
Memorial Sloan Kettering
Cancer Center

# Defining the Genetic Evolution of Epigenetic Alterations in Bladder Cancer (PD42-06)

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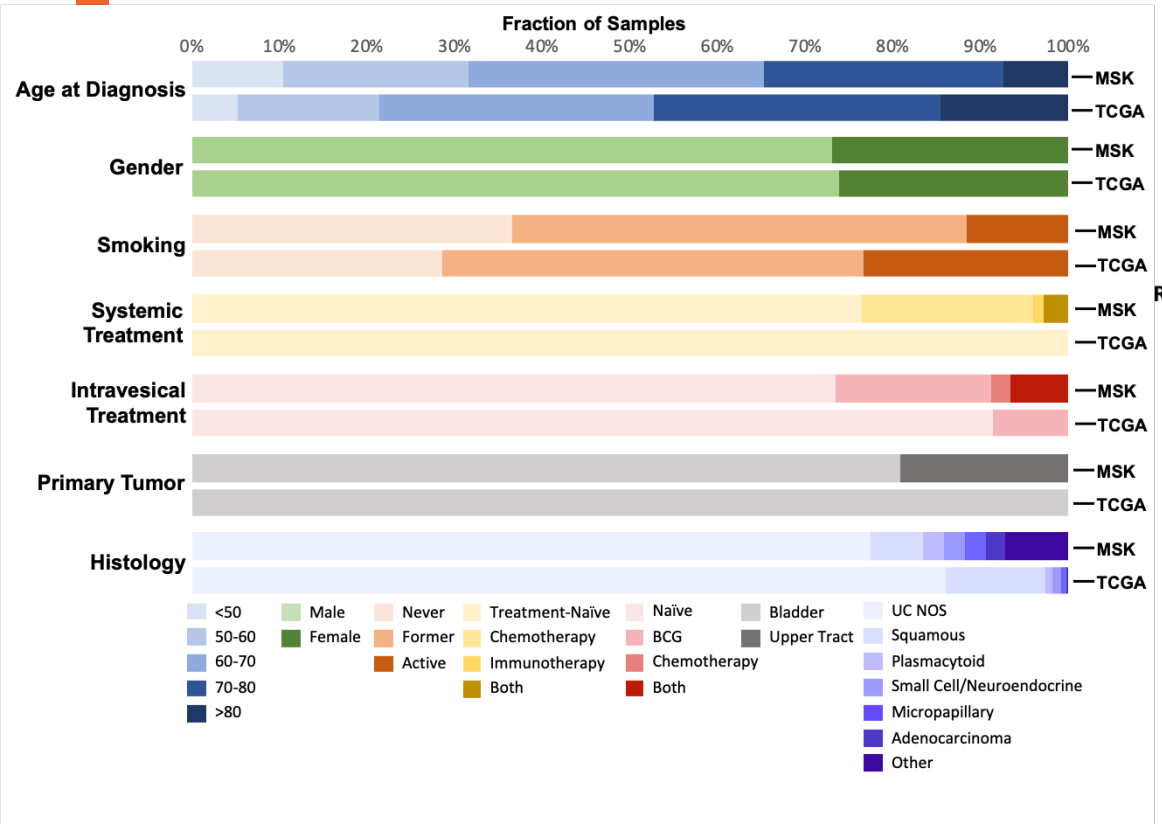
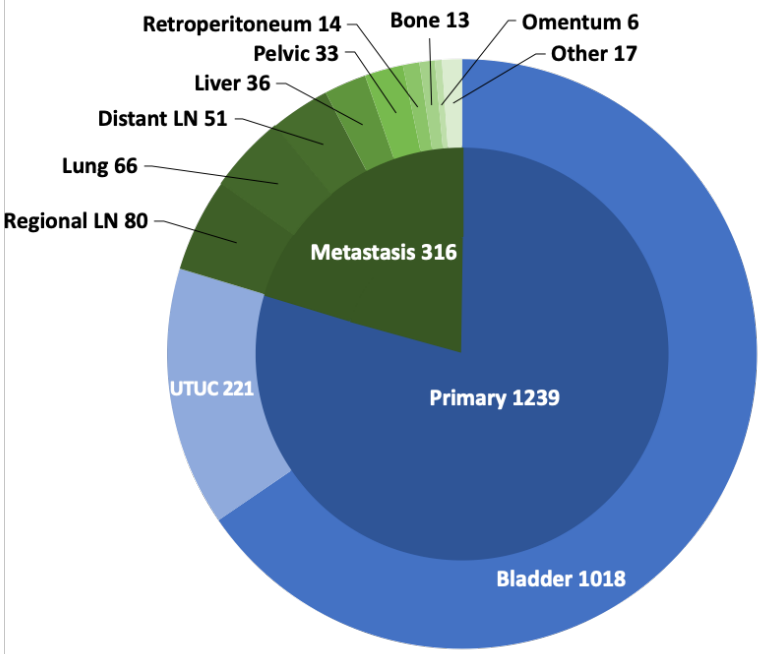
# Introduction

- Large scale retrospective studies have revealed that the majority of urothelial cancers harbor potentially actionable oncogenic mutations
- ERCC2 or other DNA repair pathway genes may be predictive of response to chemotherapy and immunotherapy
- Erdafitinib is an example of targeted therapy for patients with FGFR2/3 alterations
- High rates of mutations in genes that regulate chromatin state: KDM6A, ARID1A and KMT2D
- There remains uncertainty as to the timing at which alterations in chromatin modifying genes arise during the evolution of urothelial cancers

# MSK-IMPACT Prospective Sequencing (N=1555)

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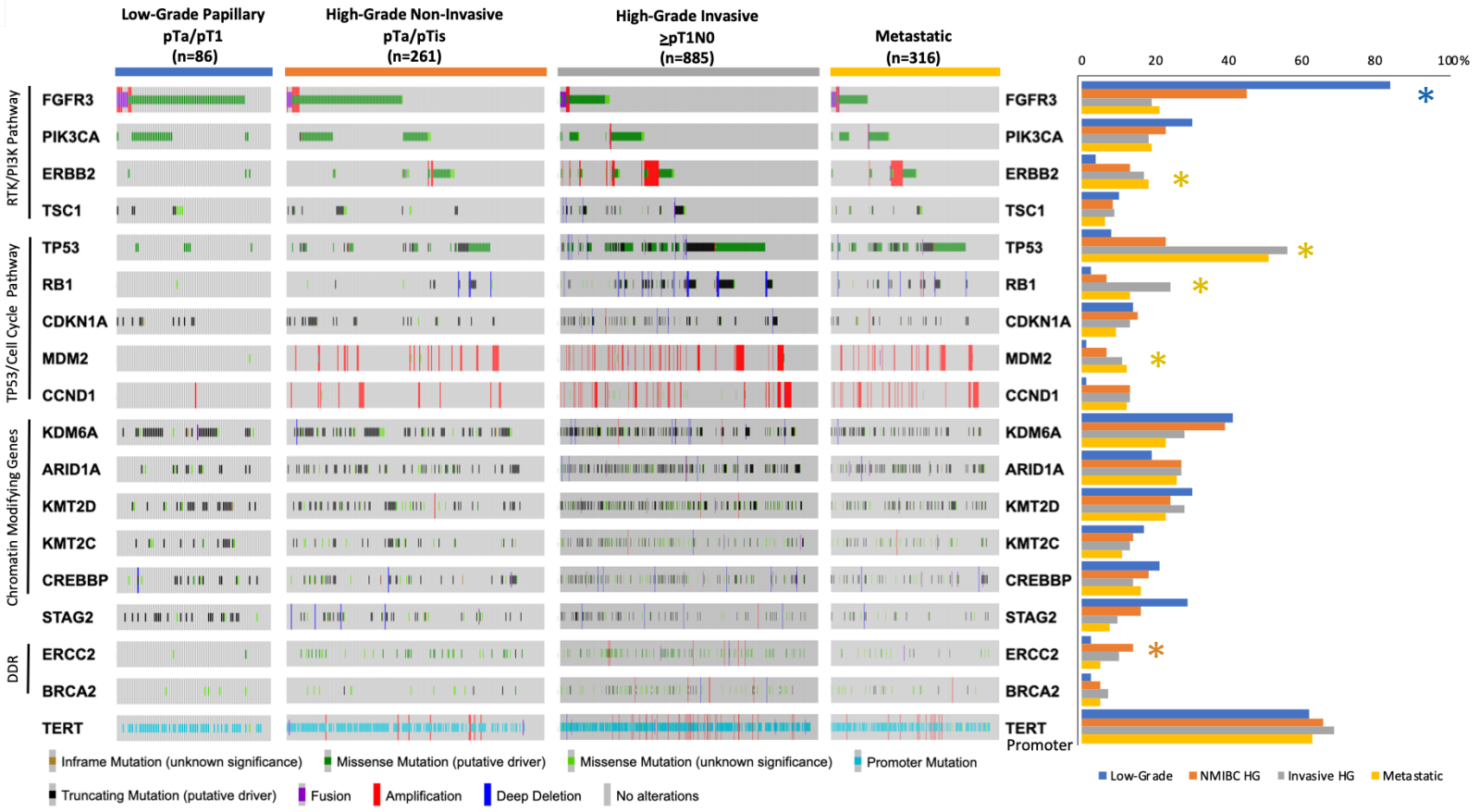
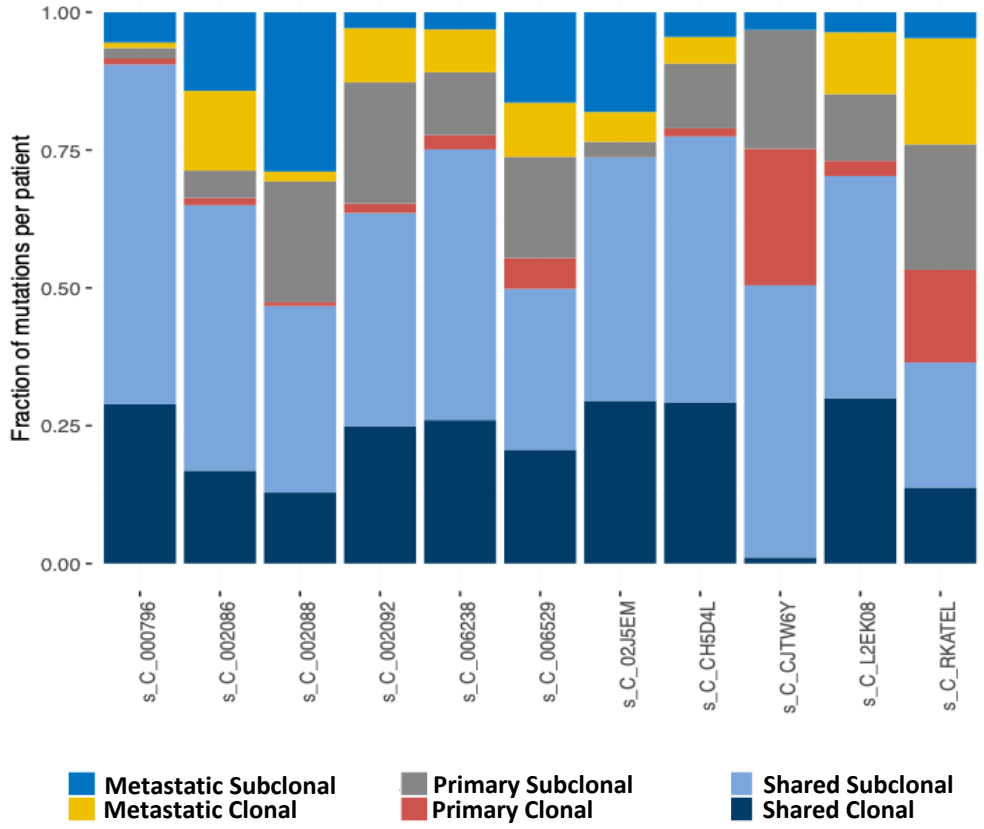
# MSK-IMPACT Prospective Sequencing



# Whole-Exome Sequencing – Concordance




- 11 matched Primary/Metastatic Pairs
- Largely concordant in oncogenic/likely oncogenic mutations

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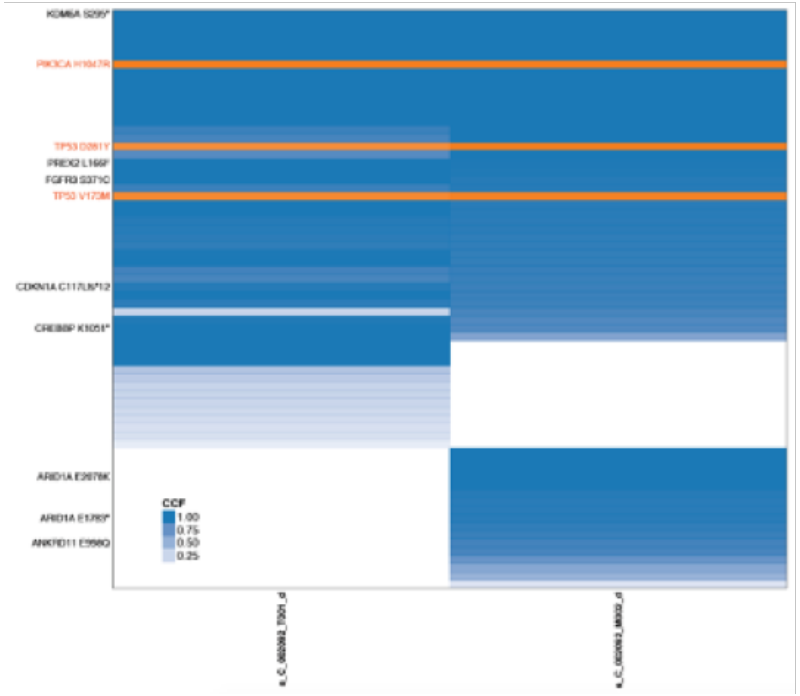
# Matched-Pairs Whole-Exome Sequencing




CDKN1A p.C117Lfs*12
CREBBP p.K1051*
ELF3 p.E256Kfs*39
FGFR3 p.S371C
KDM6A p.S295*
PIK3CA p.H1047R
TP53 p.D281Y
TP53 p.V173M

ARID1A p.E1783*
ARID1A p.E2078K

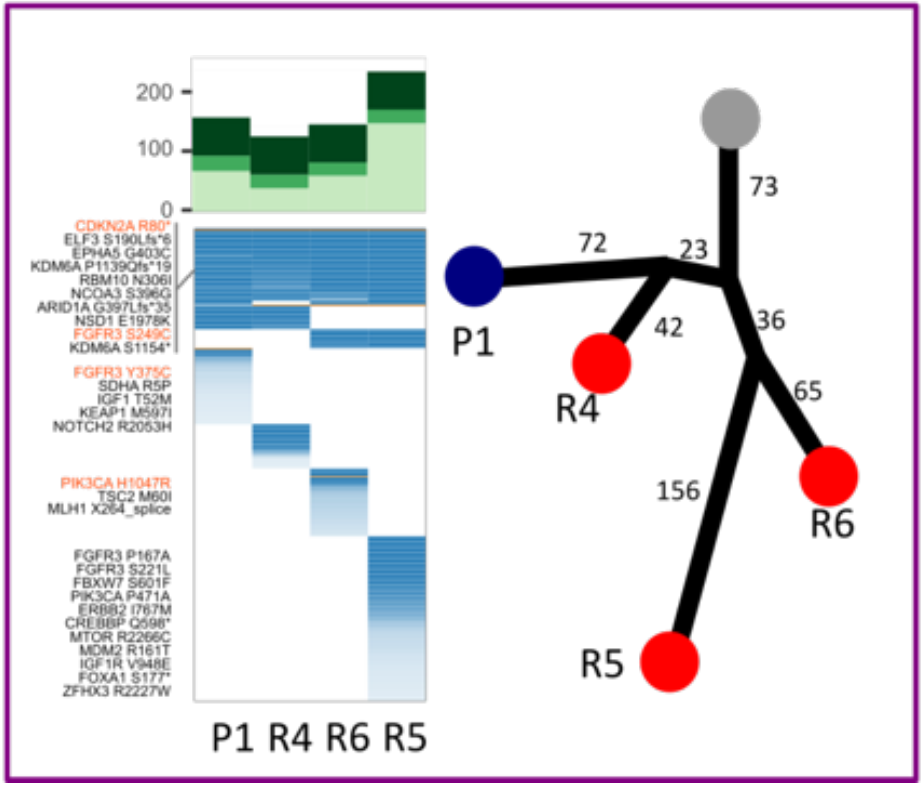
RC → Lung Met

6 months
No systemic therapies

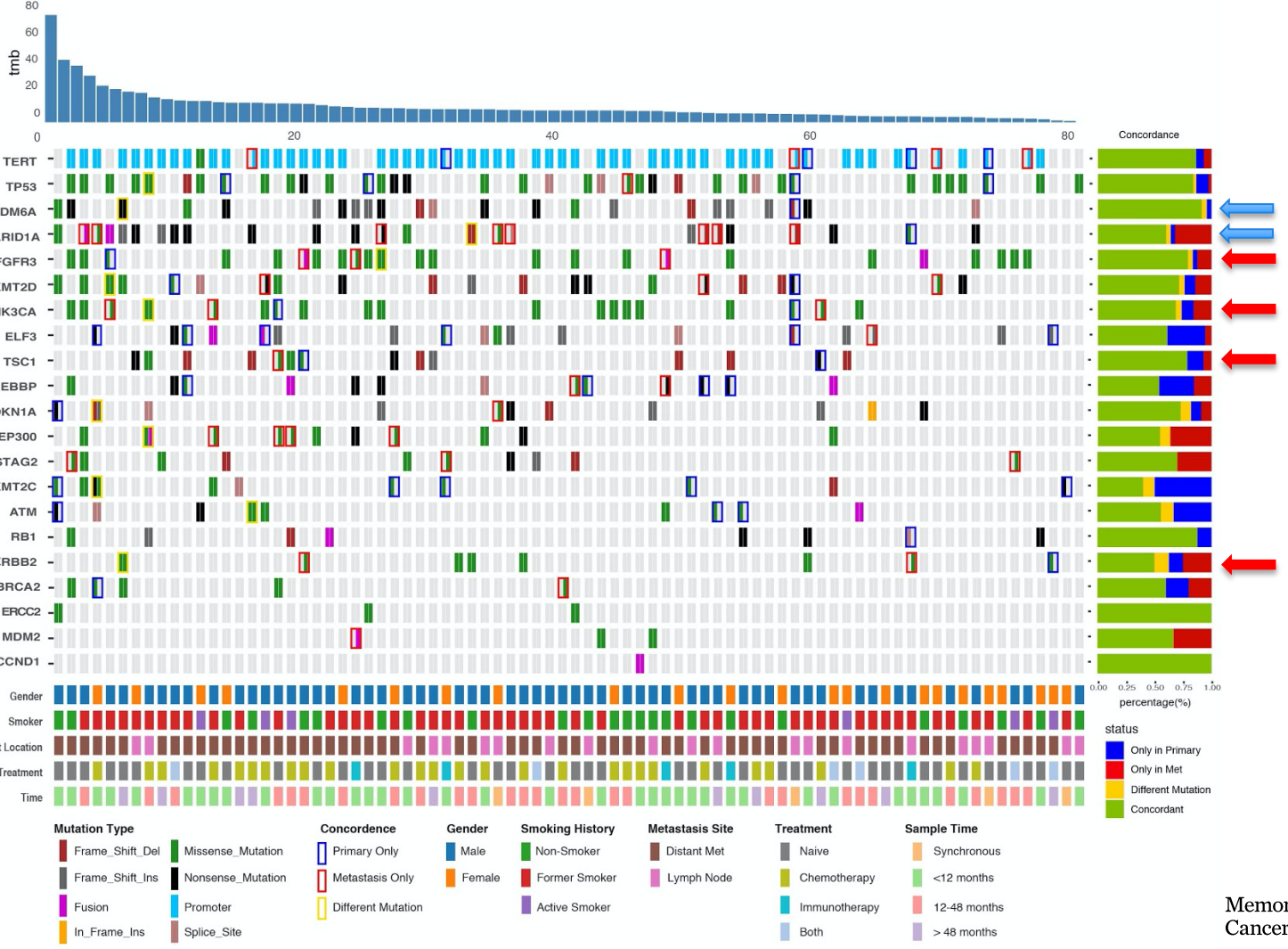
OncoKB likely oncogenic/oncogenic mutations in Brown
OncoKB leveled mutations in green
Hotspots in Orange

Shared by all samples
Shared by >1, but not all samples
Private primary
Private metastatic

# Matched-Pairs Whole-Exome Sequencing




Primary Tumor (P1) did not share the same FGFR3 mutation as three other metastatic sites that were sequenced (R4/R5/R6)

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# Conclusions

- WES and NGS suggest that chromatin modifying genes like KDM6A arise early in tumor development
- ARID1A mutations are enriched and present only in a subset of metastatic specimens
- Despite high-frequency of FGFR3 mutations in low-grade tumors, discordance is observed in a small fraction of patients
- Sequencing suggests that both primary and metastatic samples should be profiled. It may be possible that cfDNA would be preferable to identify some of these targetable alterations