

Memorial Sloan Kettering Cancer Center

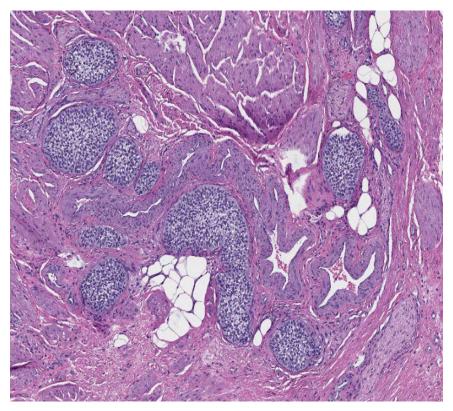
# Genomic Determinants of Nested Variant Urothelial Carcinoma (PD47-01)

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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**

### UC NOS (N=601) Nested (N=56) Mutation spectrum uwubalimboortomaaaalar Impact TMB Score FGFR3 ..... FGFR3 ERBB2 ERBB2 ERBB3 1 I I ERBB3 PIK3CA 10 100 PIK3CA **RTK/PI3K/** TSC1 ..... III I III TSC1 1 11 NF1 . . . . . 11<mark>1 |</mark> 110 | 11 | 11 NF1 KRAS . . . . . . . . . KRAS Cycle TP53 TP53 **P53/Cell** RB1 11 1 1 RB1 Nested CDKN1A CDKN1A 1 1 1 11 1. UC NOS RHOA RHOA FOXA1 FOXA1 Amp STAG2 STAG2 10.11.1 č KDM6A KDM6A ARID1A ARID1A KMT2D KMT2D CREBBP CREBBP EP300 EP300 TERT TERT nin mut Genetic Alteration Inframe Mutation (unknown significance) Missense Mutation (putative driver) Inframe Mutation (putative driver) 0 20 40 60 80 Promoter Mutation Truncating Mutation (putative driver) Truncating Mutation (unknown significance) Fusion Amplification Deep Deletion Memorial Sloan Kettering ŧ No alterations Cancer Center Mutation spectrum C>A C>G C>T T>A T>C T>G No data

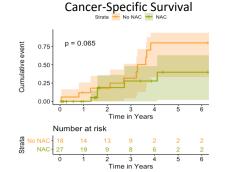
### **Classic NVUC vs UCNOS**

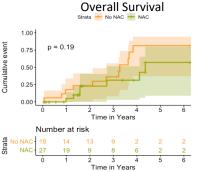
| Alterations | Nested | UC NOS | p-value | q-value |
|-------------|--------|--------|---------|---------|
| FGFR3       | 12     | 36     | <0.001  | 0.002   |
| ERBB2       | 8.3    | 17     | 0.076   | 0.31    |
| ERBB3       | 11     | 8.9    | 0.7     | 0.86    |
| PIK3CA      | 15     | 21     | 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    | 0.002   | 0.031   |
| FOXA1 AMP   | 13     | 0.6    | <0.001  | <0.001  |
| STAG2       | 6.9    | 15     | 0.1     | 0.32    |
| KDM6A       | 32     | 37     | 0.49    | 0.79    |
| ARID1A      | 14     | 27     | 0.022   | 0.17    |
| KMT2D       | 19     | 24     | 0.47    | 0.79    |
| CREBBP      | 2.8    | 14     | 0.01    | 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)

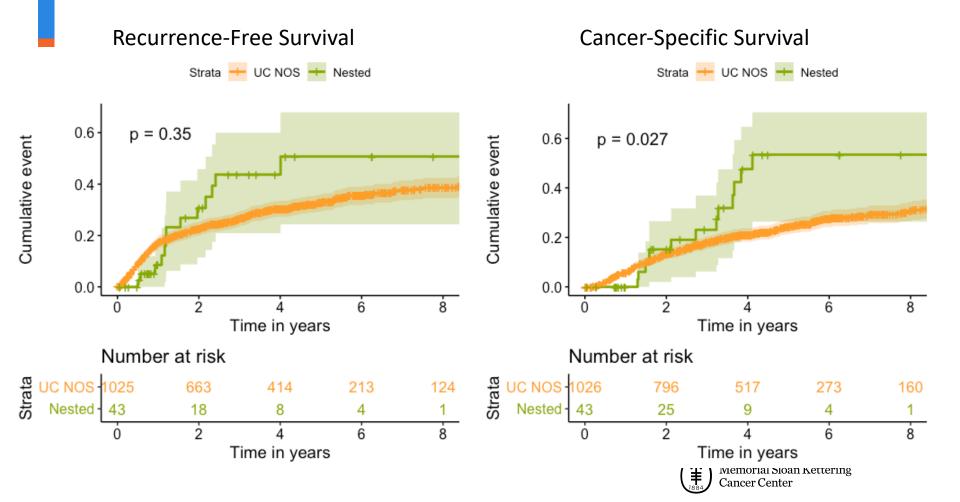




| DDR   | Nested | UC NOS | p-value | q-value |  |
|---|--------|--------|---------|---------|--|
| BRCA1   | 6.9    | 5.4    | 0.58    | 0.83    |  |
| BRCA2   | 1.4    | 6.3    | 0.11    | 0.32    |  |
| RAD50   | 7      | 1.2    | >0.99   | >0.99   |  |
| ATR   | 7      | 5      | 0.79    | 0.9     |  |
| 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     | 0.028   | 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





### 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

