGFR3 status. (A)** Histogram of number of patients by duration of therapy measured in days. Inset is a box plot showing median duration of therapy for patients with FGFR alterations compared with wild type patients. **(B)** Histogram of number of patients by duration of therapy measured in days including only patients with stable or progressive disease as the best response to ICB. Inset is a box plot showing median duration of therapy for patients with FGFR alterations compared with wild type non-responding patients.

**Supplemental Figure 3. A variation on Figure 3A showing that FGFR3-altered tumors are enriched in luminal and differentiated molecular subtypes. (A) T**he indicated molecular subtyping schema were applied to tumors using the R package from Kamoun et. al. Bar plots indicated the absolute numbers of tumors within that subtype with FGFR3-alterations. P values for Chi square test are indicated. **(B)** Response rates by molecular subtypes for various classification schemas. Absolute number CR/PR (blue) patients as well as SD/PD (red) patients given by height of each bar for the corresponding subtype. Chi-square p-values indicated above each bar.

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26 **Supplemental Figure 4. Overall survival and response rate did not correlate with the (A) individual**

27 **FTBRS, (B) EMT-stroma, and (C) immunosuppression gene signatures.** Left columns shows Kaplan-

28 meier curves for overall survival with samples segregated by signature score >0 (blue curve labeled high)

29 vs samples with signature score <0 (orange curve labeled) low.

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31 **Supplemental Figure 5. Generation of linear model for calculation of stromal and**

32 **immunosuppression residuals.** A scatterplot of tumors from the UNC dataset with RNAseq

33 (n=89) were plotted based on their CD8_Mariathasan signature score versus their stromal

34 (FTBRS or EMT_Stroma_core_18) signature or immunosuppression signature scores. Using this

35 data, a linear model was generated (dashed blue line) to determine the expected level of

36 FTBRS, EMT-Stroma, and Immunosuppression signature for a given CD8 effector signature

37 score. FTBRS, EMT-Stroma, and Immunosuppression residuals were calculated for each FGFR3

38 WT tumor and used to generate the violin plots in Figure 4C.

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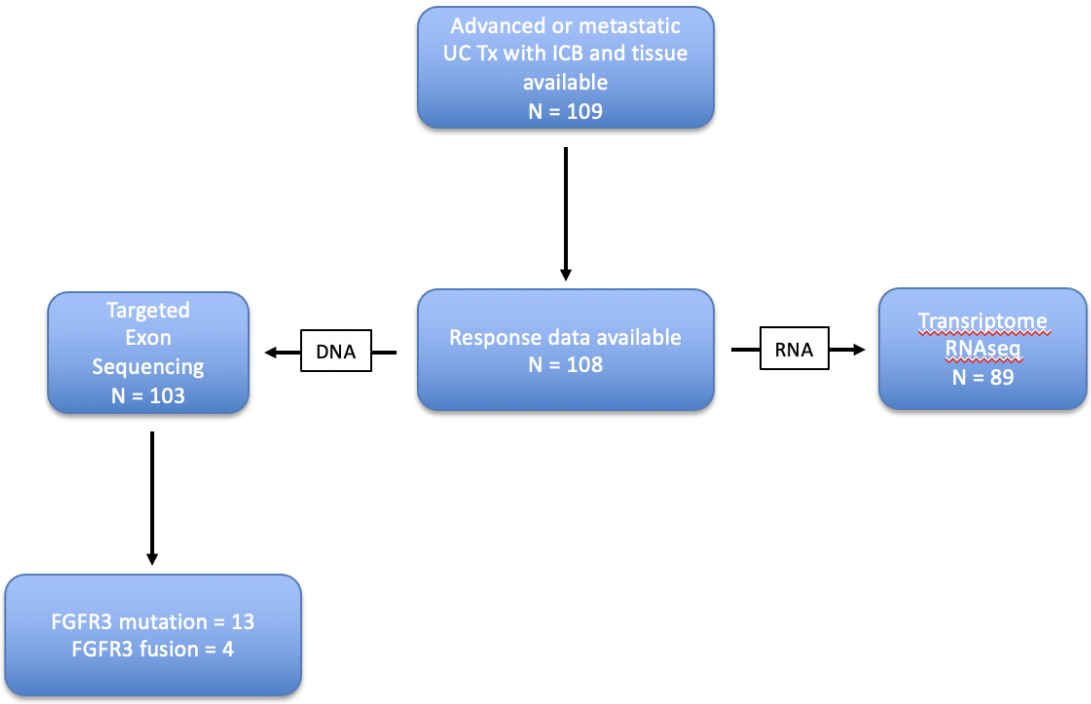
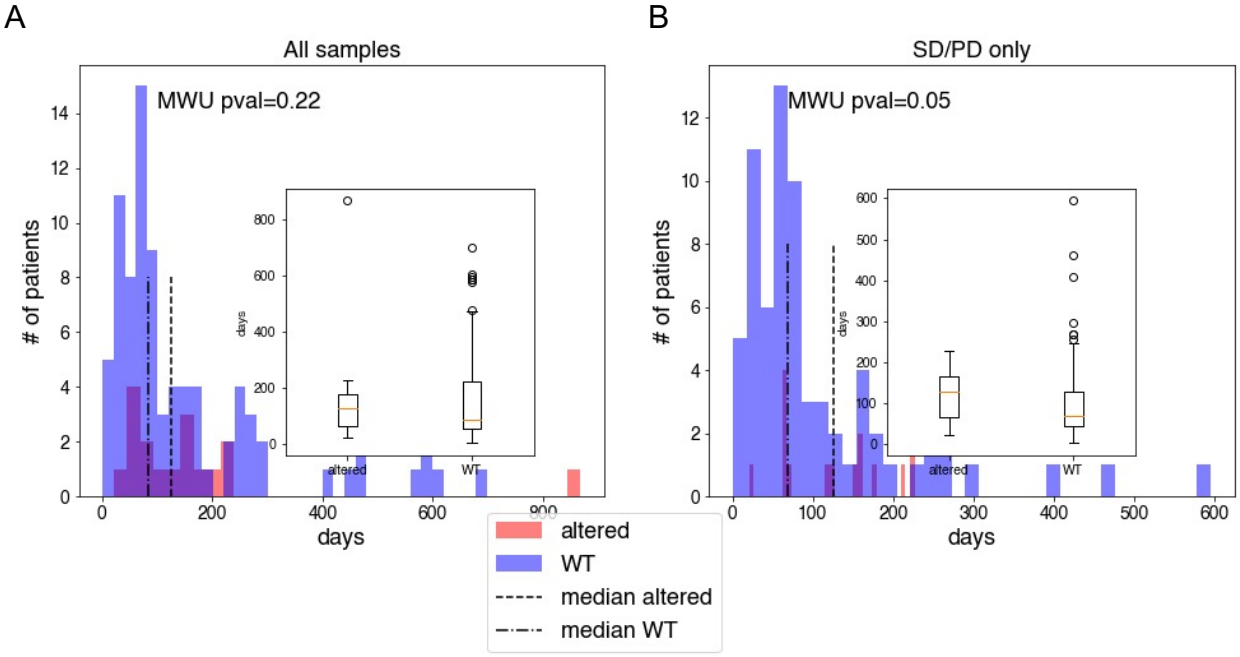
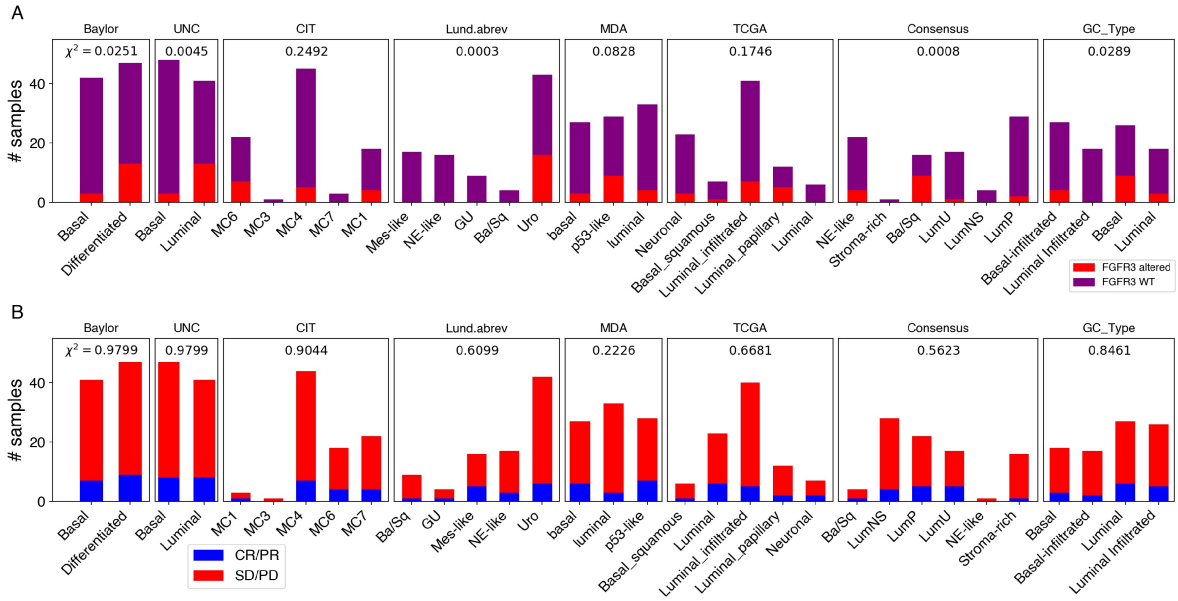
Supplemental Figure 1



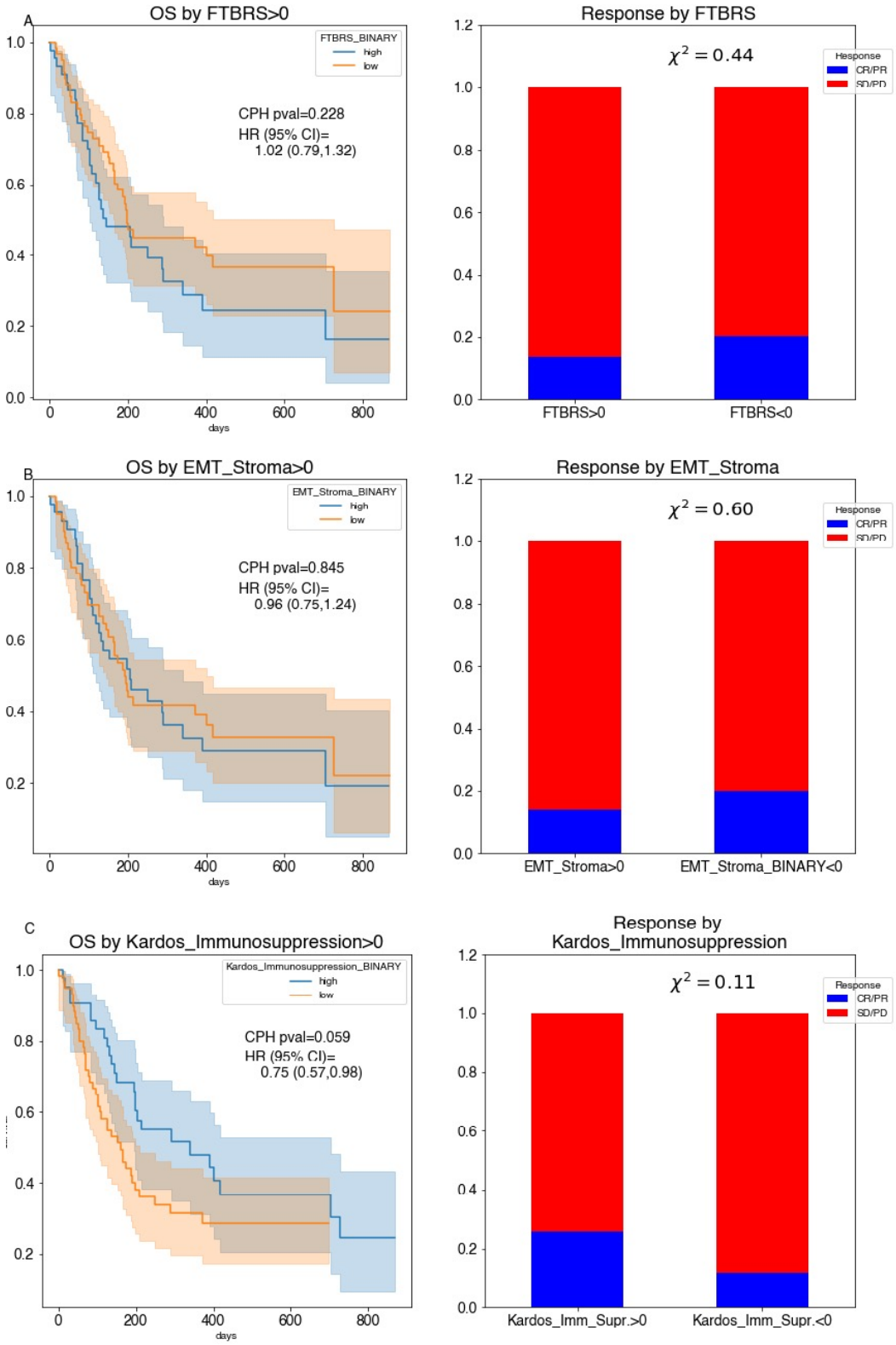
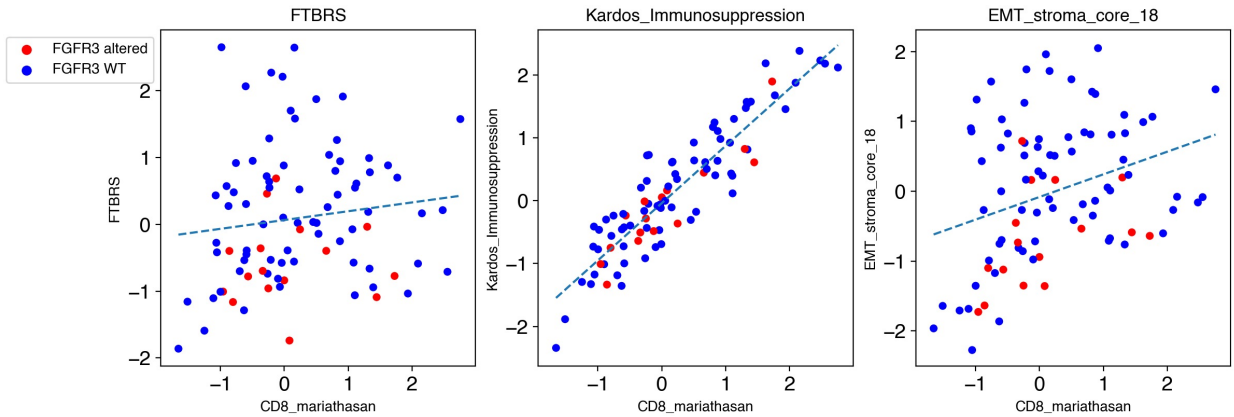
Supplemental Figure 2



# Supplemental Figure 3



# Supplemental Figure 4



# Supplemental Figure 5