Gene Expression Profiling in Wildtype and Mutant FGFR3 Metastatic Urothelial Cancer Treated With Combination Therapy With Vofatamab and Pembrolizumab

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Introduction
Metastatic Urothelial Cancer Management
- Cisplatin-based chemotherapy remains the standard front-line therapy for metastatic urothelial cancer (mUC)
- Patients who have prior platinum-based chemotherapy have a poor prognosis
- Immune checkpoint inhibition with programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) targeting agents remain the standard therapy for patients with progressive disease (PD)
- Overall response rate (ORR) with immunotherapy is sub-optimal (pembrolizumab has a response rate of ~21% for post-platinum-based chemotherapy)

Rationale for Development of Combination Therapy
- Fibroblast growth factor receptor 3 (FGFR3) mutations/fusions (mut/fus) in mUC
  - Bladder: 50% show FGFR3 over-expression and 15–20% of patients have FGFR3 mut/fus
  - Upper tract >30% have FGFR3 mut/fus
- FGFR3 inhibitors are targeted therapies and have improved safety and tolerability, ORR
- Effects of FGFR3 expression after treatment
- Pathway Alterations in Responders After Vofatamab Treatment
- Relationship Between FGFR3 Expression and Response to Therapy

Methods
FIERCE-22: Phase 1b/2 Study
Vofatamab + Pembrolizumab in 2nd Line mUC
- Aim: To obtain paired biopsies to understand the effects in the tumor microenvironment of vofatamab monotherapy prior to combination with pembrolizumab
- FGFR3 status
- Pathway alterations in responders after vofatamab treatment
- Relationship between response and immune pathway expression

Results
Patient Response by Cluster and Molecular Subtype
- Majority of luminal tumors seem to be genomically unstable
- Presence of CAFs appeared associated with lack of response to the combined therapy

Conclusions
- Compared to historical response rate (21%), the response rate of 36% (8/22) appears to be enriched regardless of FGFR3 status (WT vs mut/fus)
- 35% (7/21) responders with WT FGFR3, 40% (2/5) with FGFR3 mut/fus, and 67% (4/6) with luminal biology
- Post-exposure to vofatamab, responders had upregulation of genes associated with an inflammatory response
- Responses were enriched in the cohort with a luminal gene expression profile (immunologically cold)
- Presence of CAFs appeared associated with lack of response to the combined therapy, across all 3 subtypes
- Future larger cohort studies are needed to validate these observations

References: 1. [OMIM entry for FGFR3](https://omim.org/entry/143850)

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Presented at AACR Bladder Cancer: Transforming the Field Special Conference, May 18–21, 2019, Denver, CO