



**Kidney Cancer
Research Summit** KCRS21

Exploring the Tumor Microenvironment in Papillary Renal Cell Carcinoma: Insights into Correlates of Clinical Response

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7-8 OCTOBER, 2021 • PHILADELPHIA, PA

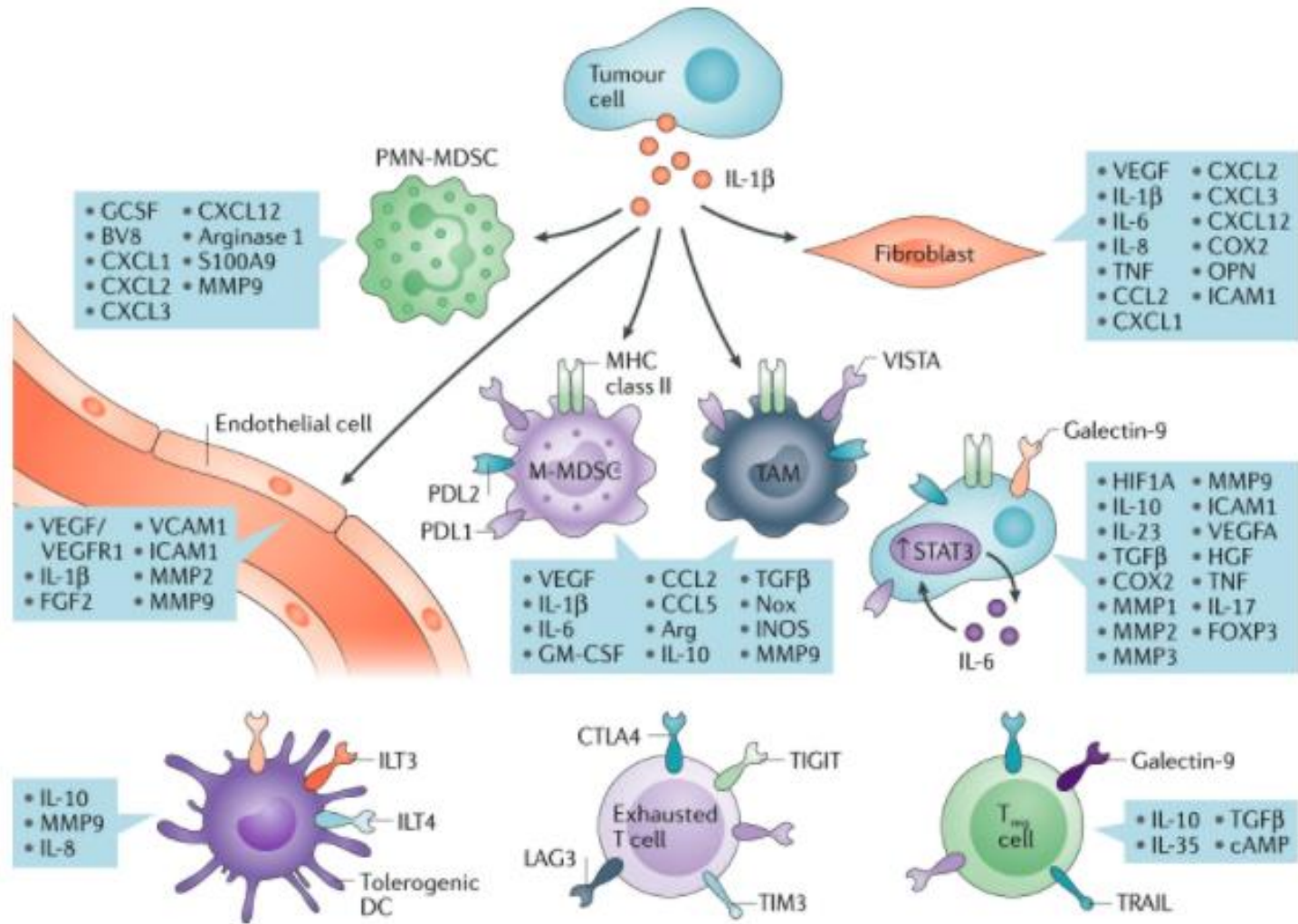
Disclosures

Nicholas Salgia: None

SKP: Research Funding from Eisai, Pfizer, Bristol Myers Squibb, Aveo, Nektar Therapeutics, Exelixis, QED

ND: Consulting from Vivreon Biosciences

Tumor Microenvironment in Renal Cell Carcinoma

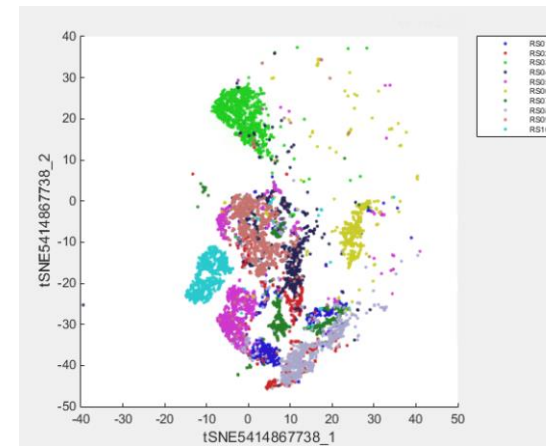
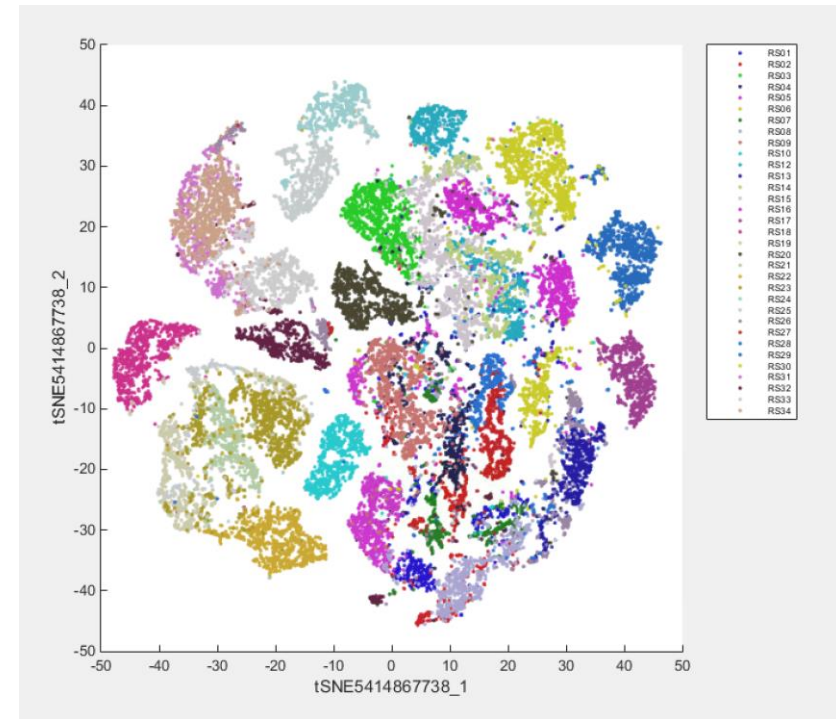


Imaging Mass Cytometry Antibodies		
Antibody Target	Rare-Metal Isotope Conjugate	Cell Marker
CD3	Erbium-170	T cell
CD4	Gadolinium-156	Helper T Cell
CD8a	Dysprosium-162	Cytotoxic T Cell
FoxP3	Gadolinium-155	Regulatory T Cell
CD68	Terbium-159	Monocyte/Macrophage
Arginase-1	Dysprosium-164	Myeloid Derived Suppressor Cell
CD33	Neodymium-145	Myeloid Stem Cell
HLA-DR	Ytterbium-174	T cell Activation and Antigen Presentation
Pan-Keratin (PanCK)	Neodymium-148	Epithelial Cell
PD-1	Holmium-165	T Cell Exhaustion
PD-L1	Neodymium-150	Immune Escape
Intercalator	Iridium-191 and Iridium-193	Live/Dead Exclusion

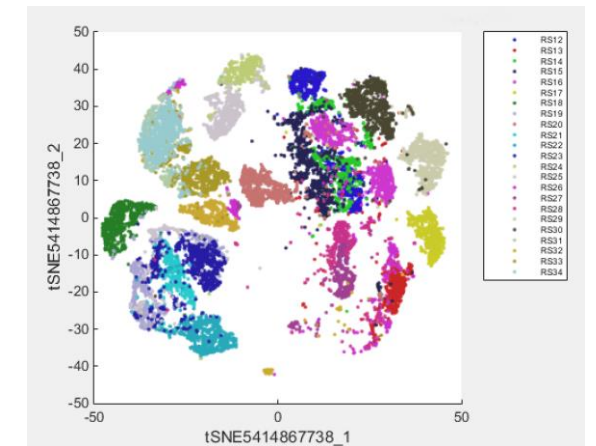
Diaz-Montero M. et al. "The immunology of renal cell carcinoma ." *Nat Rev Nephrol.* 2020.

Characteristic	Clear Cell RCC N=10 (%)	Papillary RCC N=23 (%)
Age Group		
<40	0 (0.0)	3 (13.0)
>40 and < 65	8 (80.0)	10 (43.5)
>65	2 (20.0)	10 (43.5)
Median Age at Diagnosis (Range)	59 (51-68)	62 (22-83)
Gender		
Female	2 (20.0)	5 (21.7)
Male	8 (80.0)	18 (78.3)
Median Lines of Therapy (Range)	2 (1-6)	3 (1-9)
Received Immunotherapy		
Yes	4 (40.0)	10 (43.5)
No	6 (60.0)	13 (56.5)
Received a VEGF-Inhibitor		
Yes	8 (80.0)	13 (56.5)
No	2 (20.0)	10 (43.5)
Received a MET-Inhibitor		
Yes	3 (30.0)	19 (82.6)
No	7 (70.0)	4 (17.4)
First Line Drug Class		
Chemotherapy	0 (0.0)	1 (4.3)
Cytokine Therapy	1 (10.0)	0 (0.0)
Immune Checkpoint Inhibitor	1 (10.0)	0 (0.0)
MET Inhibitor	0 (0.0)	14 (60.9)
mTOR Inhibitor	1 (10.0)	2 (8.7)
VEGF Inhibitor	7 (70.0)	6 (26.1)
Median Overall Survival, Months (Range)	63.8 (13.5-83.3)	27.5 (2.2-133.6)

All Cells



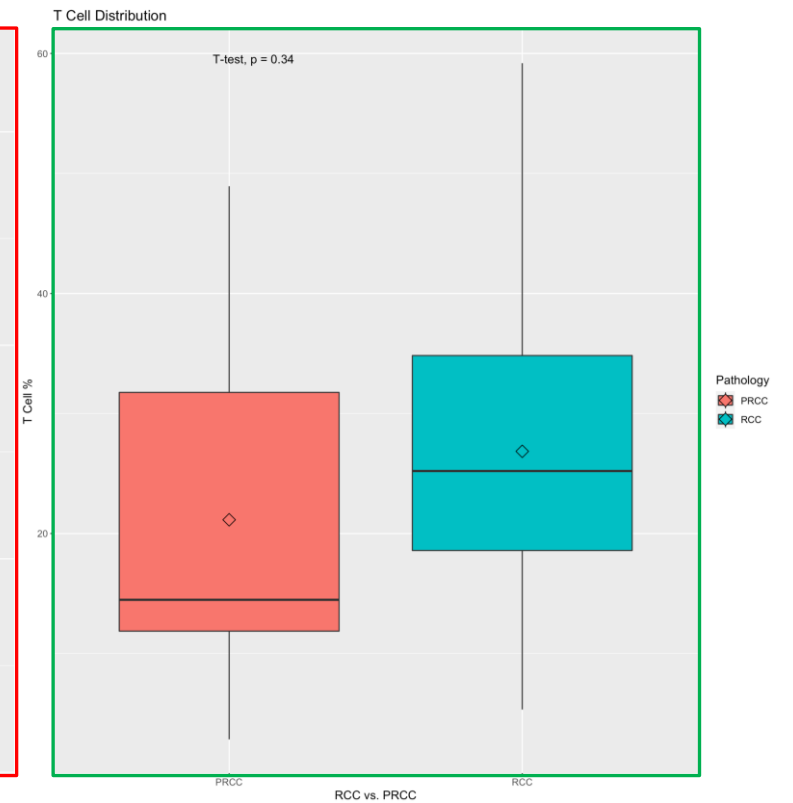
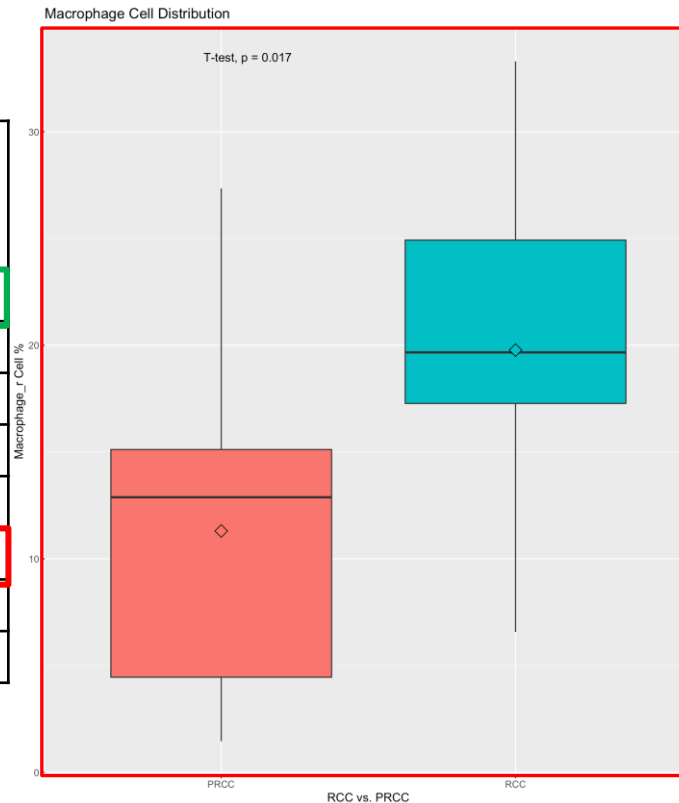
Clear Cell RCC



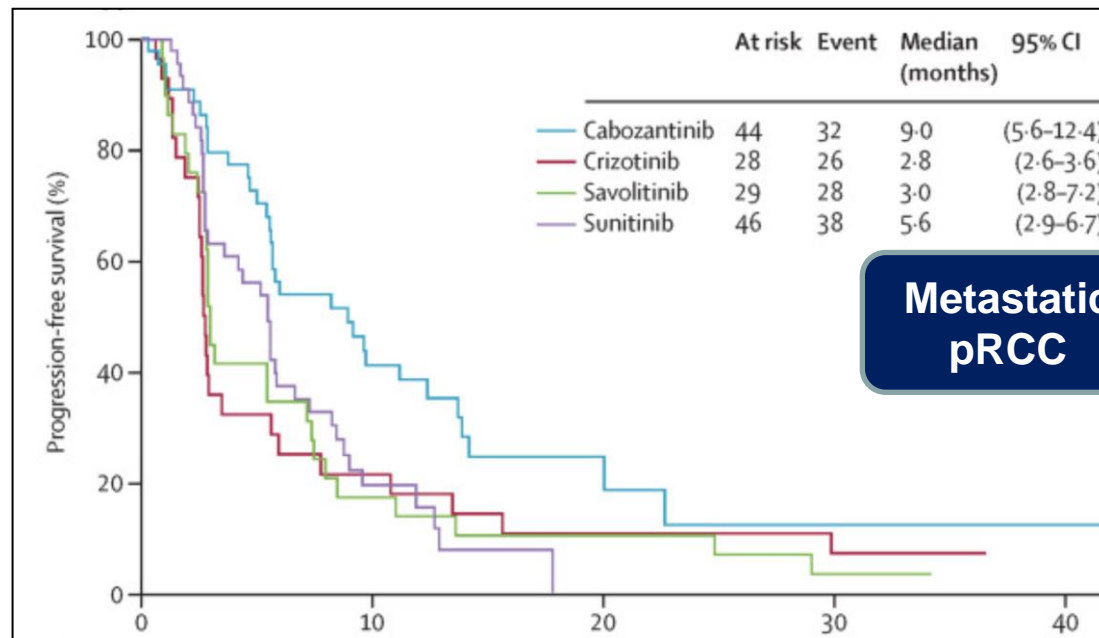
Papillary RCC

TME Composition: Clear Cell vs Papillary RCC

Marker	pRCC Mean % total cell population (Standard Deviation)	ccRCC Mean % total cell population (Standard Deviation)	p-value
CD3+	21.1 (15.0)	26.8 (15.4)	0.33
CD4+	8.0 (7.4)	11.1 (12.1)	0.51
CD8+	11.0 (6.7)	13.0 (7.9)	0.48
FoxP3	5.2 (5.6)	5.4 (2.2)	0.96
PanCK	15.5 (14.8)	10.0 (7.4)	0.29
CD68+	11.3 (7.4)	19.8 (8.5)	0.01
Arginase1+	7.9 (3.5)	21.6 (3.1)	0.02
No Marker	40.5 (18.2)	36.8 (12.3)	0.57



PAPMET: First Randomized Data Supporting MET Inhibition in Papillary RCC



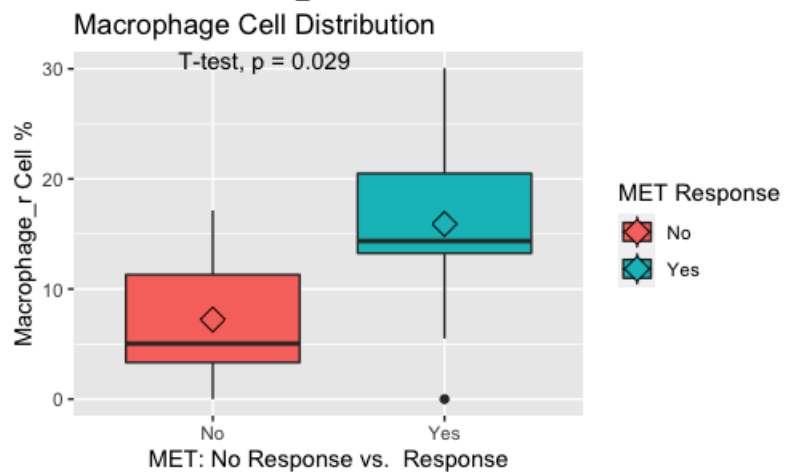
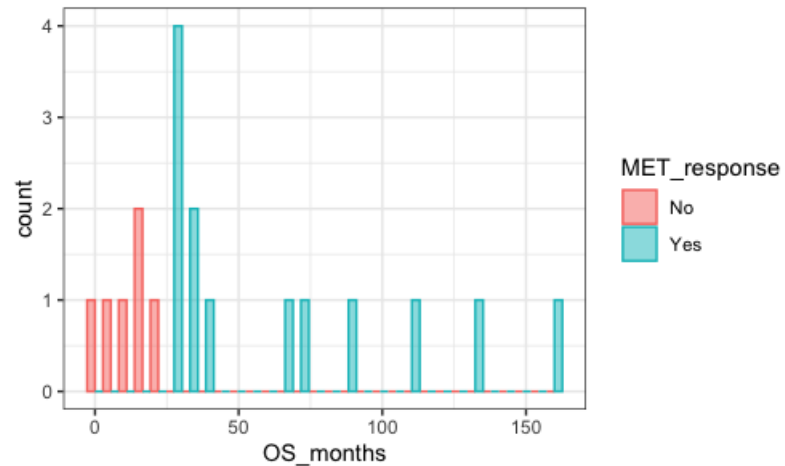
Metastatic pRCC

1:1:1:1
R

- Sunitinib
- Cabozantinib
- ~~Crizotinib~~
- ~~Savolitinib~~

Pal SK. et al. "A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomized, open-label, phase 2 trial." *Lancet*. 2021

TME Composition: Responders vs Non-Responders to MET Inhibition in Papillary RCC



Marker	No Response to MET Inhibition Mean % total cell population (Standard Deviation)	Response to MET Inhibition Mean % total cell population (Standard Deviation)	p-value
CD3+	16.7 (10.8)	24.8 *16.6)	0.30
CD4+	7.7 (8.3)	3.6 (4.6)	0.18
CD8+	8.1 (5.3)	10.9 (9.7)	0.52
FoxP3+	0.5 (0.7)	1.8 (4.4)	0.48
PanCK+	23.4 (21.3)	11.5 (8.4)	0.09
CD68+	7.2 (6.5)	15.9 (8.3)	0.03
Arginase1+	3.1 (5)	2.2 (4)	0.69
No Marker	44.7 (17.4)	41.9 (14.3)	0.71

Discussion

- The tumor microenvironment of papillary RCC is heterogenous with distinct differences from clear cell RCC
 - Papillary RCC contained lower proportions of macrophages and myeloid derived suppressor cells
- The relative proportion of tumor-associated macrophages is higher in papillary RCC patients who achieved therapeutic benefit from MET inhibitors
 - Recent evidence suggests MET is expressed on tumor-infiltrating macrophages and shifts macrophage polarization to an immunosuppressive M2-like phenotype
- The tumor microenvironment is relatively unexplored with dynamic interplays between immune, endothelial, epithelial, and carcinoid compartments and robust opportunities for future discovery in RCC
 - Integration of novel techniques interrogating the TME is prudent and may unravel further clinical correlates and/or biological targets

Nishikoba N. et al. "HGF-MET Signaling Shifts M1 Macrophages Toward an M2-Like Phenotype Through PI3K-Mediated Induction of Arginase-1 Expression." *Front. Immunol.* 2020.

Thank you!

City of Hope Genitourinary Research Team

- Sumanta Kumar Pal, MD (The Boss Man)
- JoAnn Hsu (GU Project Manager)
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