



Memorial Sloan Kettering  
Cancer Center

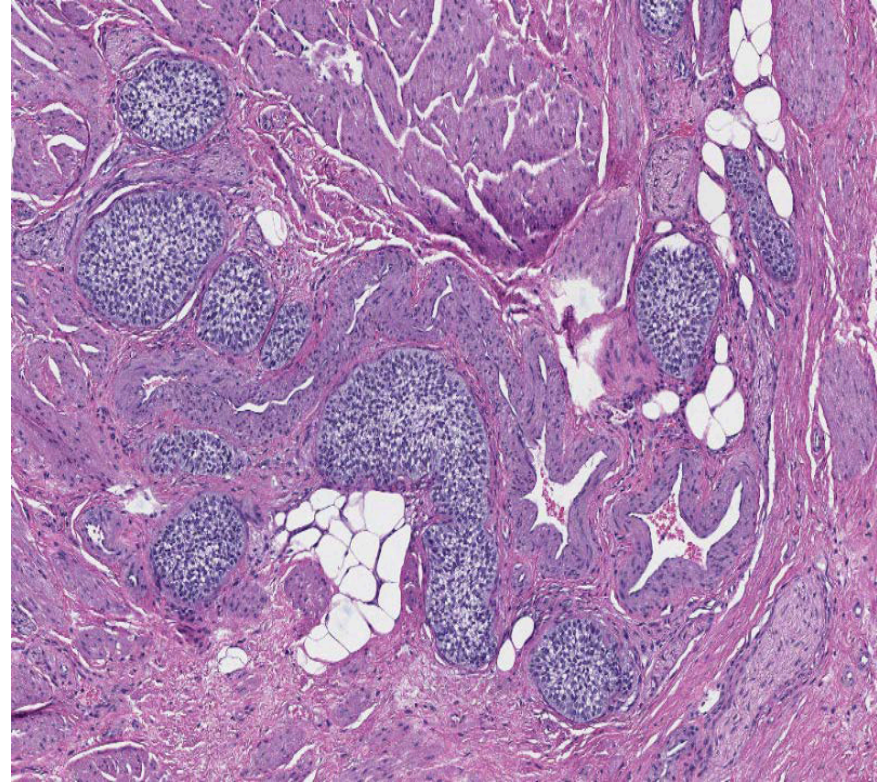
# Genomic Determinants of Nested Variant Urothelial Carcinoma (PD47-01)

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# Nested Variant Urothelial Carcinoma

- Historically aggressive variant of urothelial carcinoma
- Difficult pathologic diagnosis due to rarity and appearance
- Benign appearance resembling von Brunn nests
- Unknown genomic characterization – which may help determine treatment paradigms



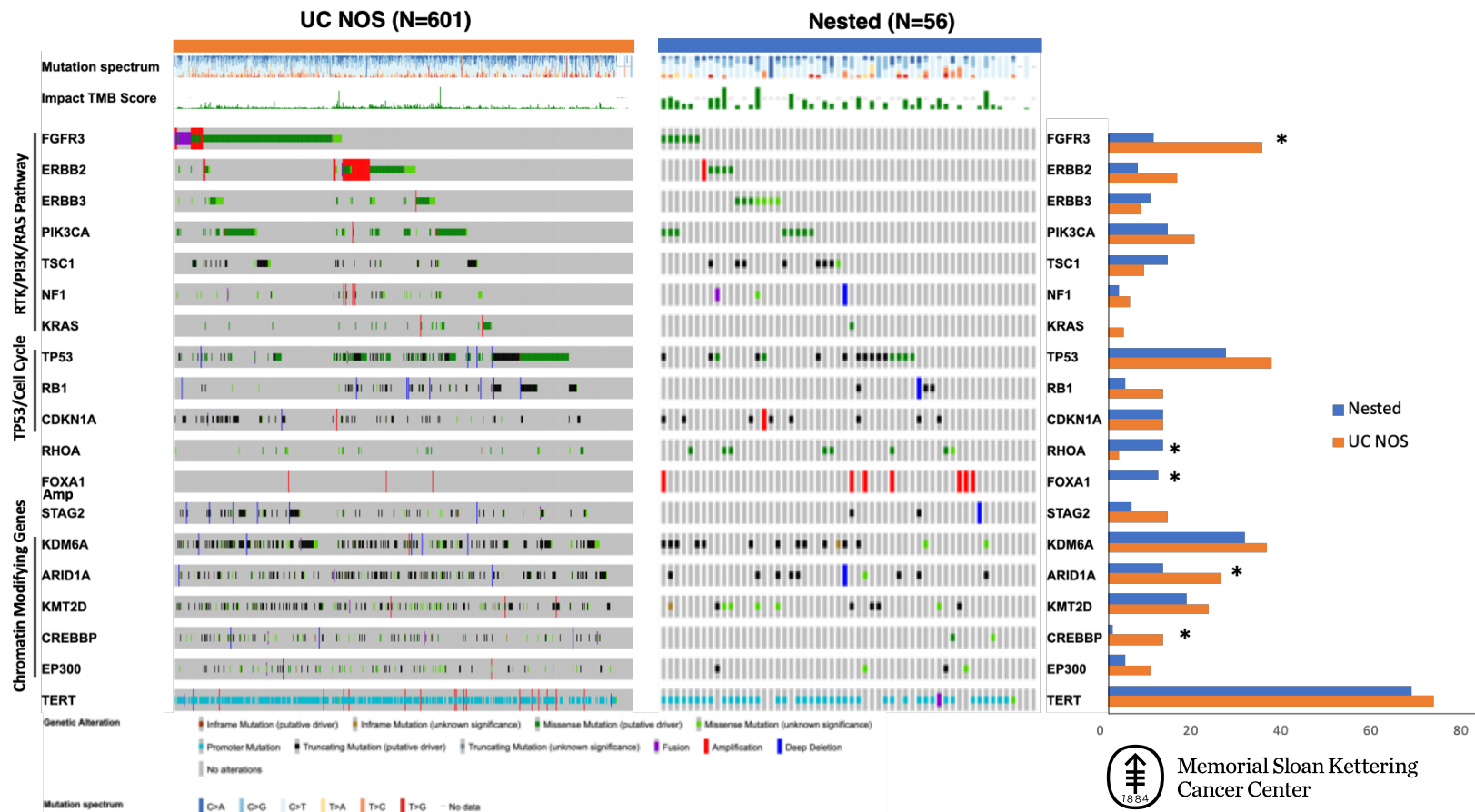


## MSKCC Nested Cases

- Pathologic re-review identified 82 cases of clinically localized NVUC
- 56 cases with classic NVUC, 26 with high-grade UC with nested features and 601 UC NOS
- Median follow-up was 4.3 years
- 468 cancer-associated genes, 136 had at least 5% mutational frequency
- Tumor mutational burden was lower in classic NVUC than UC NOS



# MSK-IMPACT of UC NOS vs Nested



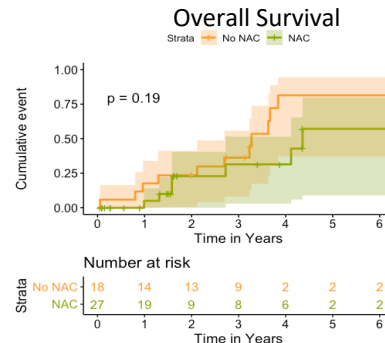
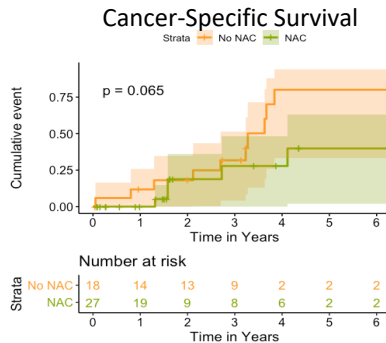
# Classic NVUC vs UCNOS

Alterations	Nested	UC NOS	p-value	q-value
FGFR3	12	36	<b>&lt;0.001</b>	<b>0.002</b>
ERBB2	8.3	17	0.076	0.31
ERBB3	11	8.9	0.7	0.86
PIK3CA	15	21	0.33	0.65
TSC1	15	9.6	0.19	0.45
NF1	4.2	6.5	0.61	0.83
KRAS	1.4	5.1	0.24	0.52
TP53	28	38	0.12	0.32
RB1	5.6	14	0.067	0.31
CDKN1A	14	14	>0.99	>0.99
RHOA	14	4.2	<b>0.002</b>	<b>0.031</b>
FOXA1 AMP	13	0.6	<b>&lt;0.001</b>	<b>&lt;0.001</b>
STAG2	6.9	15	0.1	0.32
KDM6A	32	37	0.49	0.79
ARID1A	14	27	<b>0.022</b>	0.17
KMT2D	19	24	0.47	0.79
CREBBP	2.8	14	<b>0.01</b>	0.12
EP300	5.6	11	0.21	0.49
TERT	69	74	0.4	0.74



# DNA Damage Repair Genes

- As a marker of potential chemosensitivity, evaluated DDR genes between UC NOS and NVUC
- This is a small cohort, but no difference in RFS, CSS and OS between NVUC who underwent NAC (n=27) and no NAC (n=18)



DDR	Nested	UC NOS	p-value	q-value
BRCA1	6.9	5.4	0.58	0.83
BRCA2	1.4	6.3	0.11	0.32
RAD50	7	1.2	>0.99	>0.99
ATR	7	5	0.79	0.9
ATM	9.7	9.6	>0.99	>0.99
RAD51C	0	1.5	0.61	0.83
CHEK2	0	4.2	0.1	0.32
DDR2	4	5	0.76	0.9
CDK12	1.8	4	0.5	0.79
RECQL4	0	2.7	0.71	0.86
FANCA	1.8	2.8	0.71	0.86
FANCC	0	1.3	>0.99	>0.99
ERCC2	2.8	12	<b>0.028</b>	0.18
ERCC5	1.4	0.9	0.52	0.8

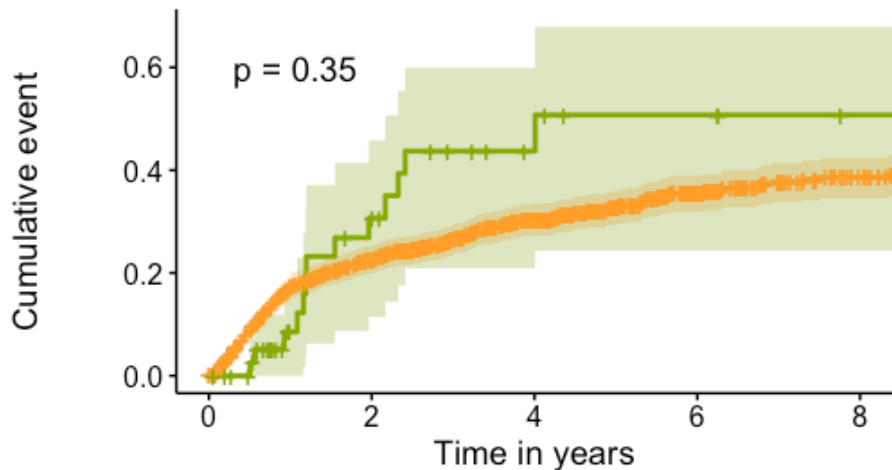
Statistical tests: Fisher's exact test; chi-square test of independence

False discovery rate correction for multiple testing

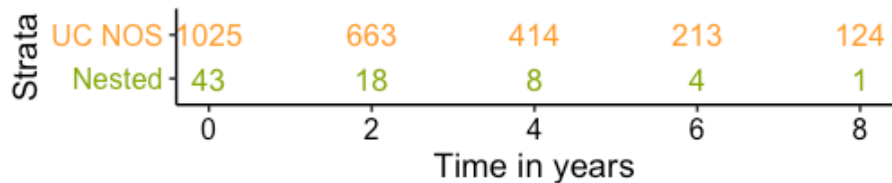


## Recurrence-Free Survival

Strata UC NOS Nested

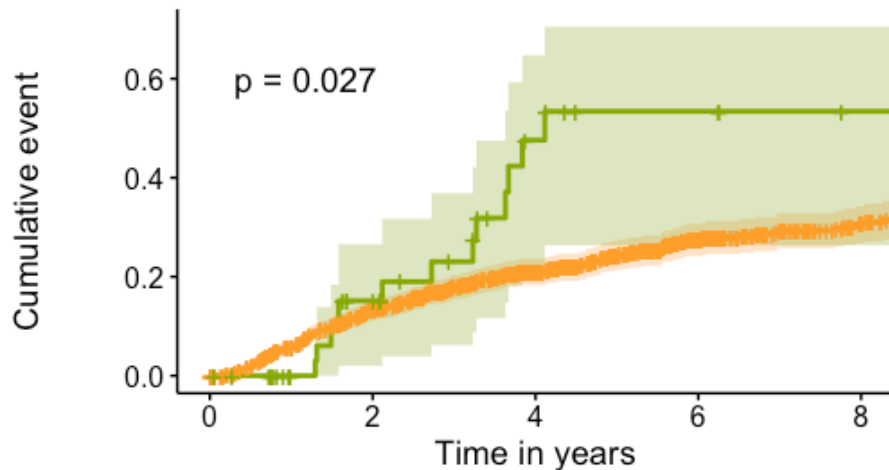


### Number at risk

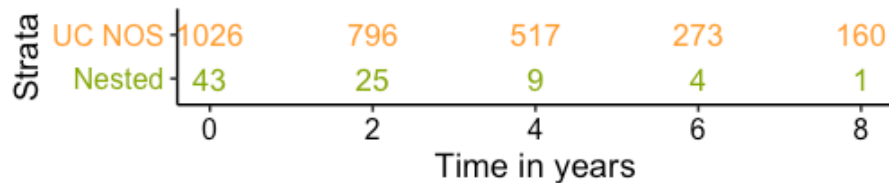


## Cancer-Specific Survival

Strata UC NOS Nested



### Number at risk





## Conclusions

- NVUC has significant overlap in the landscape of genomic alterations between UC NOS and NVUC
- NVUC are enriched for RhoA alterations and FOXA1 amplifications
- While NVUC and UC NOS have similar RFS, it has significantly worse CSS – but this is a small cohort

