Landscape Analysis of Urothelial Carcinoma (UC) by Telomerase Reverse Transcriptase (TERT) Alterations.

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Background

- TERT is a catalytic subunit of telomerase, the unique enzyme that confers immortality to cells and is expressed in > 90% of cancer cells.
- Mutations in the *TERT* promoter region (pTERTmut) are the most prevalent noncoding mutations in cancer.
- TERT is self-antigen and is immunogenic first reported by the Zanetti lab at UCSD two decades ago and subsequently by many groups worldwide.
- Immunogenic response to TERT are linked to improved outcomes for patients with cancer.
- Data suggest patients with pTERTmut have worse clinical outcomes
- However, small datasets suggest improved outcomes for patients with UC whose tumors harbor a pTERTmut when treated with immune checkpoint inhibitors
- We evaluated the molecular and immune landscape of UC with and without pTERTmut.

Methods

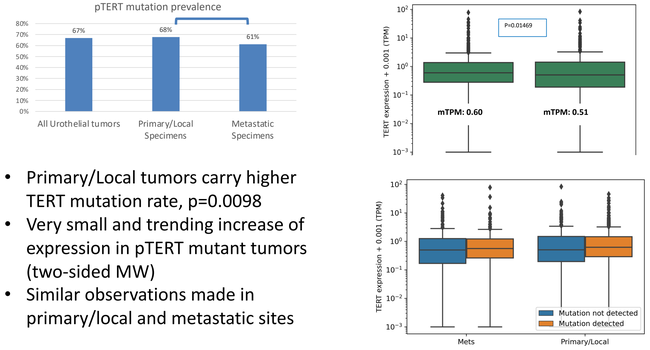
- UC tissue samples were analyzed for DNA alterations (NextSeq, 592 Genes; NovaSeq, WES) and mRNA expression (NovaSeq, WTS).
- Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine).
- PD-L1 expression was assessed by immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ).
    - SP142: FDA approved clone; IC (immune cell staining); Cutoff: >=5%
    - 22c3: CPS score (combine positive score: calculated as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total viable tumors cells, multiplied by 100. Cutoff: >=10)
- MSI/MMR was tested by fragment analysis, IHC and NGS. TMB-H was based on a cut-off of > 10 mut/MB.
- We compared alterations between samples with and without detected pathogenic pTERTmut. Significance was determined by Mann–Whitney U, X^2, and Fischer-Exact and p adjusted for multiple comparisons (q) was < 0.05 using Benjamini-Hochberg.

Results

Table 1: Tumor characteristics

		All Urothelial tumors	Primary/Local Specimens	Metastatic Specimens
Mutant		1126	810	305
Mutation Not Detected	Indeterminate	293	195	92
	Wild Type	267	191	102
	Total	1686	1196	499

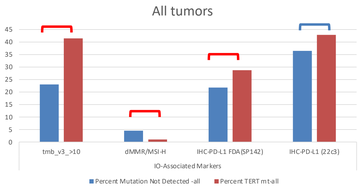
Figure 1: TERT promoter mutation and expression

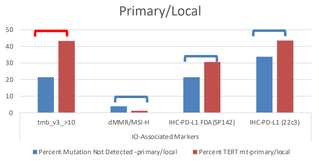


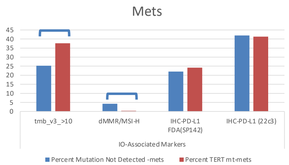
- Primary/Local tumors carry higher TERT mutation rate, p=0.0098
- Very small and trending increase of expression in pTERT mutant tumors (two-sided MW)
- Similar observations made in primary/local and metastatic sites

Figure 2: IO-associated biomarkers in pTERT mut vs. pTERT wt

Red brackets: significant differences between MT and WT (p<0.05 and q<0.05); blue: trending (p<0.05 and q>0.05)







- 41 % of pTERTmut are TMB-H
- pTERTmut are NOT associated with MSI-H
- pTERTmut are more often associated with a PDL1-High, though this difference is only seen in primary lesions

Results

Figure 3a: Co-occurring molecular alterations in pTERTmut vs pTERT wt

Red brackets: significant differences between MT and WT (p<0.05 and q<0.05)

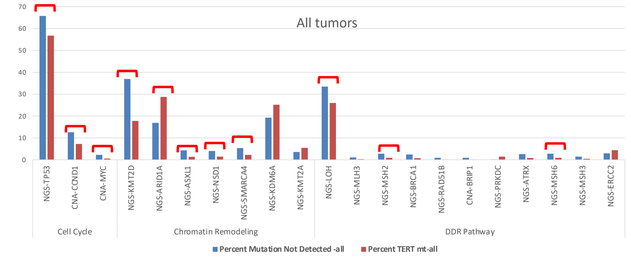
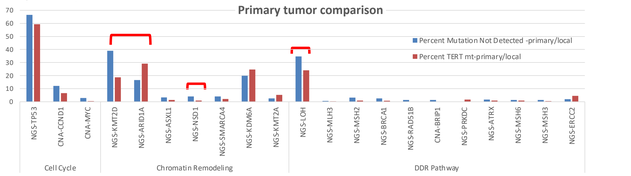


Figure 3b: Co-occurring molecular alterations in pTERTmut vs pTERT wt by site

Red brackets: significant differences between MT and WT (p<0.05 and q<0.05)



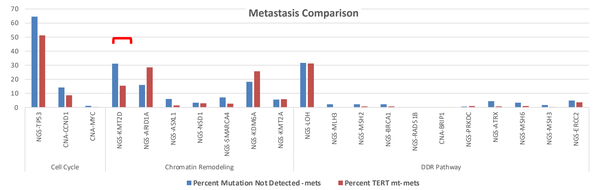


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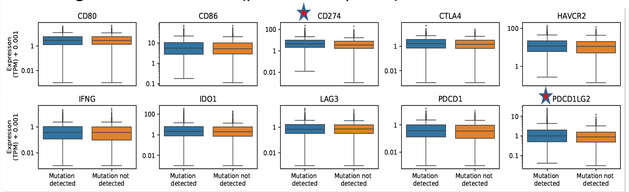
Figure 4: Immune related genes comparison

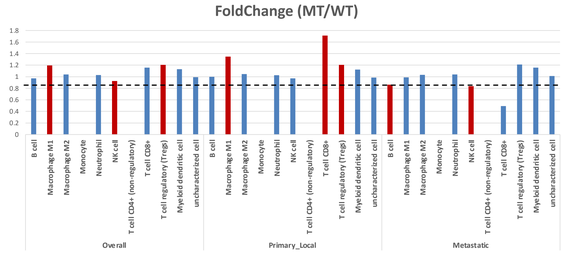
Stars: significant differences (p<0.05 and q<0.05)



- Significantly higher PD-L1 (CD274) and PD-L2 (PDCD1LG2) are seen in pTERT mutant tumors
- Overexpression of PD-L1, PD-L2 and TIM3 associated with pTERT mutations seen in Primary/Local sites, but not metastatic lesions (Data Not Shown)

Figure 5: Comparisons of cell populations in tumor microenvironment

Red bars: significant differences (p<0.05 and q<0.05)



- In primary tumors, pTERTmut associated with: increased M1 macrophage, increased CD8+ and Tregs
- In mets, pTERT associated with: decreased B-cells and NK cells

Conclusions

- This is the largest analysis looking at the molecular and immune landscape of pTERTmut UC tumors.
- pTERTmut was associated with an immune landscape linked to response to ICI; however, this was predominantly seen with primary tumors and not metastatic sites, suggesting a need to further evaluate the genomic and immune landscape of UC by tumor site.
- Further work is needed to understand differences in these molecular cohorts and the association of these data with clinical outcomes.