Hypoxia drives tumorigenesis and therapy resistance in renal medullary carcinoma

Pavlos Msaouel, MD, PhD
Assistant Professor
Genitourinary Medical Oncology & Translational Molecular Pathology
University of Texas MD Anderson Cancer Center
Disclosures

- **Advisory Boards / Honoraria:**
  - Mirati Therapeutics, Bristol-Myers Squibb, Exelixis, Axiom Healthcare Strategies

- **Non-branded educational programs:**
  - Exelixis, Pfizer

- **Clinical Trials with Grant Support:**
  - Bristol-Myers Squibb, Mirati Therapeutics, Takeda Pharmaceutical Company
Renal Medullary Carcinoma (RMC)

- Extremely aggressive\(^1,2\)
- Predominantly affects young African Americans with sickle cell trait or other sickle hemoglobinopathies\(^1,2\)
- More common in men (70\%)\(^1,2\)
- \(3\) times more common on right kidney (~75\% of cases)\(^1,2\)
- Defined by loss of the SMARCB1 (INI1) protein\(^1,2\)
- May be associated with high-intensity, but not moderate intensity, exercise\(^3\)

\(^2\) Msaouel P, et al. *Clin Cancer Res*; 24(9);2044-2049. PMID: 29440190
\(^3\) Shapiro D. et al. *Cancers (Basel)*; 13(23):6022. PMID: 34885132
Hypoxia is a hallmark of RMC

Sickled RBCs increase renal medulla hypoxia

RMC arises under extreme hypoxia

Contrast with ccRCC: pseudohypoxia due to VHL loss


$^2$Msaouel P, et al. Clin Cancer Res; 24(9);2044-2049. PMID: 29440190
RMC is resistant to anti-VEGF therapies

- No response to anti-VEGF TKIs (e.g., sunitinib, axitinib, cabozantinib, lenvatinib) or mTOR inhibitors (everolimus, temsirolimus)\(^1\),\(^2\)

- **SMARCB1** regulates hypoxic stress response in sickle cell trait\(^3\)

\(^1\)Shah AY et al. *BJU Int*. 2017 Dec;120(6):782-792. PMID: 27860149

Melinda Soeung  Giannicola Genovese

2022 Kidney Cancer Research Research Summit
Erlotinib + bevacizumab in RMC

- Clinically active post-cytotoxic chemotherapy and proteasome inhibition:\n  - SD in 7/10 patients
  - PR in 2/10 patients
  - PD in 1/10 patients
  - Median PFS 3.5 months

- EGFR inhibition but not VEGF inhibition is a viable therapeutic strategy for RMC

1Wiele et al. et al. Cancers (Basel). 2021 Apr 30;13(9):2170. PMID: 33946504
Safety and Efficacy of Panitumumab Plus Neoadjuvant Chemotherapy in Patients With Primary HER2-Negative Inflammatory Breast Cancer

Naoko Matsuda, MD1,2; Xiaoping Wang, PhD1,2; Bora Lim, MD1,2; et al

Author Affiliations | Article Information

- Panitumumab + carboplatin + nab-paclitaxel showed the highest pCR rate ever reported in triple-negative IBC.
- Carboplatin + nab-paclitaxel backbone is a preferred salvage regimen in RMC
- Panitumumab may be preferable to erlotinib in EGFR wild-type tumors
Panitumumab + carboplatin + nab-paclitaxel in RMC

- 68 yo M w/ metastatic RMC to the lungs, LNs, liver, adrenal and bone
- PS 3, rapidly progressing following second-line ixazomib + gemcitabine + doxorubicin. Hospice discussed.
- Deep PR with panitumumab triplet

Carboplatin + paclitaxel  
6 months

Ixazomib + gemcitabine + doxorubicin  
4 months

Panitumumab + carboplatin + nab-paclitaxel  
6 months (ongoing response)
Conclusions

- The loss of SMARCB1 protects RMC from anti-angiogenic pathway therapies
- EGFR pathway is a therapeutic vulnerability for RMC

Subsequent steps:
- Can the biological adaptations of RMC to hypoxia be therapeutically targeted?
- Validate panitumumab triplet in more patients
- Identify resistance mechanisms to EGFR targeting:
  - Phenotypic transformation
  - Tumor heterogeneity
  - Microenvironmental upregulation of ligands/growth factors
  - Bypass pathway activation/mutation
Acknowledgements

MD Anderson Cancer Center:
Msaouel Lab: Menuka Karki, Rong He, Jean-Philippe Bertocchio
Genitourinary Oncology: Nizar M. Tannir, Giannicola Genovese, Jianjun Gao, Eleonora Dondossola, Luigi Perelli, Jianfeng Chen
Genomic Medicine: Melinda Soeung, Sanjana Srinivasan
Urology: Niki Millward, Christopher Wood, Jose Karam, Manuel Ozambela, Kyle Blum
Radiation Oncology: Chad Tang
Translational Molecular Pathology: Ignacio Wistuba, Ximing Tang, Wei Lu, Cara Haymaker
Pathology: Priya Rao
Bioinformatics: Linghua Wang, Xinmiao Yan, Xiaoping Su, Hui Yao
Biostatistics: Peter Thall, Ying Yuan, Rebecca Slack
Molecular and Cellular Oncology: Chunru Lin, Liuqing Yang, Zilong Zhao
Cancer Biology: Katharina Schlacher
Institute for Applied Cancer Science: Timothy P. Heffernan, Alessandro Carugo, Virginia Giuliani

This work was supported in part by MD Anderson's Prometheus informatics system and the Department of Genitourinary Medical Oncology's Eckstein Laboratory

Baylor College of Medicine:
Cheryl L. Walker, Durga N. Tripathi, Cristian Coarfa, Sandy Grimm

University of Wisconsin:
Daniel D. Shapiro

Funding Agencies:
DOD KCRP Translational Research Partnership Award
DOD KCRP Concept Award
V Foundation Translational Research Award
Andrew Sabin Family Foundation
ASCO YIA Award
ASCO CDA Award
Kidney Cancer Association YIA Award
KCCure Research Award
The Sheikh Khalifa Bin Zayed Al Nahyan Scholarship