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

W. Choi[1], D. McConkey[1], I.D. Lee[2], G. Currie[3], E. Abella[3], W. Kelly[2], A.O. Siefker-Radtke[2]

[1]Johns Hopkins Greenberg Bladder Cancer Institute, Johns Hopkins University School of Medicine, Baltimore, MD; [2]University of Texas MD Anderson Cancer Center, Houston, TX; [3]Rainier Therapeutics, San Leandro, CA

1040 Davis St. #202
San Leandro, CA 94577
info@rainierrx.com
925-413-6140

Introduction

Metastatic Urothelial Cancer Management

- Cisplatin-based chemotherapy remains the standard front-line therapy for metastatic urothelial cancer (mUC)
- Patients who failed 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 remains 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% post-platinum-based chemotherapy)[1]

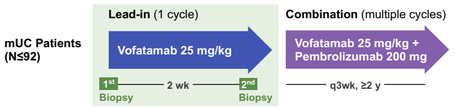
Rationale for Development of Combination Therapy

- 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: ~35% have FGFR3 mut/fus
- FGFR3 inhibitors are targeted therapies and have improved the clinical management of mUC—FDA recently approved erdifitinib
- Vofatamab (B-701) is a fully human monoclonal antibody against FGFR3 that blocks activation of both the wildtype (WT) and activating FGFR3 mutations
- FIERCE-22 (NCT03123055) is a study of vofatamab (B-701) in combination with pembrolizumab in treatment of locally advanced or metastatic urothelial cell carcinoma

Methods

FIERCE-22: Phase 1b/2 Study
Vofatamab + Pembrolizumab in 2nd Line mUC

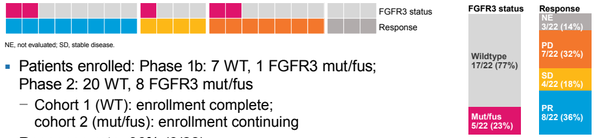
- **Aim:** To obtain paired biopsies to understand the effects in the tumor microenvironment of vofatamab monotherapy prior to combination with pembrolizumab



- ~52 sites in US, EU, Asia
- **Eligibility criteria:** mUC progressed on ≥1 platinum-based chemotherapy; anti-PD-1/PD-L1–naïve
- **Primary endpoints:** safety and tolerability, ORR
- **Secondary endpoints:** overall survival (OS), progression-free survival (PFS), FGFR3 target modulation

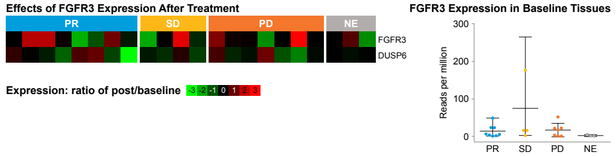
Results

Patient Characteristics

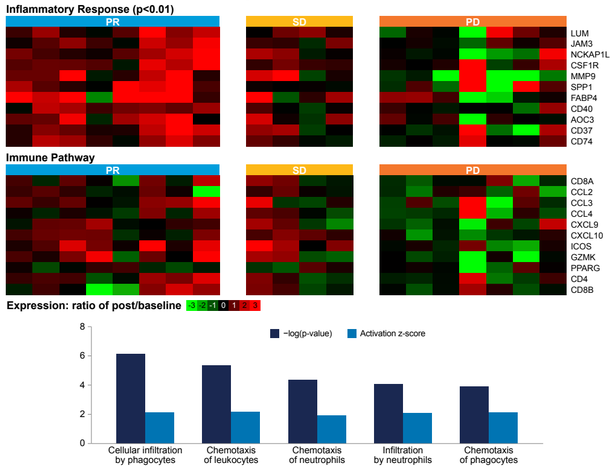


- Patients enrolled: Phase 1b: 7 WT, 1 FGFR3 mut/fus; Phase 2: 20 WT, 8 FGFR3 mut/fus
  - Cohort 1 (WT): enrollment complete; cohort 2 (mut/fus): enrollment continuing
- Response rate: 36% (8/22)
- 22 patients had matched pre- and post-treatment biopsies
- FGFR3 mut/fus: 23% (5/22)

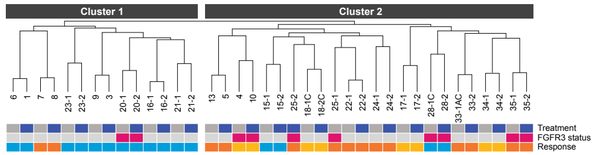
Relationship Between FGFR3 Expression and Response to Therapy



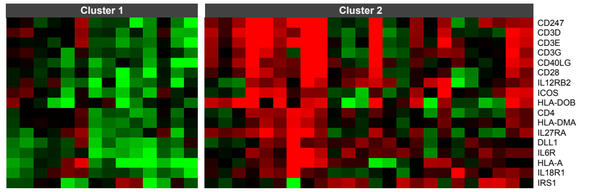
Pathway Alterations in Responders After Vofatamab Treatment



Unsupervised Cluster Analysis Using Global Gene Expression Pattern

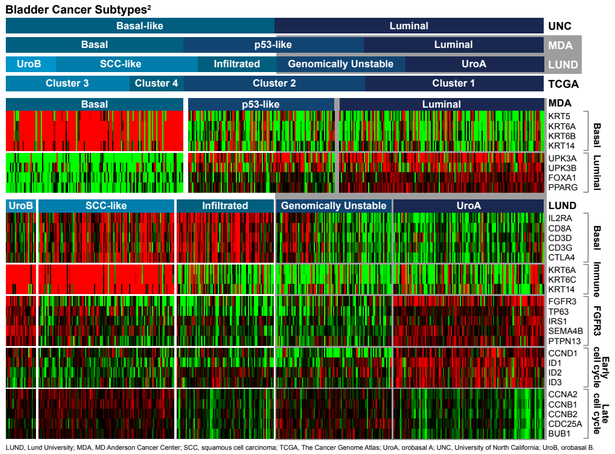


Genes in Immune Pathway Expression in Clusters



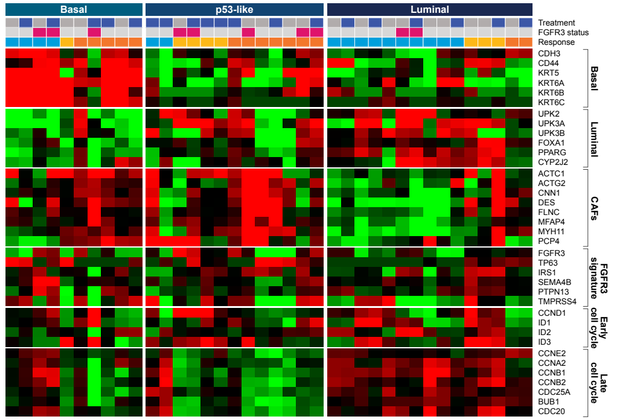
Responders were enriched in Cluster 1 that is immunologically cold → Relationship between response and molecular subtypes? (basal, luminal, p53-like tumors?)

Molecular Subtypes of Bladder Cancer



LUND, Lund University; MDA, MD Anderson Cancer Center; SCC, squamous cell carcinoma; TCGA, The Cancer Genome Atlas; UroA, orobasal A; UNC, University of North California; UroB, orobasal B.

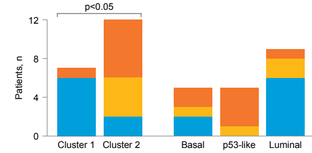
Association Between Molecular Subtypes and Response to Combination Therapy



CAF, cancer-associated fibroblast.

Patient Response by Cluster and Molecular Subtype

- Majority of luminal tumors seem to be genomically unstable
- CAFs signature is enriched in nonresponders in each subtype



Conclusions

- Compared to historical response data (21%), the response rate of 36% (8/22) appears to be enriched regardless of FGFR3 status (WT vs mut/fus)
  - 35% (6/17) responders with WT FGFR3, 40% (2/5) with FGFR3 mut/fus, and 67% (6/9) 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. Bellmunt J, et al. N Engl J Med 2017;376:1015-26; 2. Kamat AM, et al. Lancet 2016;388:2796-2810.

Acknowledgments: We extend our thanks to the patients and their families. This study was funded by Rainier Therapeutics.

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