PPARG AMPLIFICATION IS ASSOCIATED WITH LACK OF RESPONSE TO ANTI-PD1 IN MUSCLE-INVASIVE UROTHELIAL CANCER

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Background
Although immune checkpoint inhibitor (ICI) approval has changed the treatment landscape of metastatic urothelial carcinoma, approximately 70% of patients succumb to refractory or acquired resistance. Tumor-cell intrinsic upregulation of PPARG is associated with lack of response to anti-PD1 and an immunosuppressive tumor-microenvironment (TME), characterized by anti-inflammatory cytokine signaling, decreased T-cell infiltration, T-cell dysfunction and increased myeloid-derived suppressive cells.

Methods
Tumors collected from 1393 patients with muscle-invasive urothelial cancer (MIUC) were sequenced using the Tempus xT assay (DNA-seq of 648 genes at 500x coverage; RNA-seq (1389 patients both, 1365 patients DNA only). Within the dataset, 275 patients received anti-PD1 therapy. Pre-anti-PD1 treatment tissues were analyzed (threshold ≤90 days from start-of-treatment to tissue-collection). PD-L1 expression was assessed using the PD-L1 IHC 22C3 PharmDx assay (Combined Proportion Score [CPS] cut-off of 10%). Gene expression values were normalized by transcripts-per-million (TPM). Immune infiltration was quantified with mcpCounter package in R. Patients were binned in 'Amplified' (AMP) vs ‘Non-Amplified’ (non-AMP) groups by PPARG copy-number cut-off of 3. Kaplan-Meier analyses were performed based on real-world Progression Free Survival (rw-PFS) and PPARG amplification.

Results
The median mRNA expression level of PPARG was significantly higher in the PPARG AMP group (n = 194) compared to PPARG non-AMP group (n = 1167) (8.81 Log2[TPM+1] vs 7.39 Log2[TPM+1]; p< 2.2e-16). PPARG expression was also higher in the PD-L1-negative tumors (CPS < 10) compared to PDL1-positive tumors (7.79 Log2[TPM+1] vs 7.28 Log2[TPM+1]; p=0.026). PPARG AMP tumors exhibited a cold immune-phenotype compared to the PPARG non-AMP tumors, associated with lower CD8+ T-cell infiltration signature score (3.99 Log2[TPM+1] vs 5.73 Log2[TPM+1]; p=0.0025) and lower expression of other immune cells (table 1). Survival analysis in patients treated with anti-PD1 showed significant shorter rwPFS (p = 0.034) for patients with PPARG AMP (n = 41) compared to the non-AMP group (n = 222).

Conclusions
PPARG overexpression and amplification in a large MIUC cohort correlates with low PD-L1 expression, a cold immune-phenotype and lack of response to anti-PD1. Others have demonstrated the significant role PPARG plays in immune modulation of the TME. FX-909, a first-in-class covalent PPARG inverse agonist that will be evaluated in a Ph1 trial this year, will offer an opportunity to investigate the impact of PPARG inhibition on the TME of MIUC patients. FX-909 combination with ICI therapy potentially provides a ‘one-two punch’ strategy to overcome resistance to immuno-therapy in MIUC patients with high PPARG expression.