Biomarkers in Renal Cell Cancer

Yousef Zakharia MD

Professor of Medicine
Interim Chair, Genitourinary Malignancy Disease Group
Program Leader: Kidney Cancer
Mayo Clinic Enterprise

Leader, Experimental Therapeutics and Phase I Clinics
Mayo Clinic Arizona

MaTOS
March 2025

NCI Designated Comprehensive Cancer Center

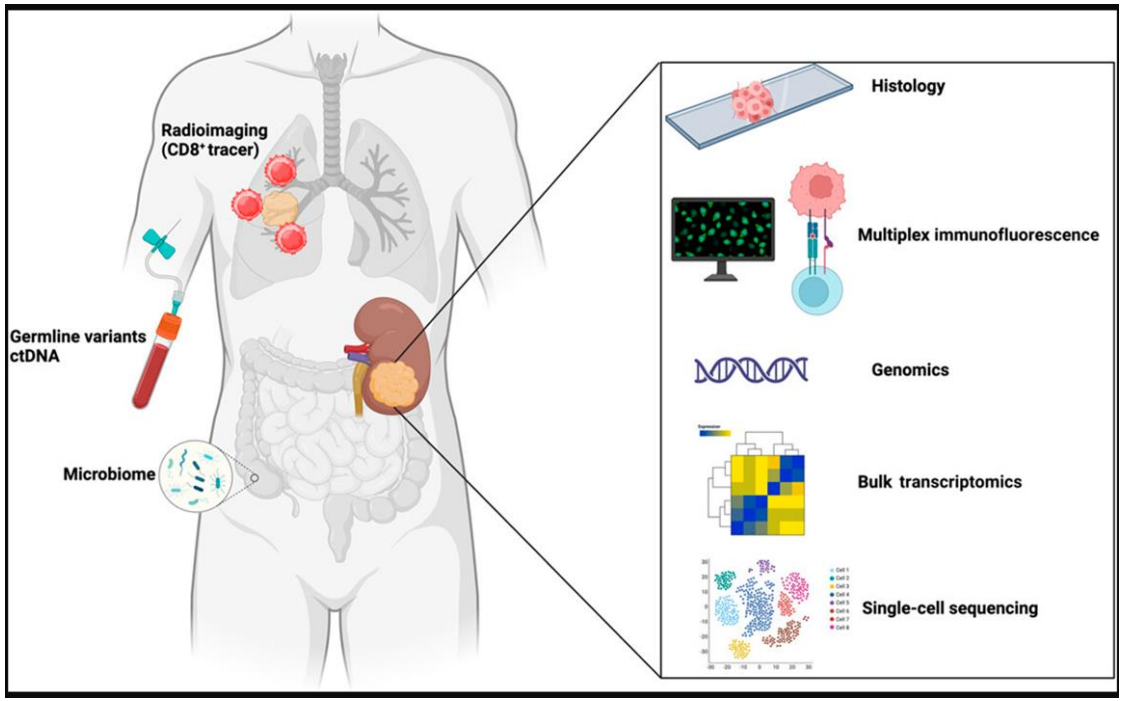
@ZakhariaYousef

Long Story Short

- Nothing ready for prime time, but…

Long Story Short

- Nothing ready for prime time, but…. We see the tip of the iceberg:
  - Histology
  - Genomics
  - RNA seq
  - Single Cell RNA seq
  - Serum (KIM-1, ctDNA)

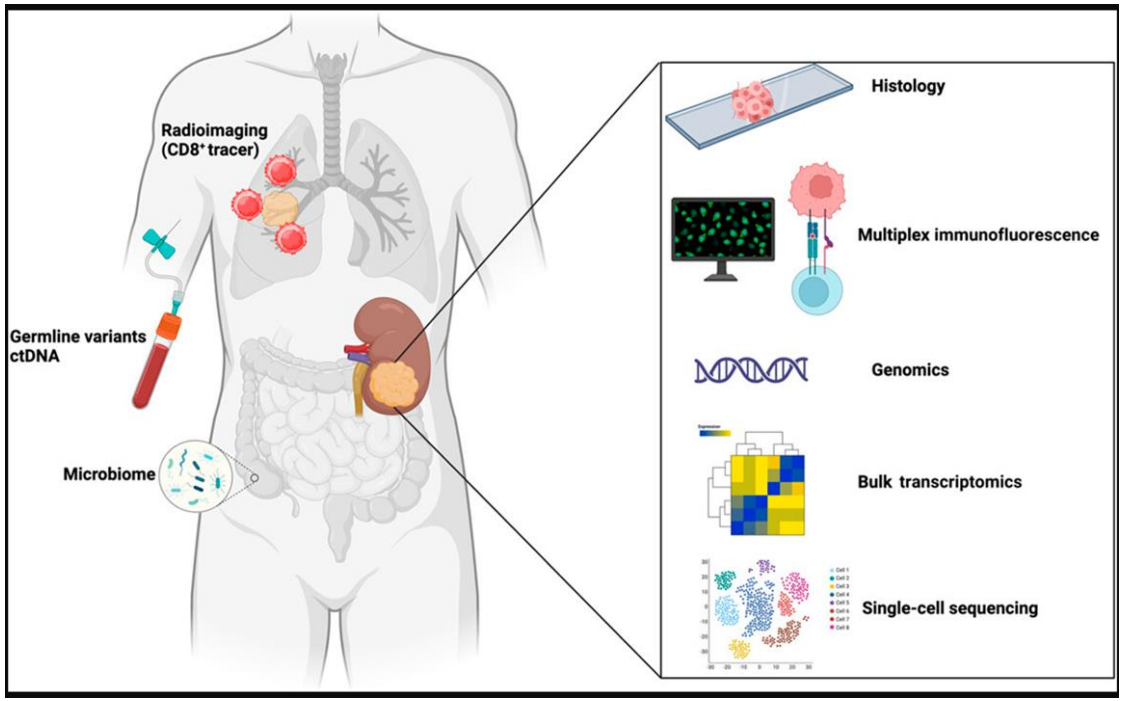


Saliby, ASCO 2024

@ZakhariaYousef

Long Story Short

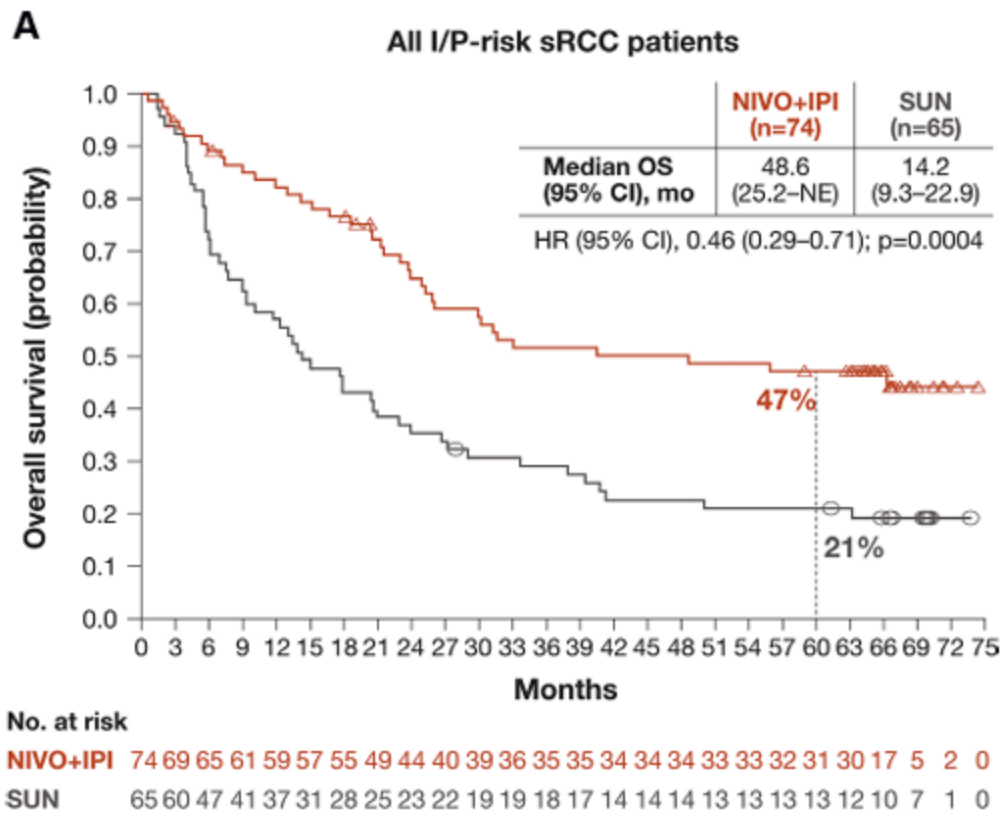
- Nothing ready for prime time, but…. We see the tip of the iceberg:
  - Histology
  - Genomics
  - RNA seq
  - Single Cell RNA seq
  - Serum (KIM-1, ctDNA)

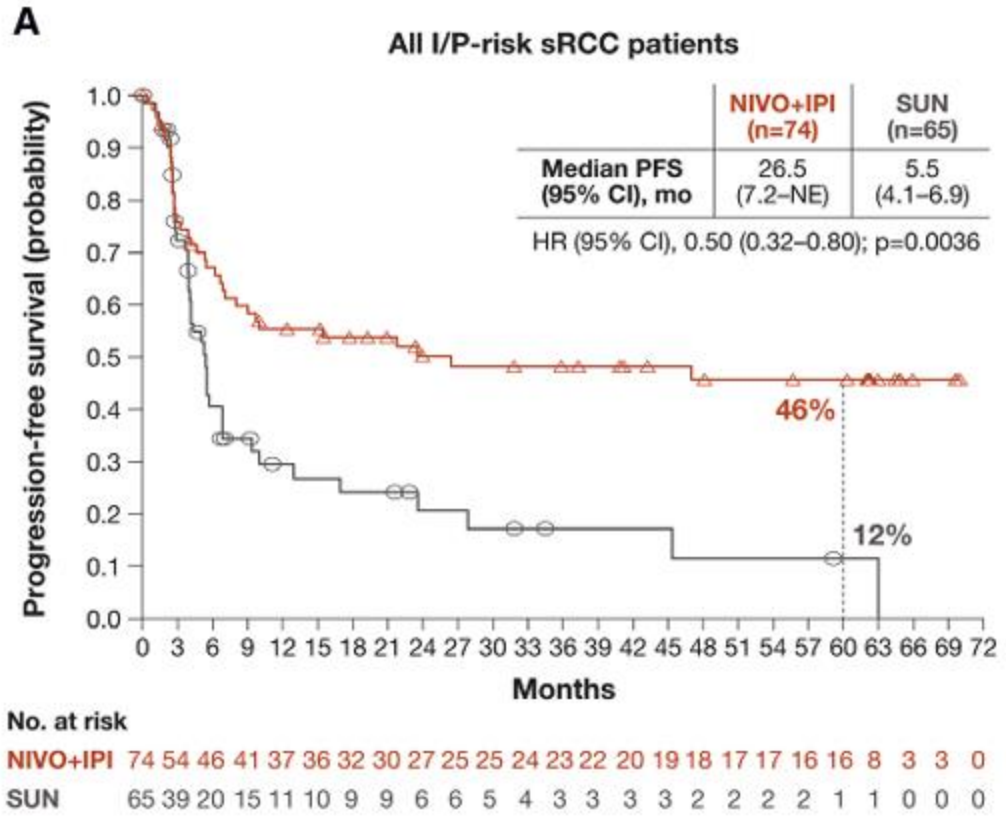


Saliby, ASCO 2024

@ZakhariaYousef

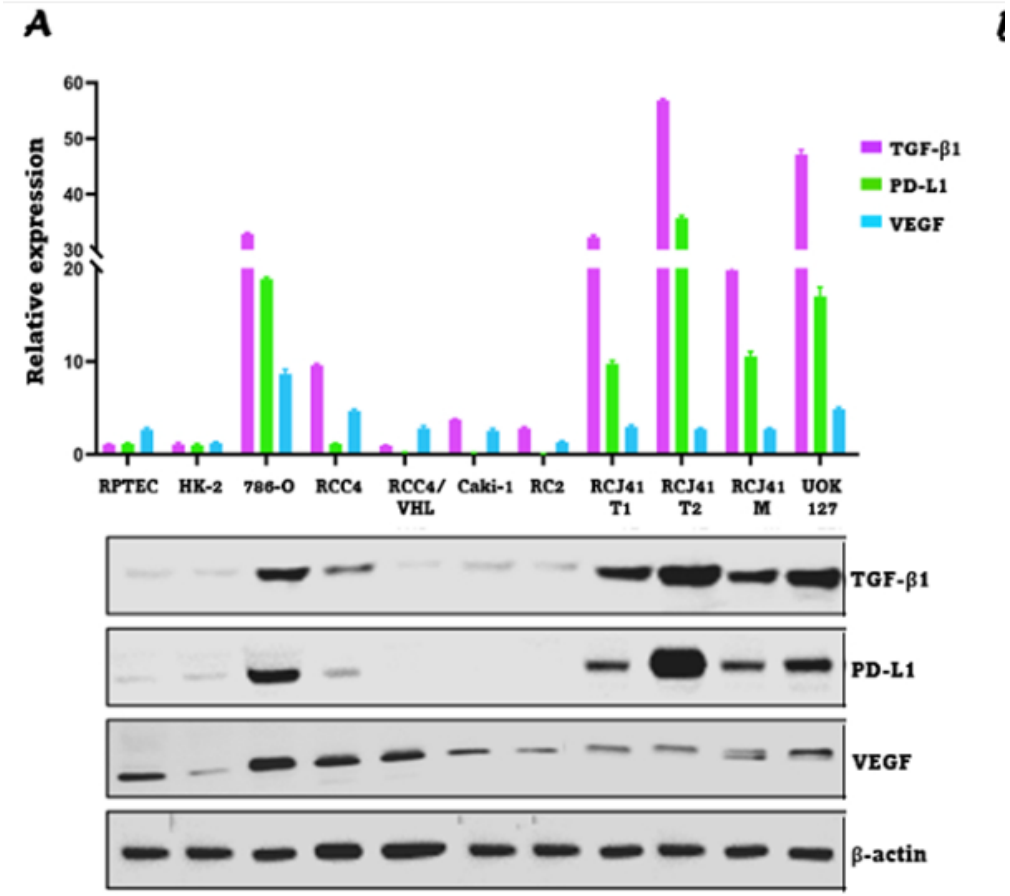
Sarcomatoid ccRCC form Checkmate 214

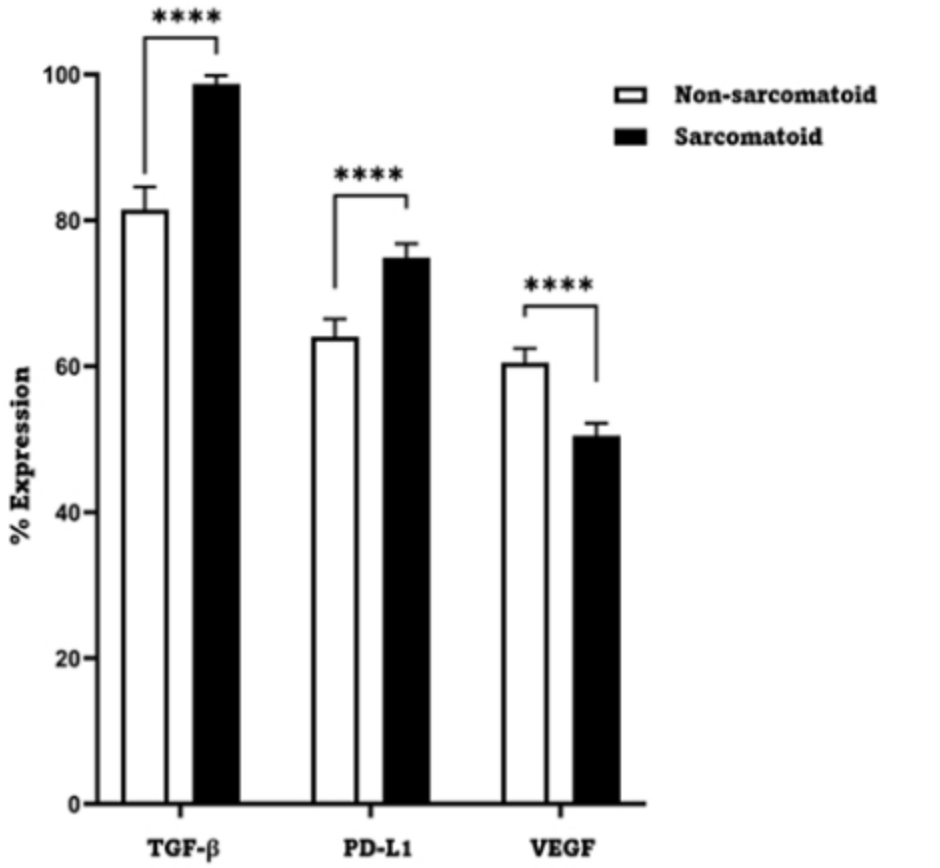




Rini et al: JITC 2022

@ZakhariaYousef



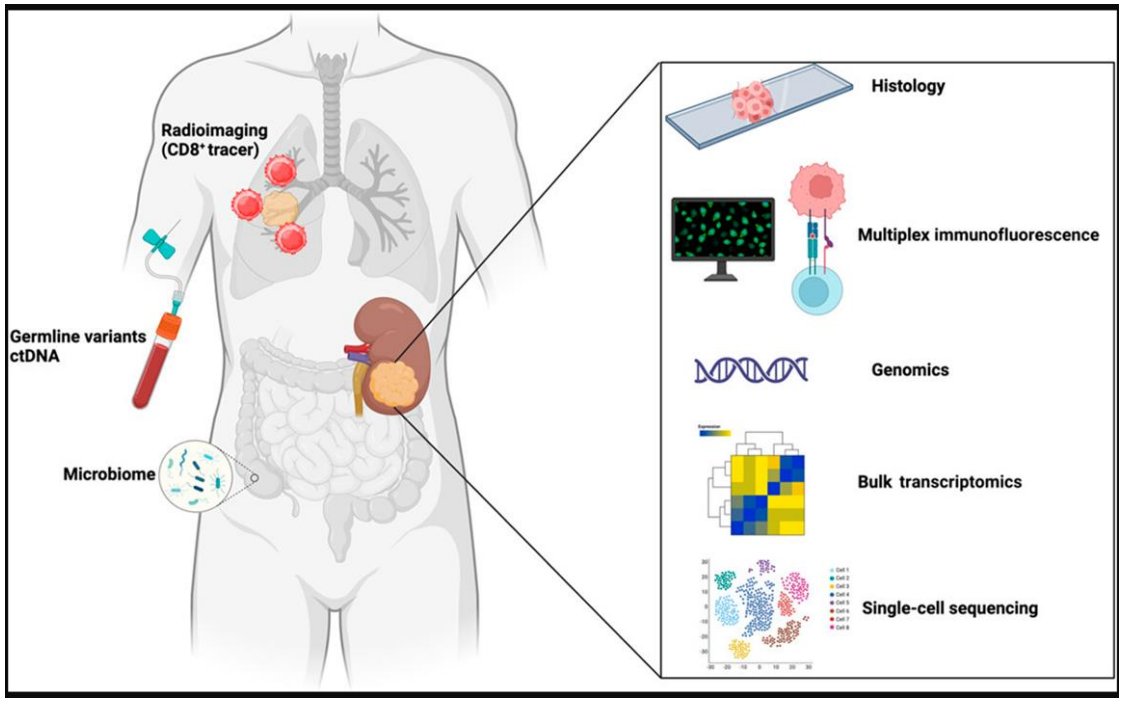


Rataan A, Zakharia Y et al: Cancer Treat Res Commun 2025

@ZakhariaYousef

Long Story Short

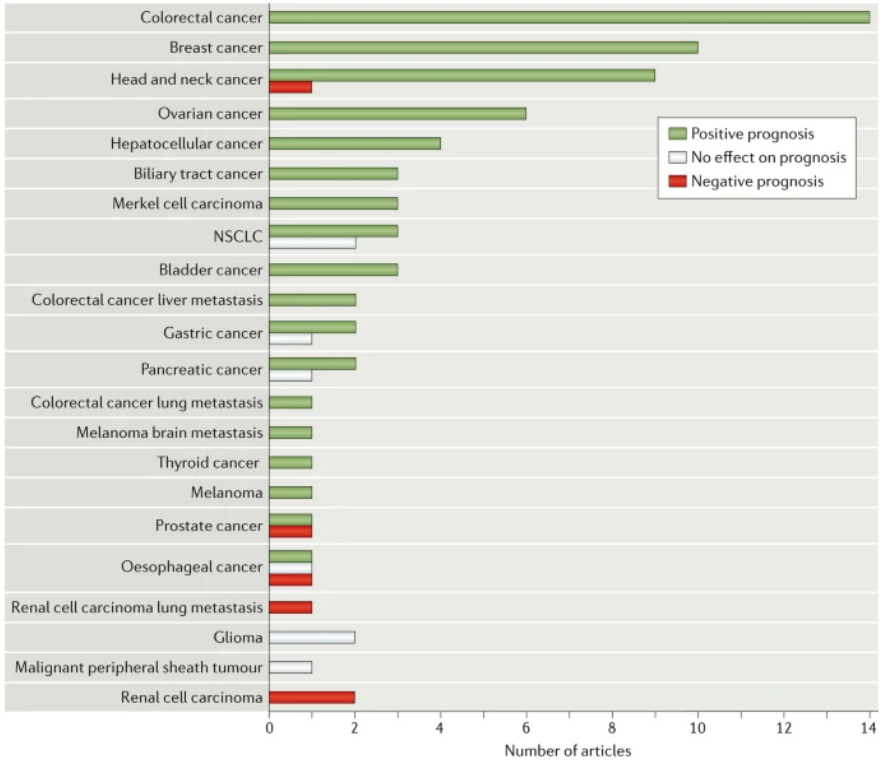
- Nothing ready for prime time, but…. We see the tip of the iceberg:
  - Histology
  - Genomics
  - RNA seq
  - Single Cell RNA seq
  - Serum (KIM-1, ctDNA)

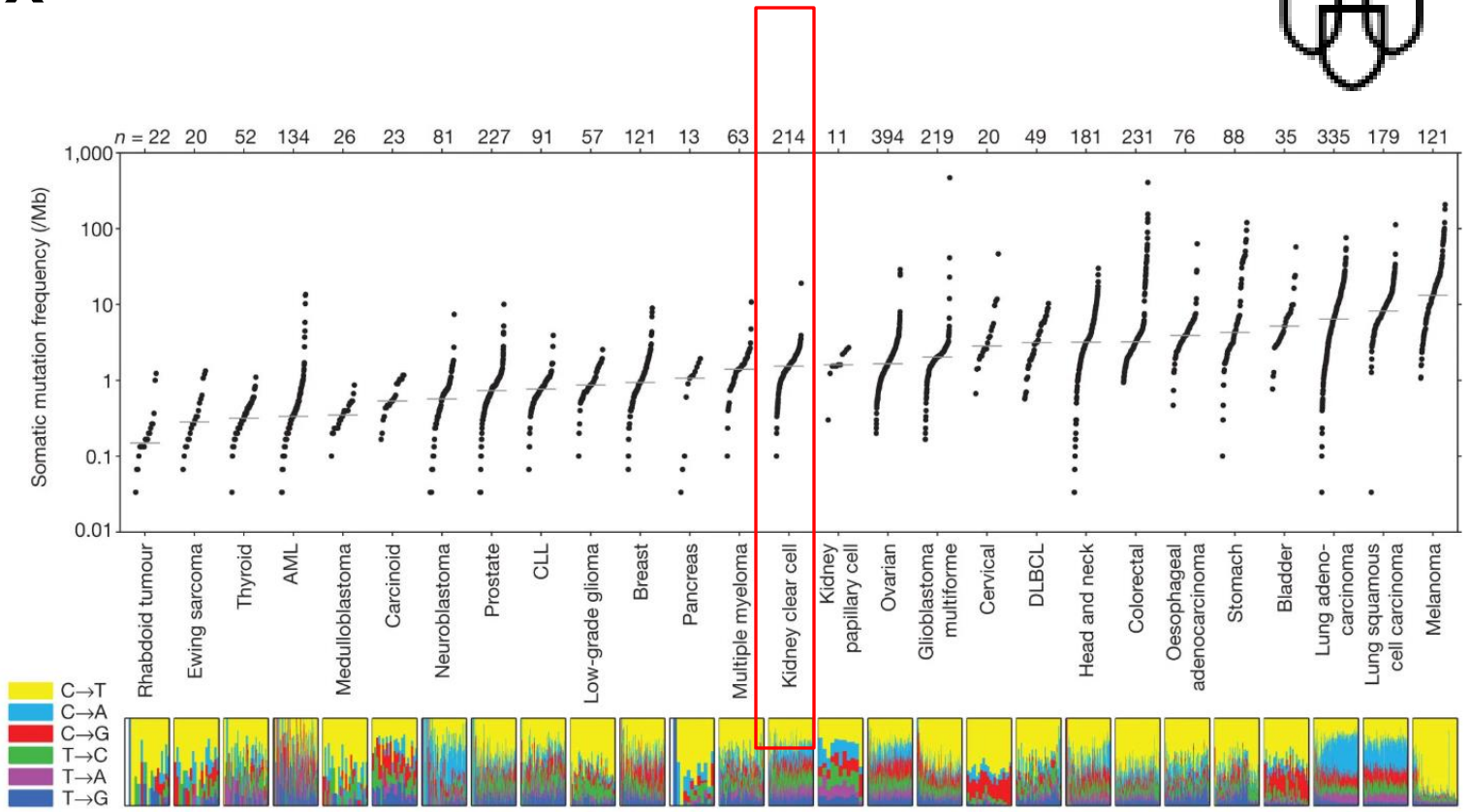


Saliby, ASCO 2024

@ZakhariaYousef

Kidney Cancer Paradox





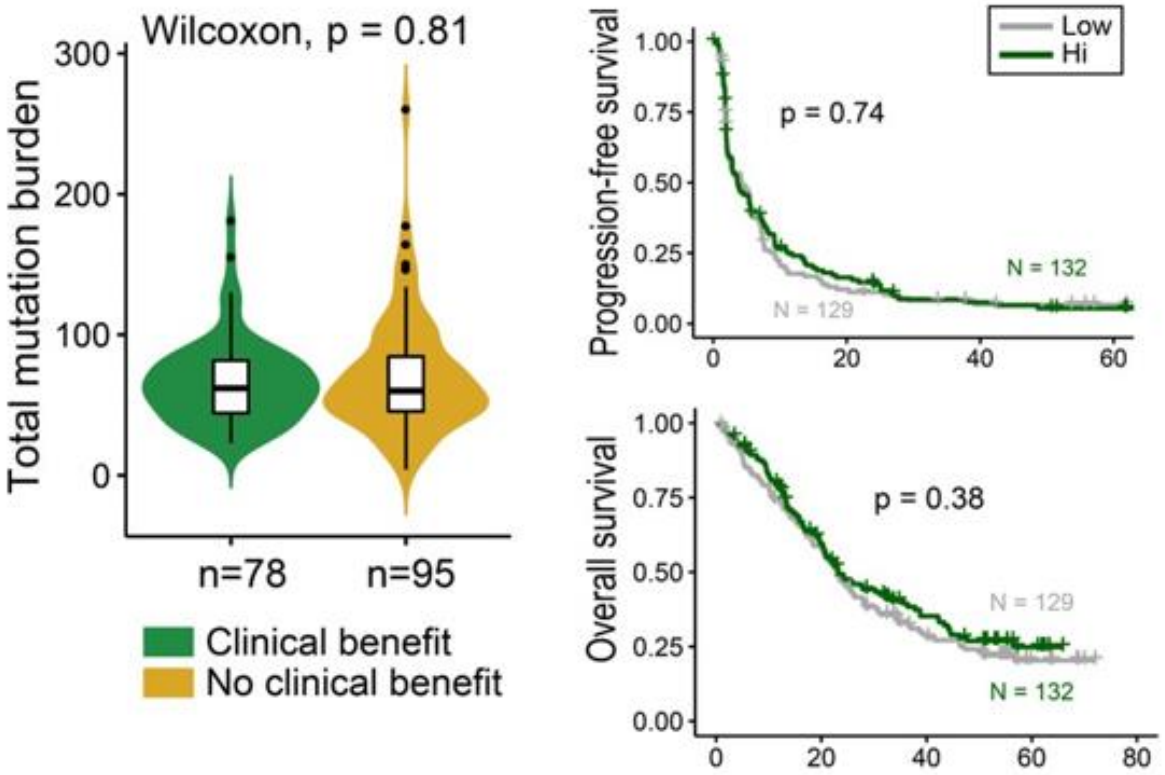
Inverse correlation of CD8⁺ T cells infiltration and OS in RCC

Modest TMB Compared to other tumors

1. Fridman, Nat Rev Clin Oncol; 2. Lawrence, Nature 2013

@ZakhariaYousef

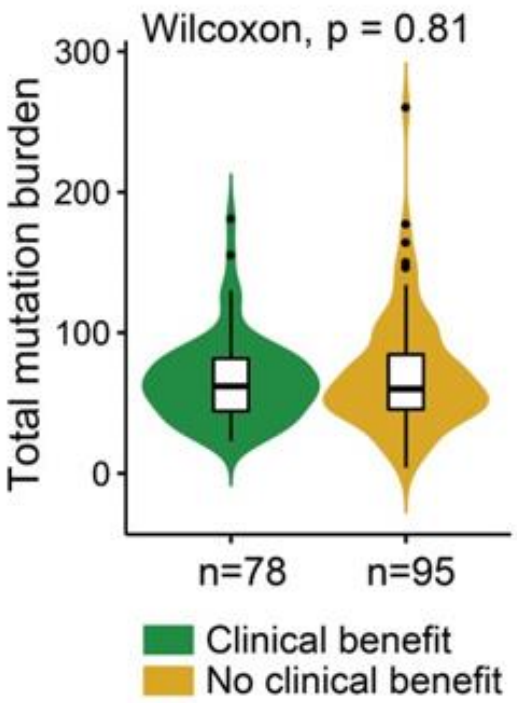
TMB does not impact ICI response in RCC

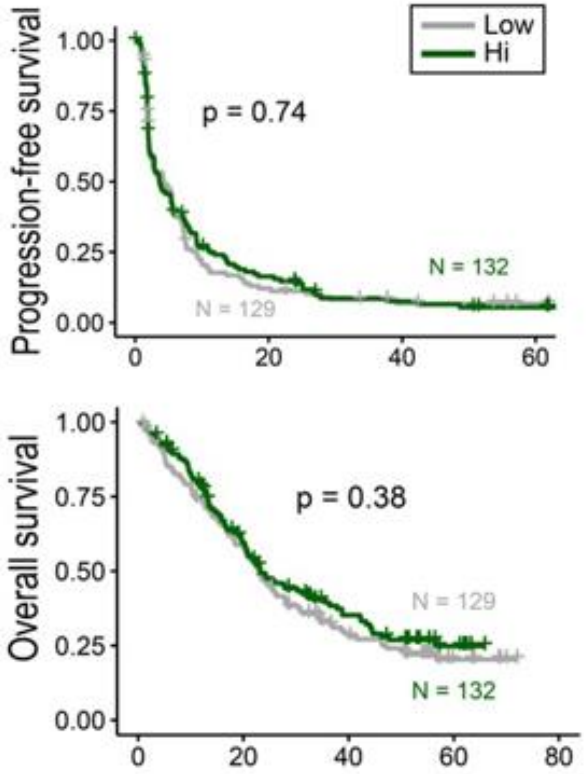


Braun D et al: Nature Medicine 2020

@ZakhariaYousef

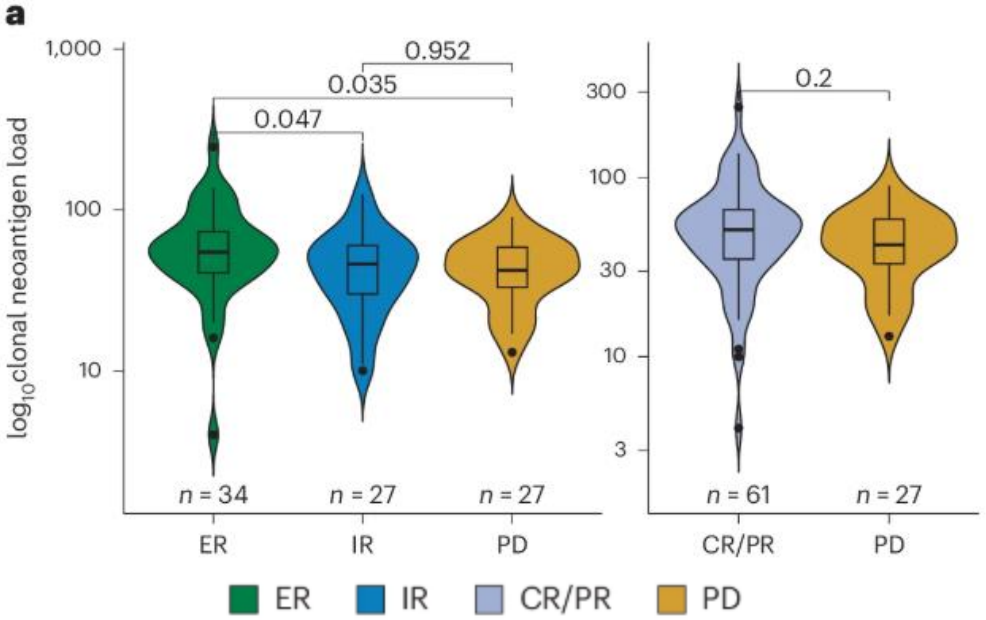
TMB does not impact ICI response in RCC

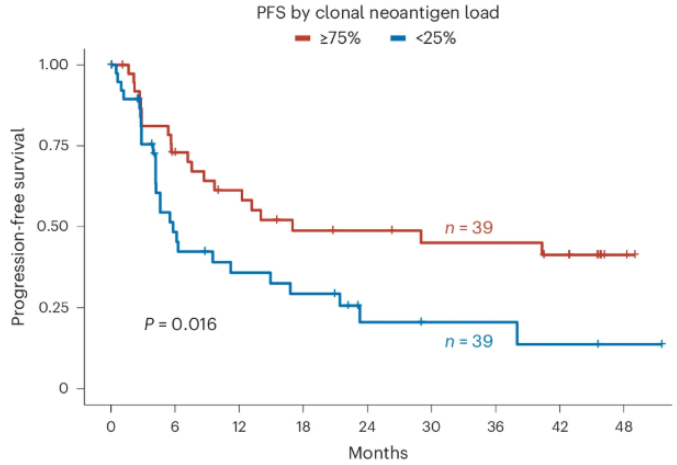




Braun D et al: Nature Medicine 2020

Baseline Clonal Neoantigen is associated with ER to IO/IO therapy

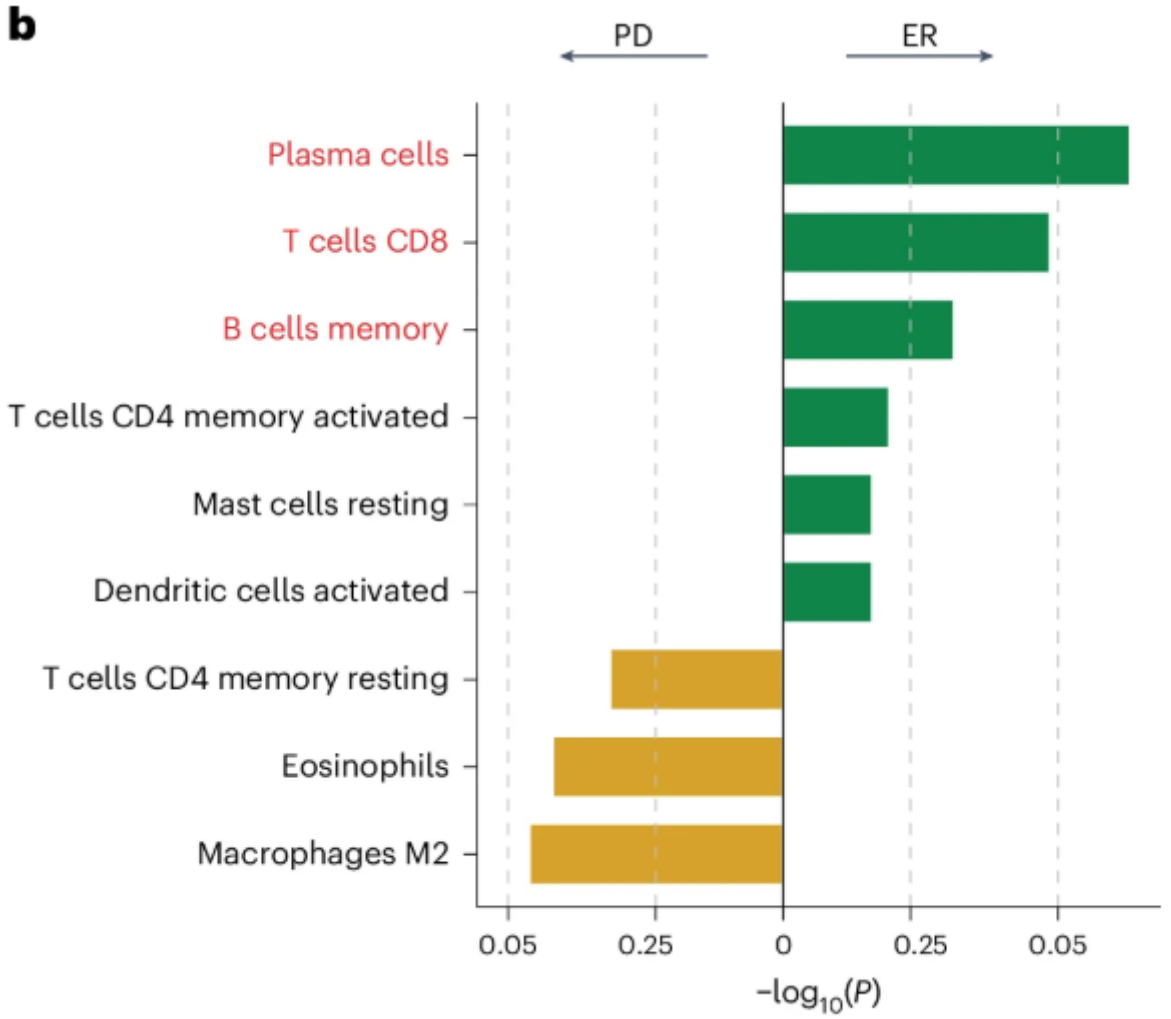




Jammihal D et al: Nature Cancer 2025

@ZakhariaYousef

ER participants displayed strong enrichment of B cell receptor signaling-related pathways

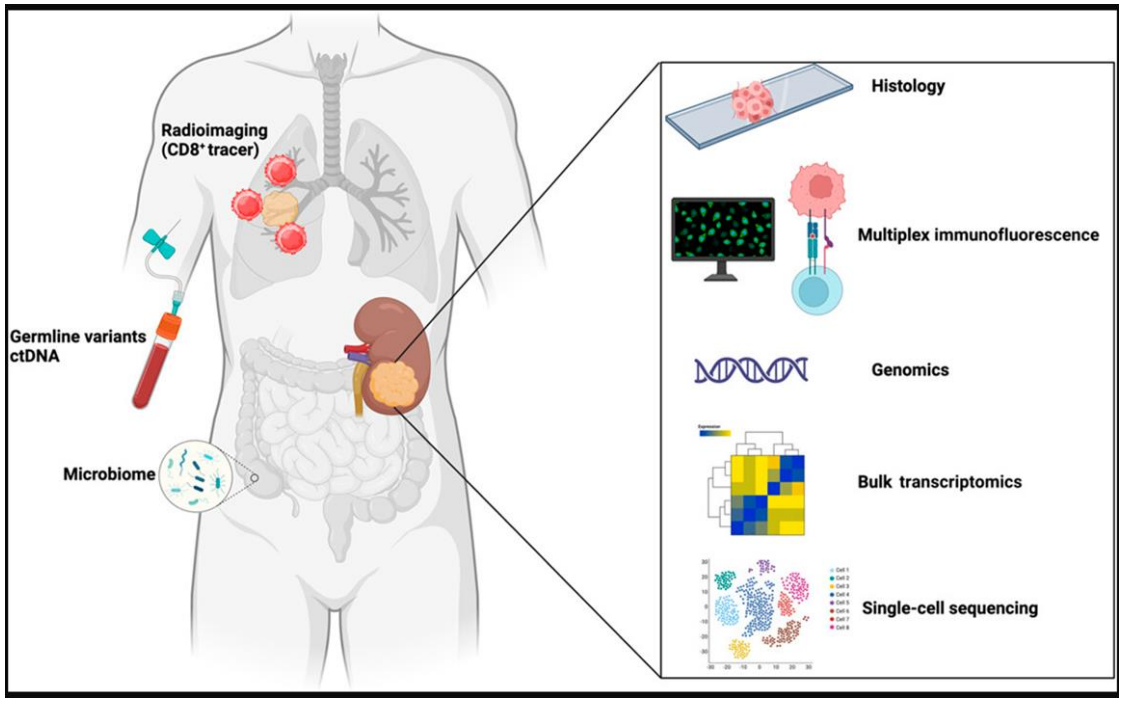


Jammihal D et al: Nature Cancer 2025

@ZakhariaYousef

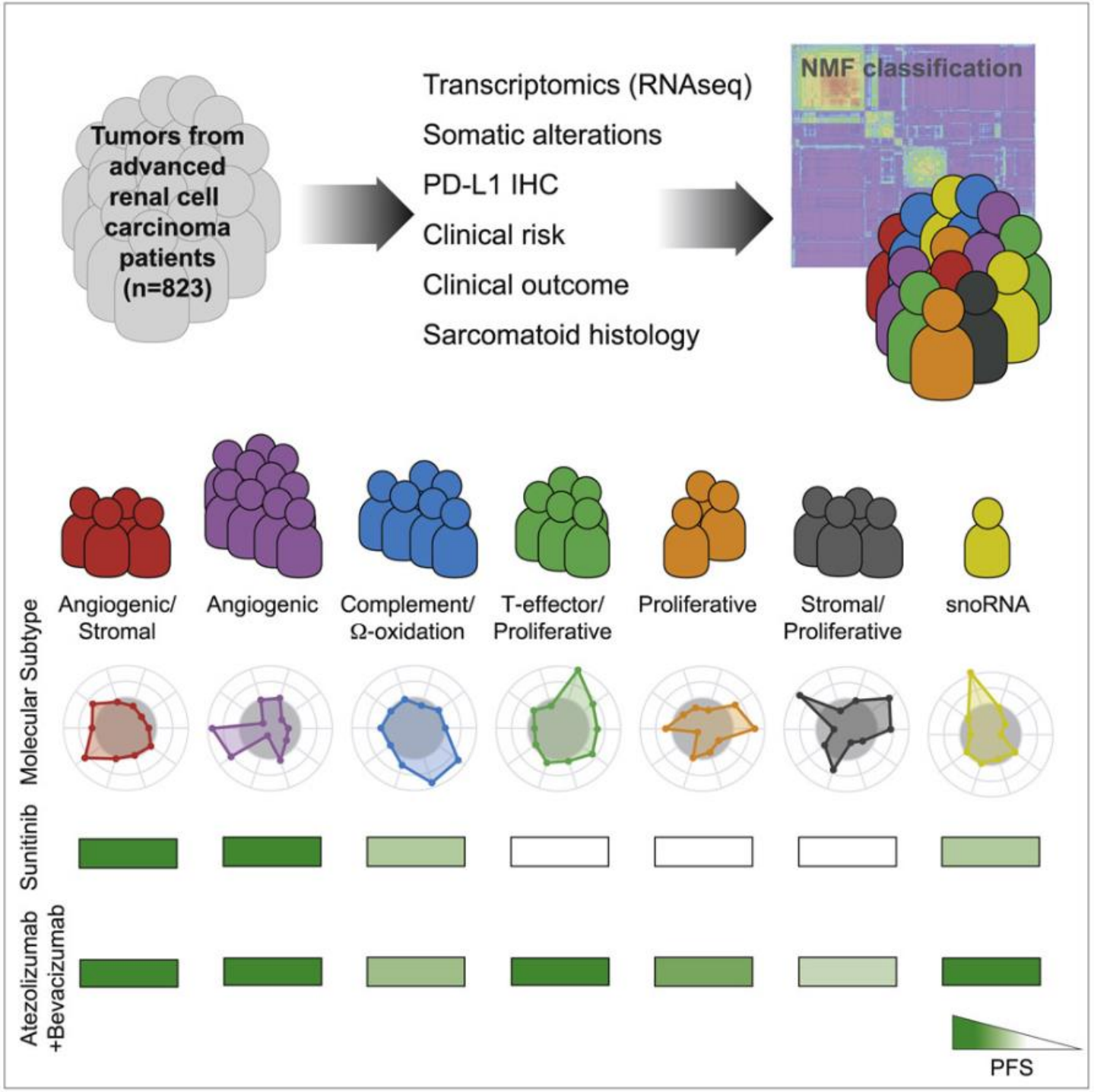
Long Story Short

- Nothing ready for prime time, but… We see the tip of the iceberg:
  - Histology
  - Genomics
  - RNA seq
  - Single Cell RNA seq
  - Serum (KIM-1, ctDNA)



Saliby, ASCO 2024

@ZakhariaYousef

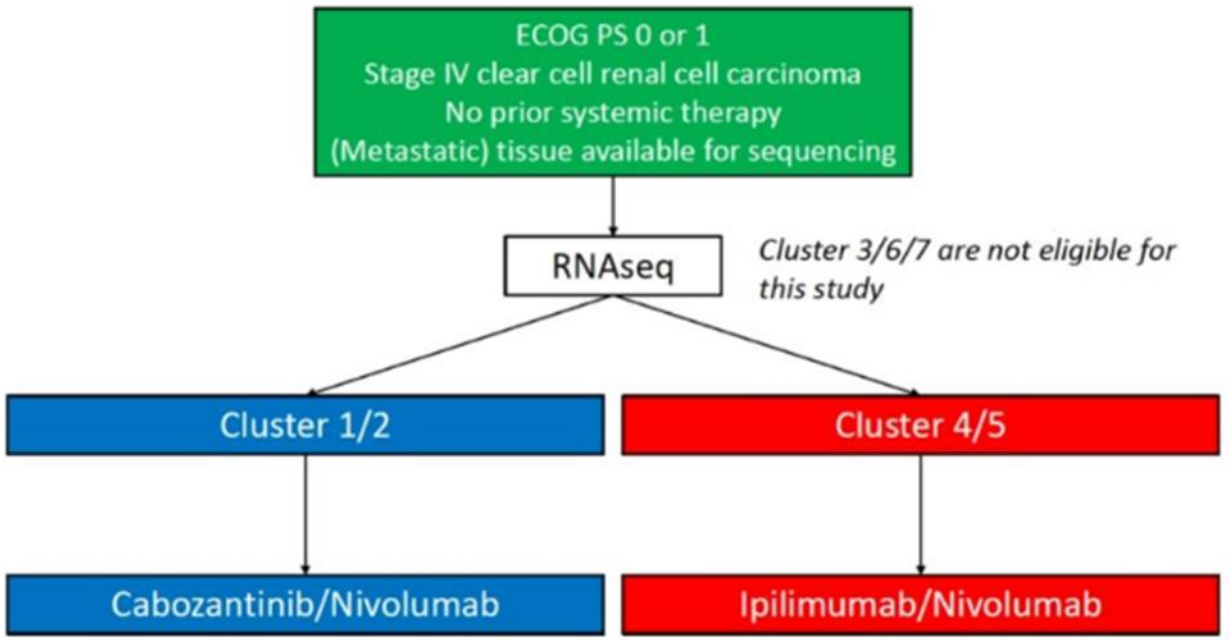


MAYO CLINIC

Motzer: Cancer Cell 2020

@ZakhariaYousef

- OPTIC (NCT05361720)



1. Reddy, *ASCO Annual meeting (Abs: 4525)*, 2023.

KEYNOTE-426: $Tcell_{inf}$GEP, Angiogenesis, PD-L1

	Pembrolizumab + axitinib			Sunitinib		
Biomarker	**ORR**	**PFS**	**OS**	**ORR**	**PFS**	**OS**
$Tcell_{inf}$GEP	**<0.0001(+)**	**<0.0001(+)**	**0.002(+)**	NS	NS	NS
Angiogenesis	NS	NS	**0.004(+)**	**0.002(+)**	**<0.001(+)**	**<0.0001(+)**
PD-L1 CPS	NS	NS	NS	NS	NS	**0.025(-)**

- Higher $Tcell_{inf}$GEP was associated with improved clinical outcome within the pembrolizumab + axitinib arm
- Higher angiogenesis gene expression was associated with improved clinical outcome within the sunitinib arm
- PD-L1 CPS was negatively associated with OS within the sunitinib arm

Rini et al, ASCO 2024 #4505

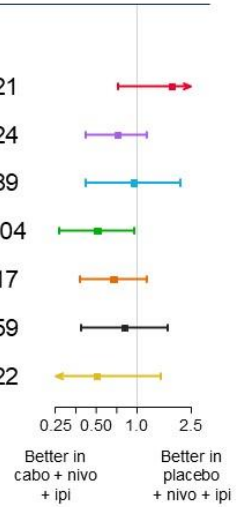
COSMIC-313 Study

Association of Molecular Clusters With PFS and OS

- No clear association between molecular clusters and clinical outcomes was observed; however, the sample sizes in each cluster were small

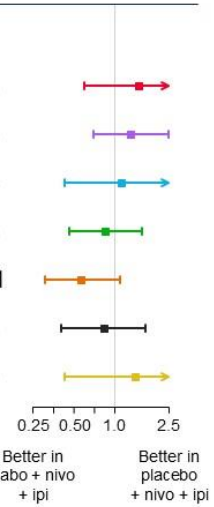
Progression-free survival

Subgroup	HR [95% CI]	Cabo + nivo + ipi (n)	Placebo + nivo + ipi (n)	*P*
Molecular subsets				
1 – Angiogenic/stromal	1.8 [0.73–4.3]	9.4 (21)	24.9 (18)	0.21
2 – Angiogenic	0.72 [0.42–1.2]	22.3 (40)	13.9 (43)	0.24
3 – Complement/Ω oxidation	0.95 [0.42–2.1]	NR (27)	NR (31)	0.89
4 – T-effector/proliferative	0.52 [0.27–0.98]	32.2 (30)	11.2 (36)	0.004
5 – Proliferative	0.68 [0.39–1.2]	11.2 (40)	7.6 (36)	0.17
6 – Stromal/proliferative	0.81 [0.39–1.7]	9.5 (23)	5.9 (19)	0.59
7 – snoRNA	0.51 [0.18–1.5]	NR (16)	27.7 (18)	0.22



Overall survival

Subgroup	HR [95% CI]	Cabo + nivo + ipi (n)	Placebo + nivo + ipi (n)	*P*
Molecular subsets				
1 – Angiogenic/stromal	1.5 [0.59–3.9]	29 (21)	NR (18)	0.38
2 – Angiogenic	1.3 [0.7–2.5]	34.8 (40)	NR (43)	0.38
3 – Complement/Ω oxidation	1.1 [0.43–2.8]	52.1 (27)	53.1 (31)	0.84
4 – T-effector/proliferative	0.86 [0.46–1.6]	41.9 (30)	28.7 (36)	0.63
5 – Proliferative	0.56 [0.3–1.1]	47.9 (40)	26.8 (36)	0.081
6 – Stromal/proliferative	0.83 [0.4–1.7]	34.5 (23)	25.4 (19)	0.62
7 – snoRNA	1.4 [0.43–4.7]	NR (16)	NR (18)	0.56

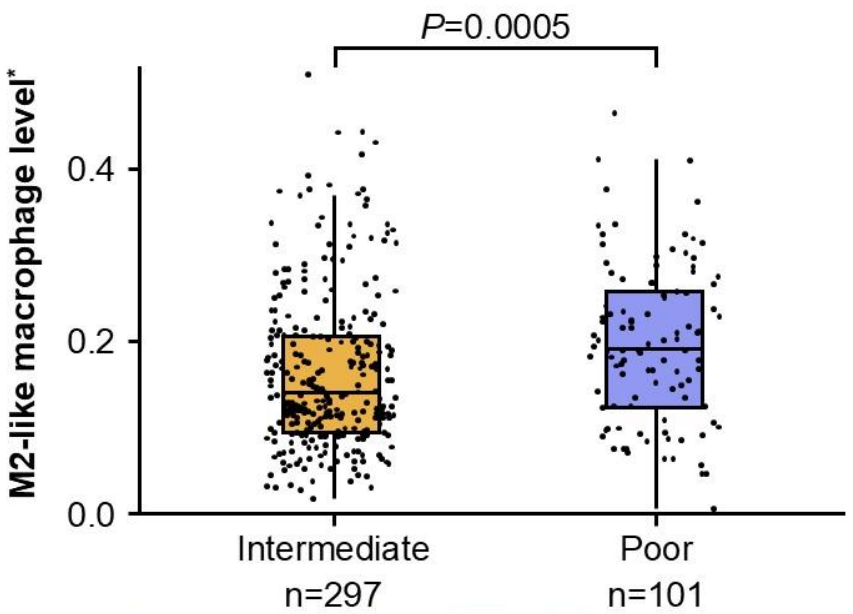


Median follow-up of 45.0 months.

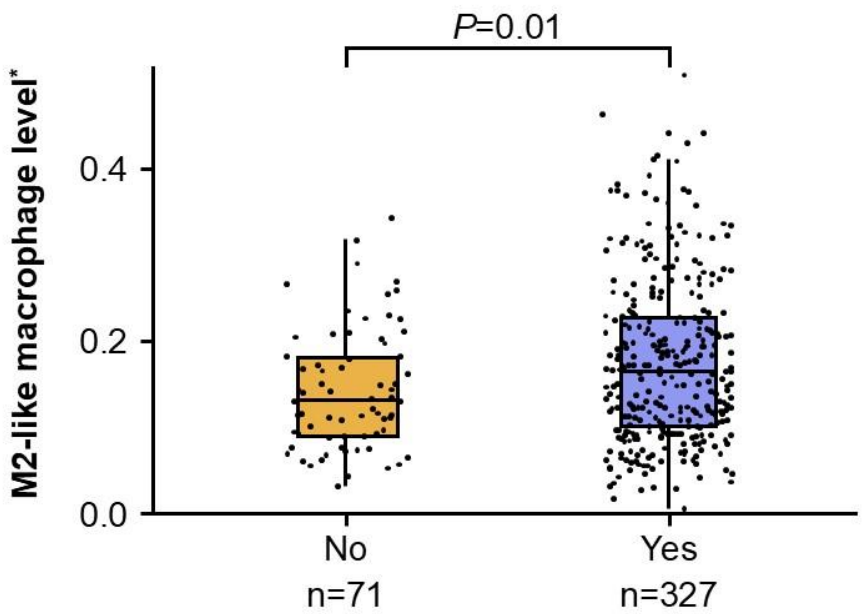
Association of M2-like Macrophage Levels and Baseline Prognostic Factors

- M2-like macrophages contribute to tumor growth, invasion, and metastasis by suppressing the immune response, and have been associated with a poor prognosis in different cancers[1–3]
- Patients with IMDC poor risk disease and those with visceral metastasis exhibited higher levels of M2-like macrophages

IMDC risk group



Visceral metastasis



*Proportion of M2-like macrophages from CIBERSORT.

[1]DeRyckere D, et al. *Nat Rev Clin Oncol*. 2023;20(11):755-779; [2]Zhang W, et al. *Biomed Pharmacother*. 2024;177:11690; [3]Wang S, et al. *NPJ Precis Oncol*. 2024;8(1):31.

The Addition of Cabo to Nivo + Ipi Overcomes M2-like Macrophage-Mediated Immune Suppression

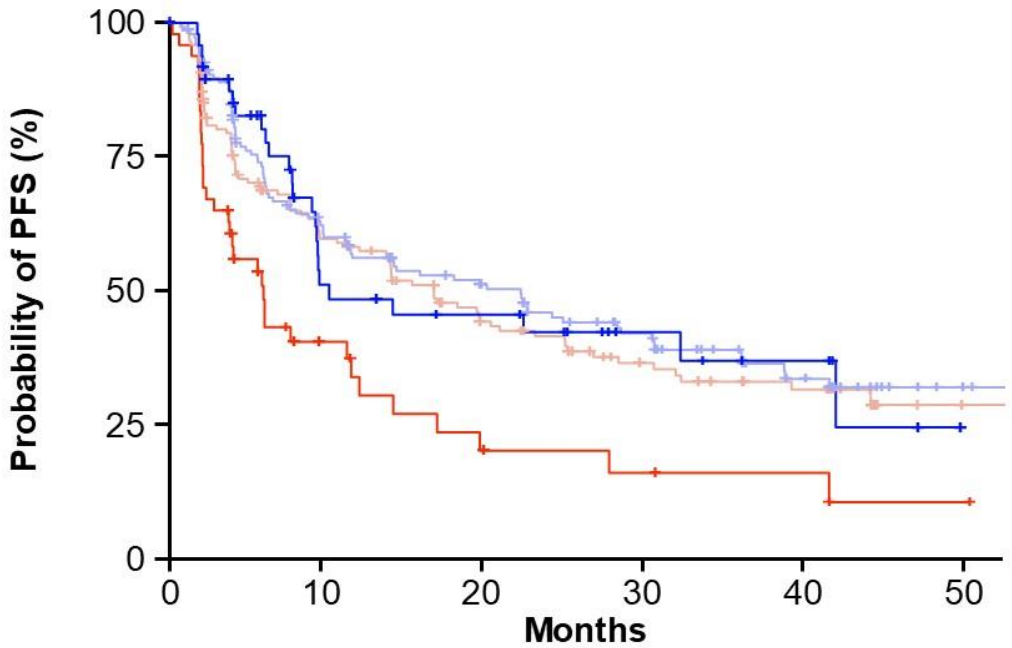
Progression-free survival

M2-like low	Median PFS (95% CI), months
Cabo + nivo + ipi (n=147)	22.1 (11.4–30.6)
Placebo + nivo + ipi (n=151)	16.7 (12–25)

HR, 0.89 (95% CI, 0.66–1.2), *P*=0.44

M2-like high	Median PFS (95% CI), months
Cabo + nivo + ipi (n=50)	10.1 (9.23–NE)
Placebo + nivo + ipi (n=50)	5.95 (3.81–12)

HR, 0.48 (95% CI, 0.29–0.81), *P*=0.0058



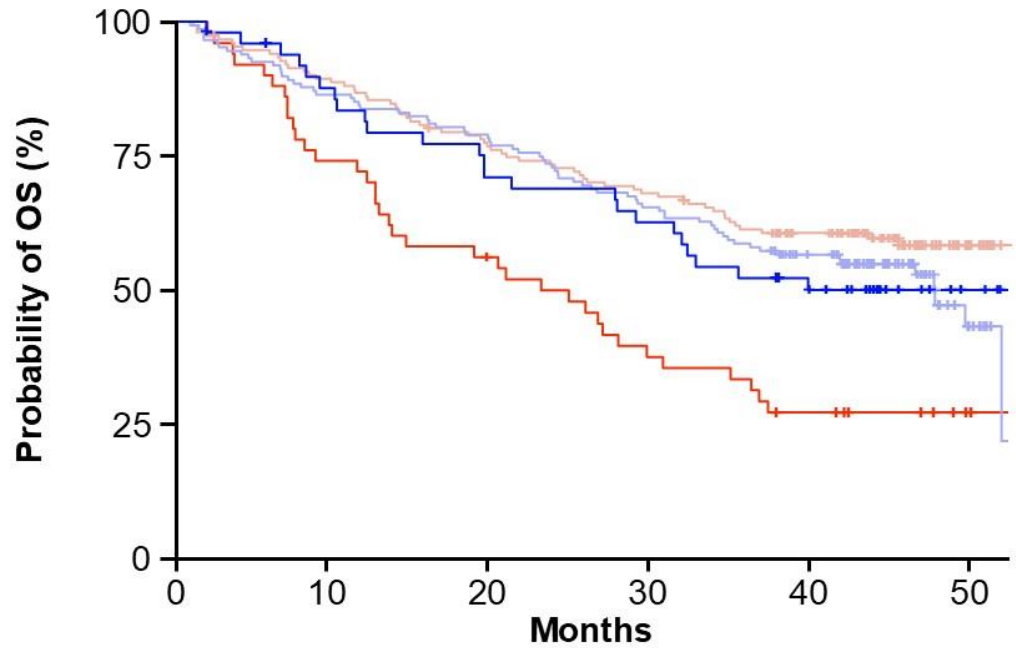
Overall survival

M2-like low	Median OS (95% CI), months
Cabo + nivo + ipi (n=147)	47.8 (36.8–NE)
Placebo + nivo + ipi (n=151)	NE (NE–NE)

HR, 1.2 (95% CI, 0.88–1.7), *P*=0.23

M2-like high	Median OS (95% CI), months
Cabo + nivo + ipi (n=50)	39.9 (31.4–NE)
Placebo + nivo + ipi (n=50)	23 (13.4–35)

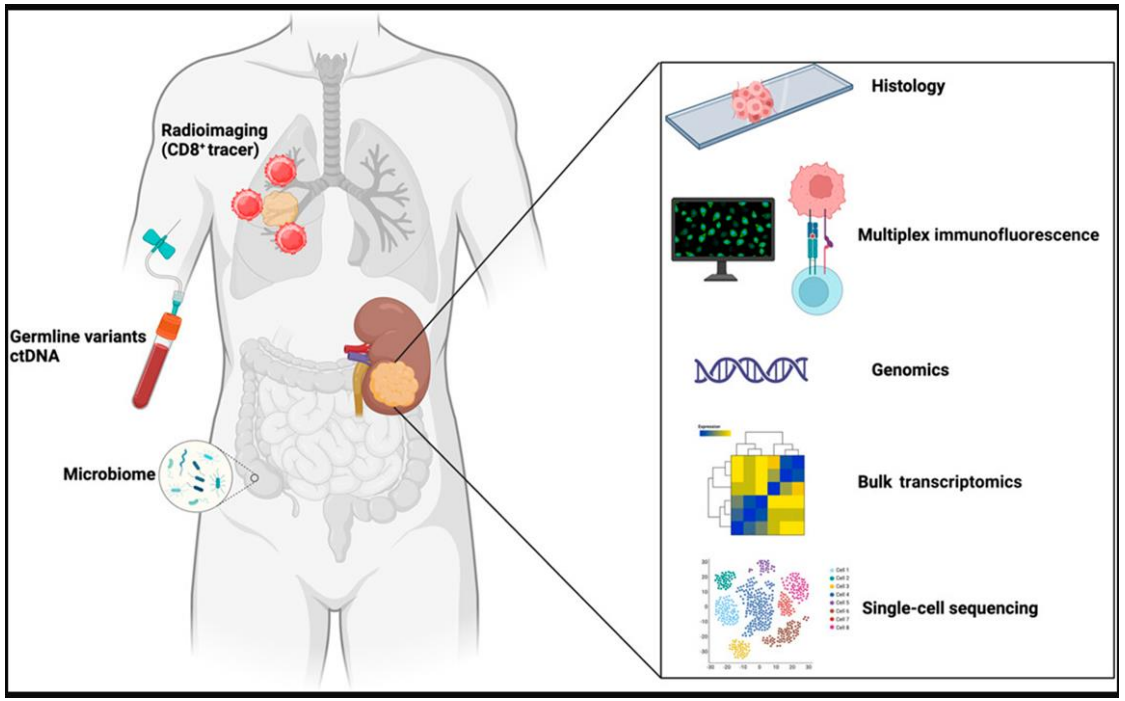
HR, 0.51 (95% CI, 0.31–0.86), *P*=0.012



Median follow-up of 45.0 months.
A cox univariate model with different quantiles of M2-like macrophage level was used to determine the cutoff with the minimum hazard ratio. Patients with M2-like macrophage level in the top 25% were classified as M2-like high.

Long Story Short

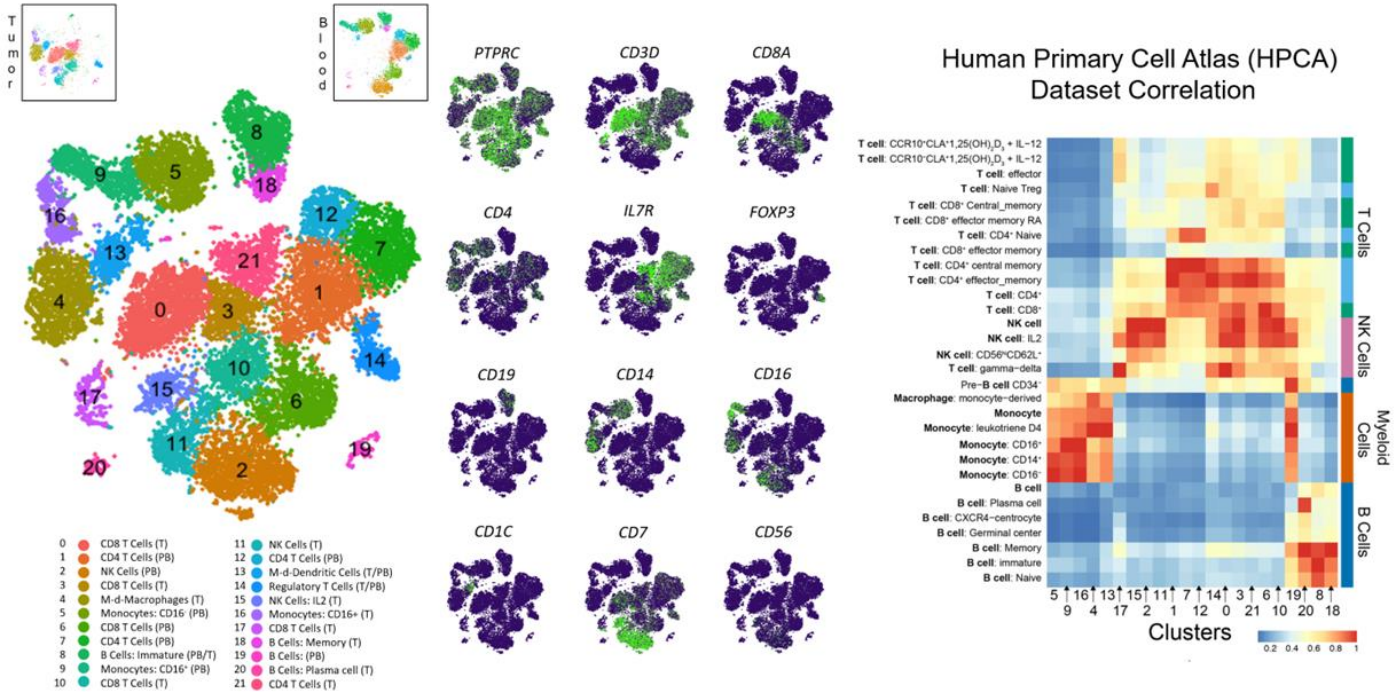
- Nothing ready for prime time, but… We see the tip of the iceberg:
  - Histology
  - Genomics
  - RNA seq
  - Single Cell RNA seq
  - Serum (KIM-1, ctDNA)



Saliby, ASCO 2024

@ZakhariaYousef

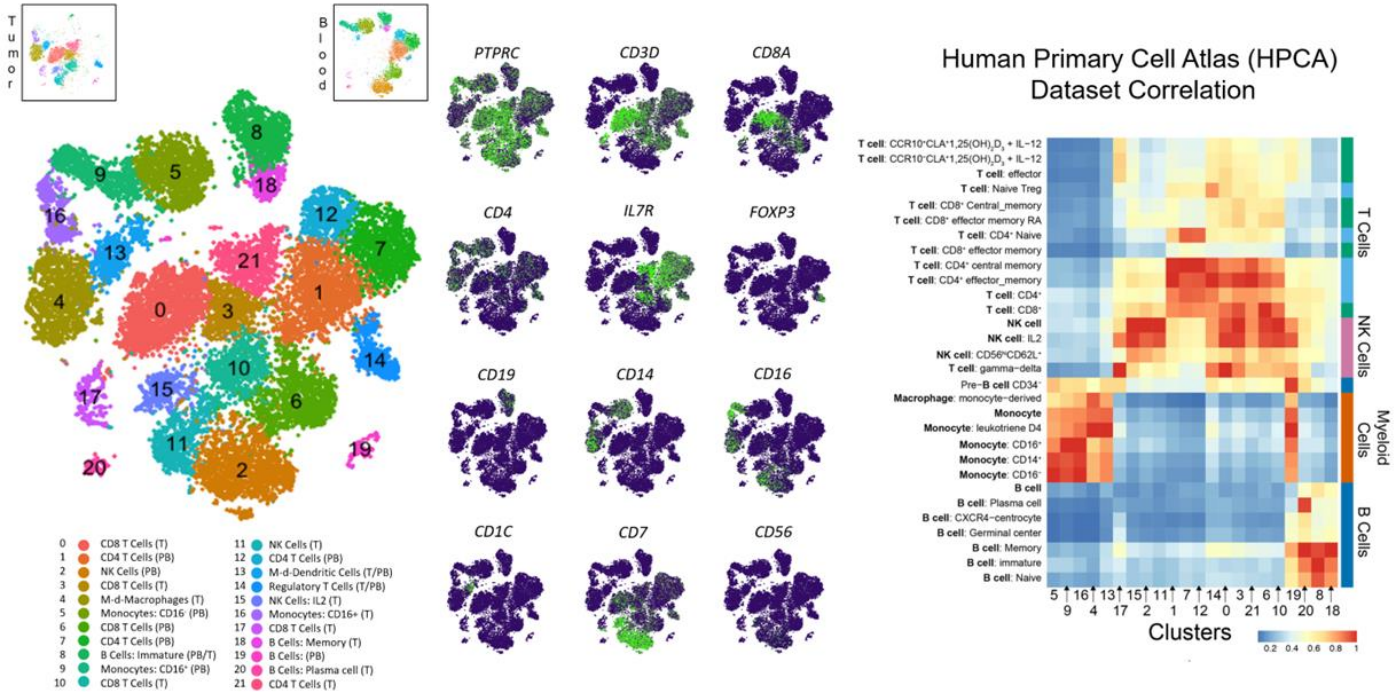
Cell Type Annotation

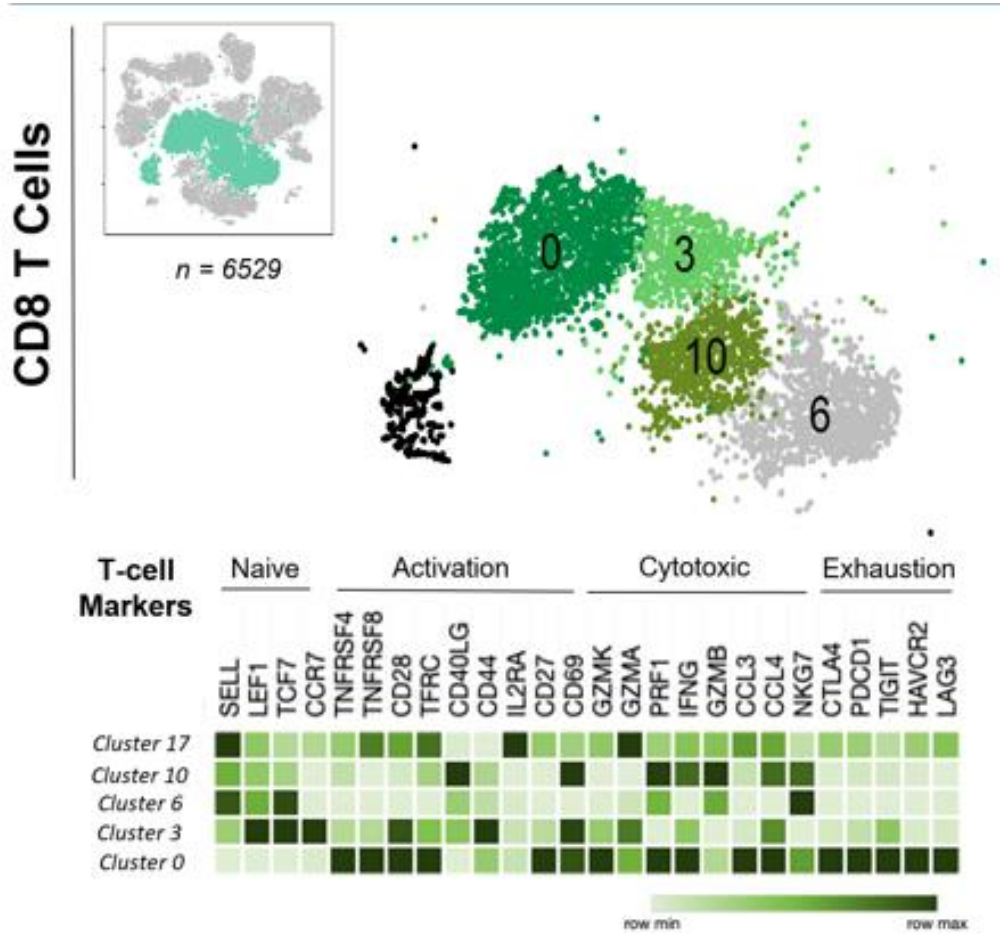


Borcherding N, Zakharia Y et al: Communication Biology 2021

@ZakhariaYousef

Cell Type Annotation



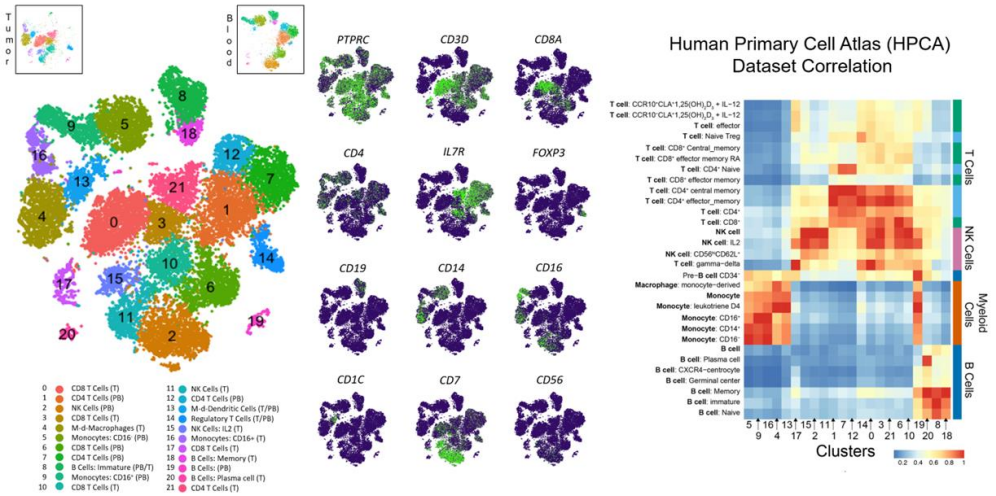


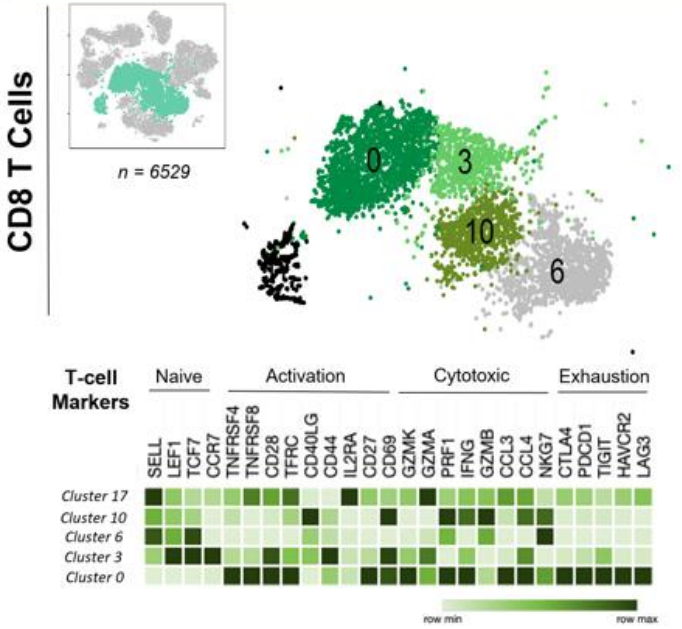
Borcherding N, Zakharia Y et al: Communication Biology 2021

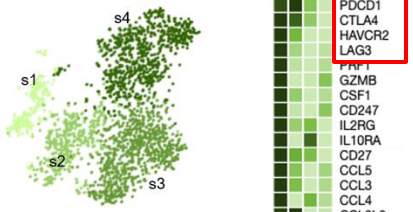
NCI Designated Comprehensive Cancer Center

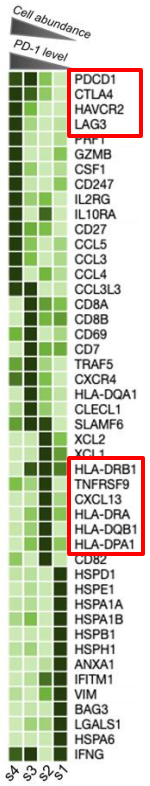
@ZakhariaYousef

Cell Type Annotation

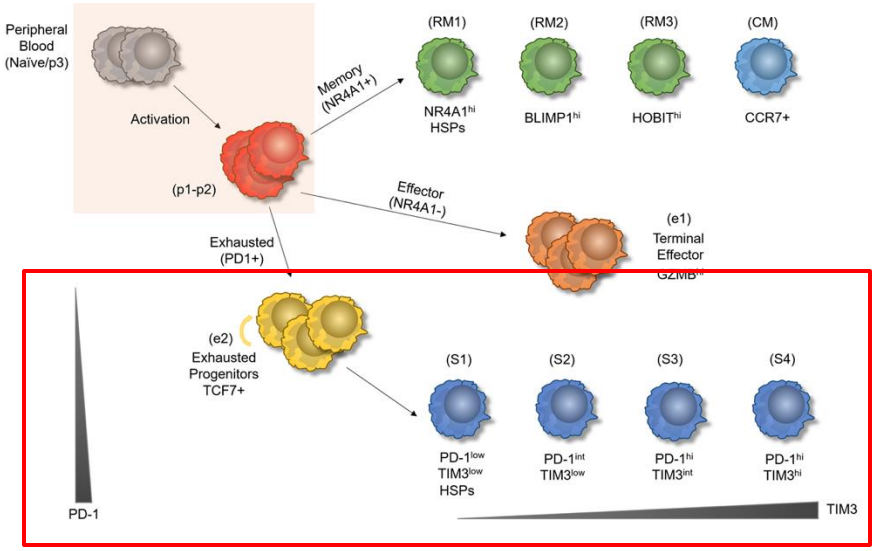








Abundance of CD8 PD-1+/ TIM-3+
Low frequency of TCF7+ progenitor exhausted cells.
High frequency of HLA-DR expressing T cells (marker of T reg)

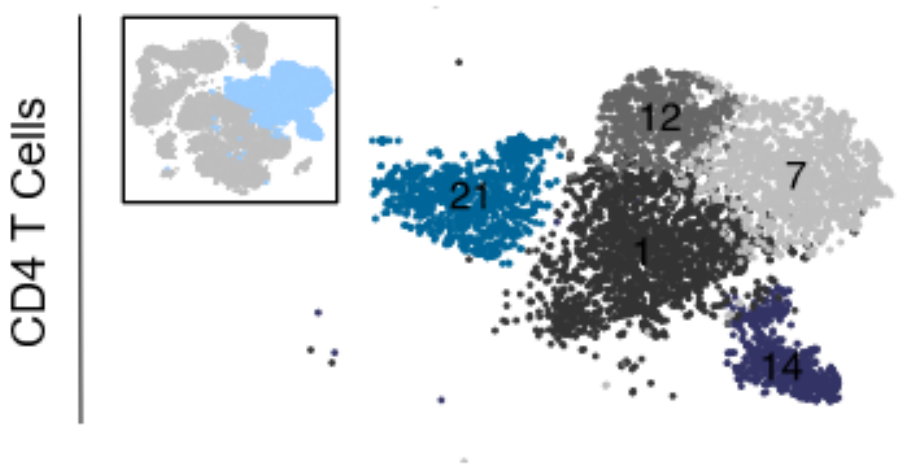


Borcherding N, Zakharia Y et al: Communication Biology 2021

NCI Designated Comprehensive Cancer Center

@ZakhariaYousef

CD4+ T Cells in ccRCC Tumors

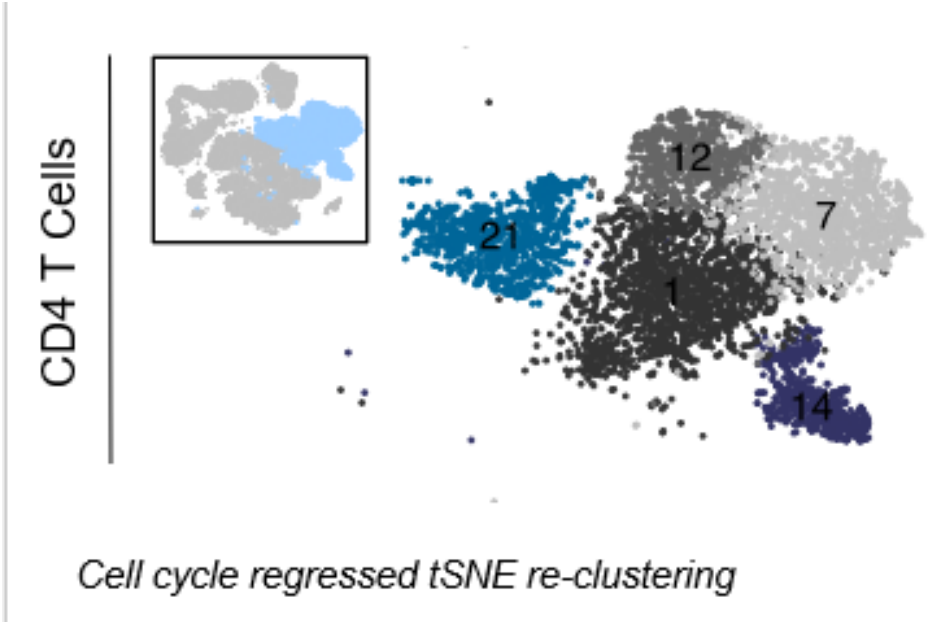


Cell cycle regressed tSNE re-clustering

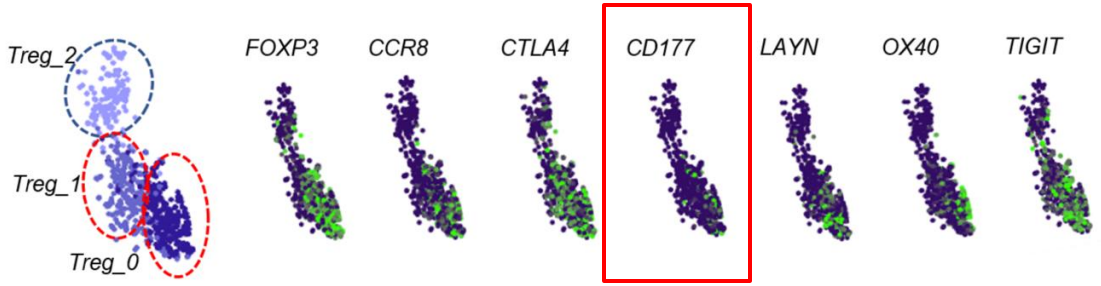
Myung-Chul K, Zakharia Y et al: Nature Communication 2021

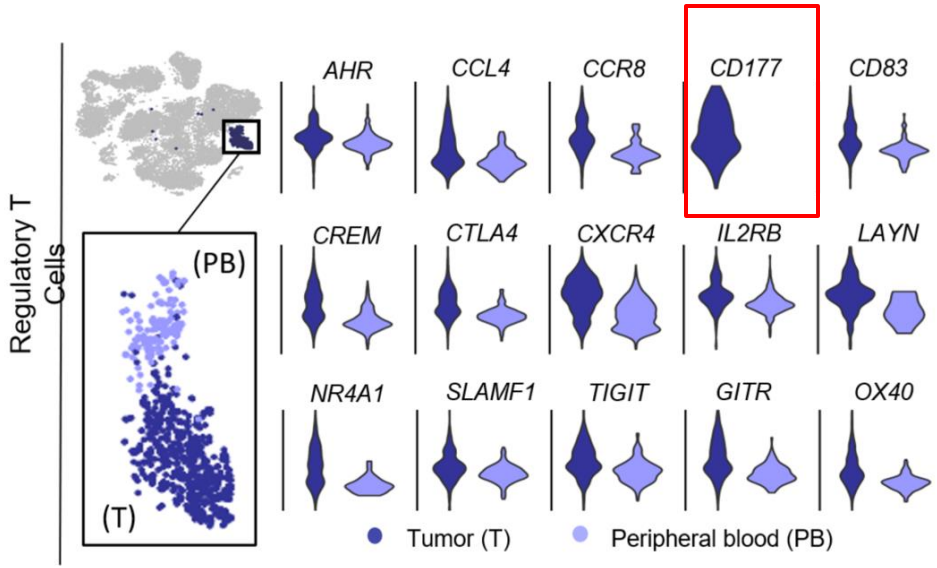
@ZakhariaYousef

CD4+ T Cells in ccRCC Tumors

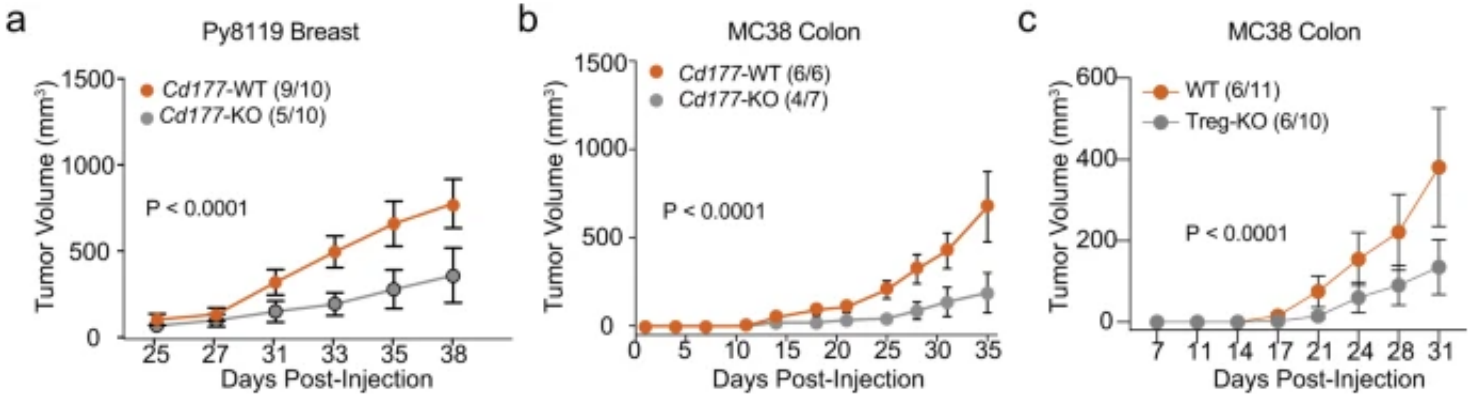


Cell cycle regressed tSNE re-clustering





KO of Cd177 leads to reduced tumor growth

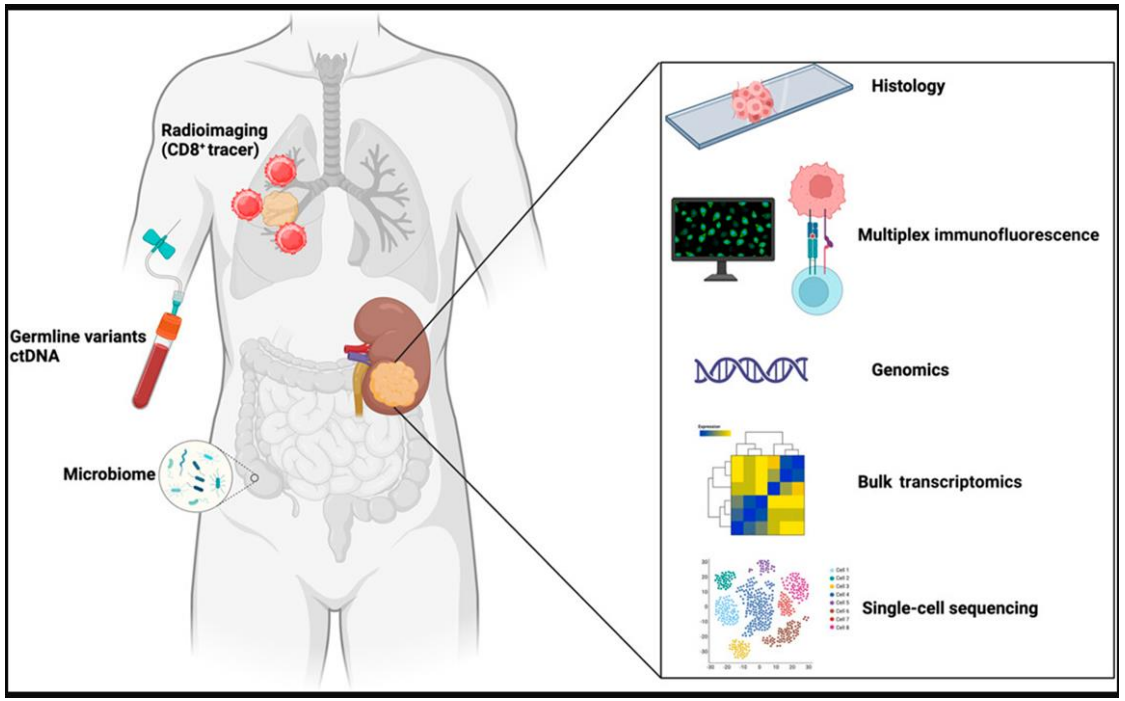


Myung-Chul K, Zakharia Y et al: Nature Communication 2021

@ZakhariaYousef

Long Story Short

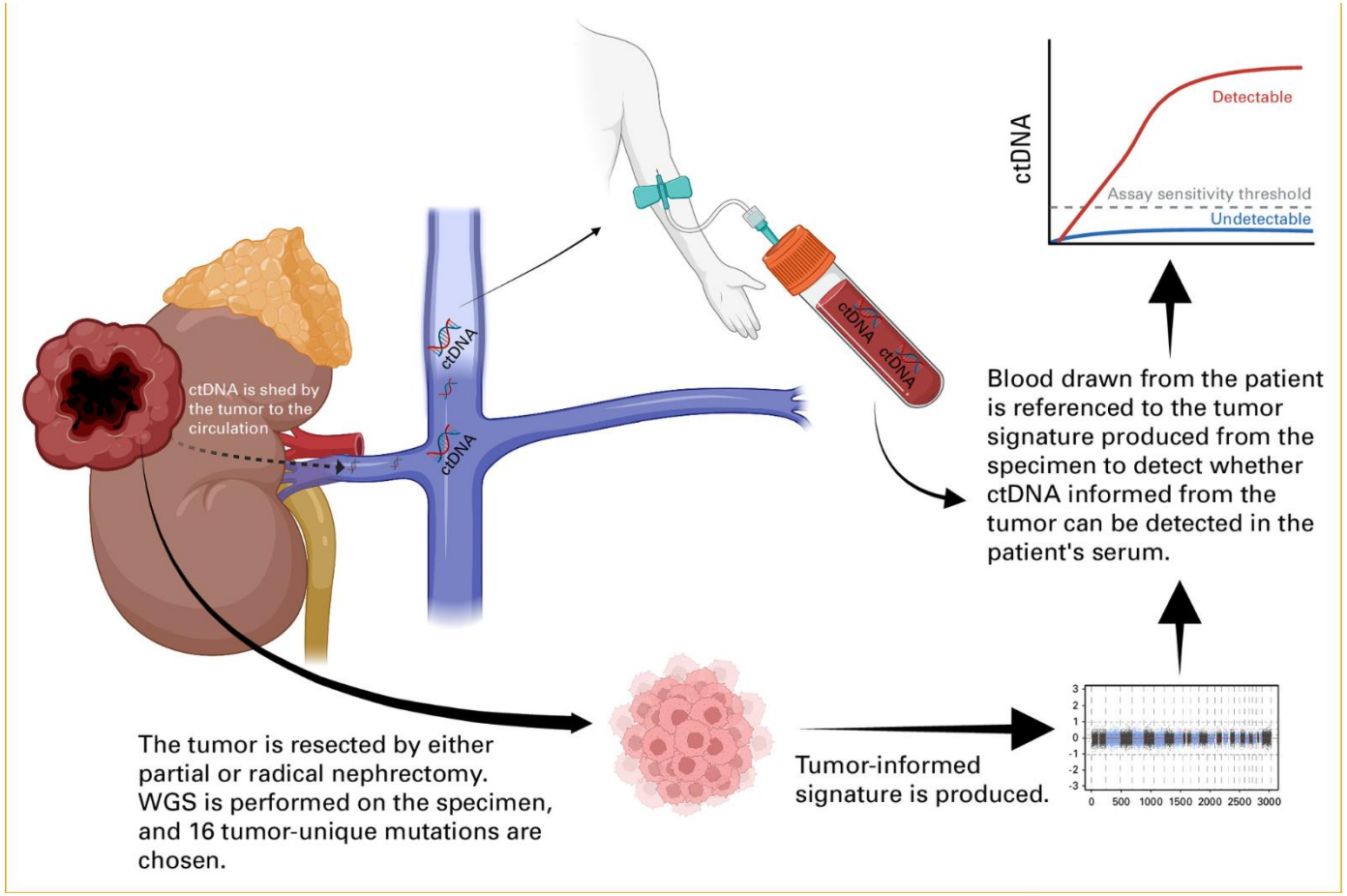
- Nothing ready for prime time, but… We see the tip of the iceberg:
  - Histology
  - Genomics
  - RNA seq
  - Single Cell RNA seq
  - Serum (KIM-1, ctDNA)



Saliby, ASCO 2024

@ZakhariaYousef

ctDNA

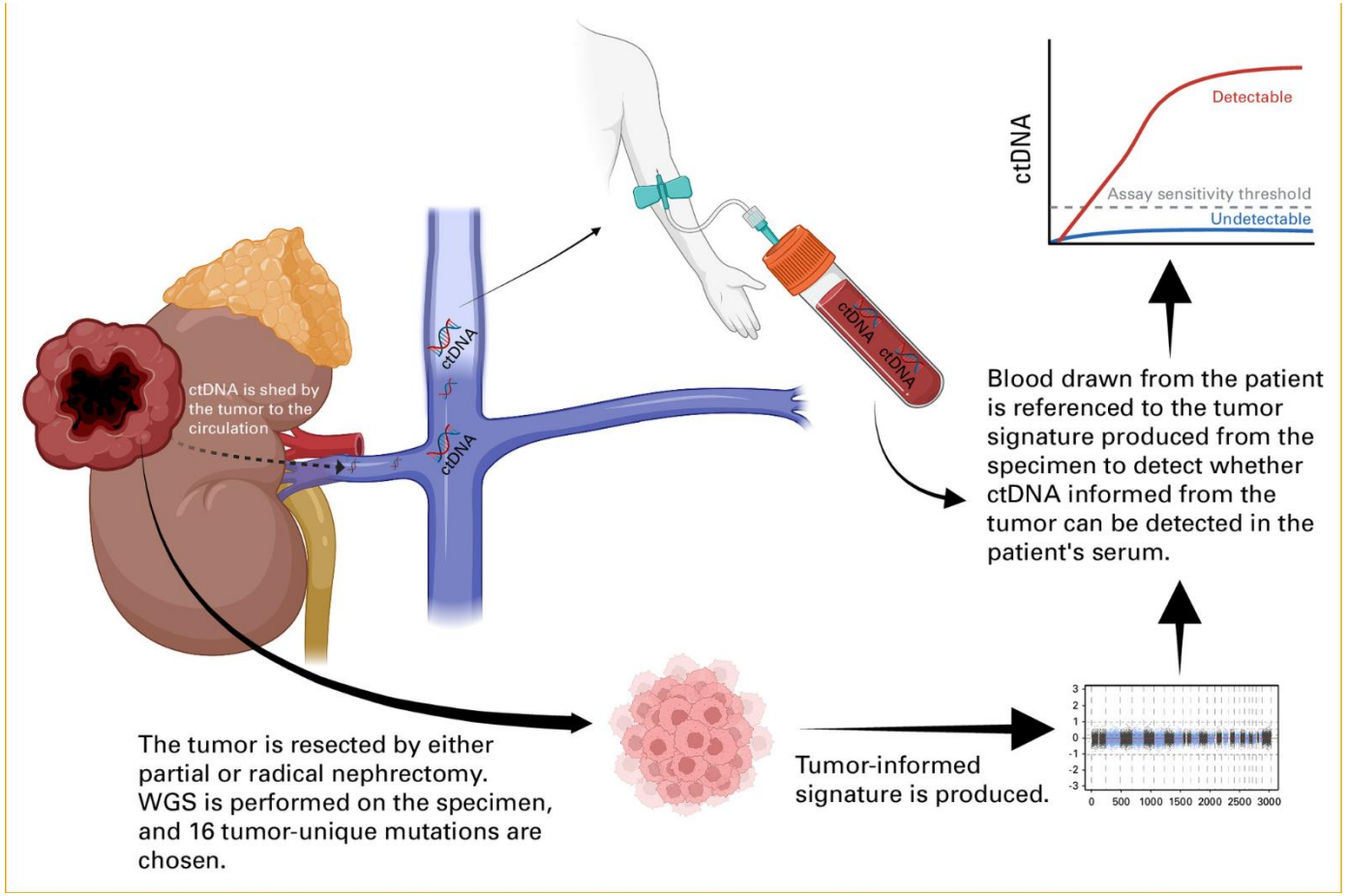


Preoperative ctDNA: 61%
Postoperative ctDNA: 6%

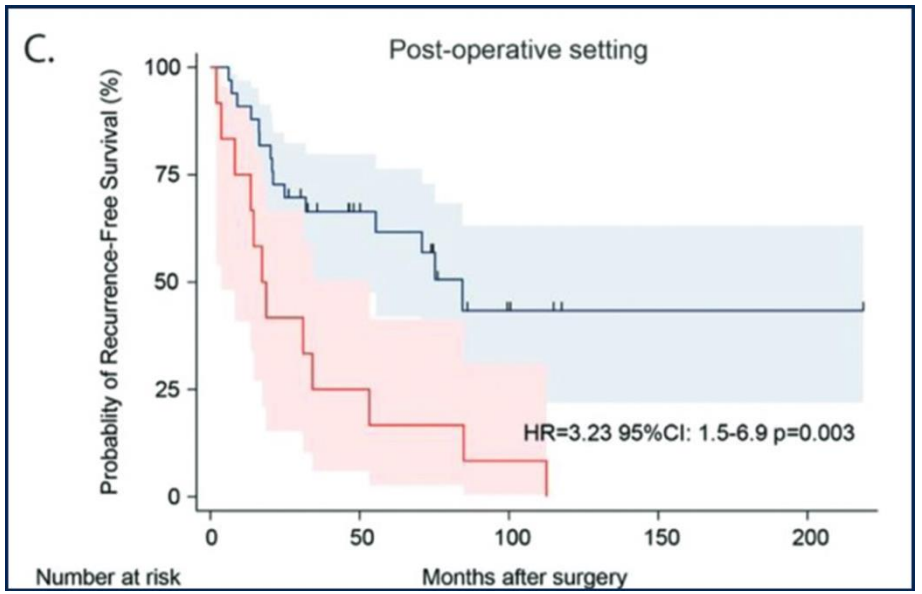
Ben-David et al: JCO Precision Oncology 2024

@ZakhariaYousef

ctDNA



Preoperative ctDNA: 61%
Postoperative ctDNA: 6%



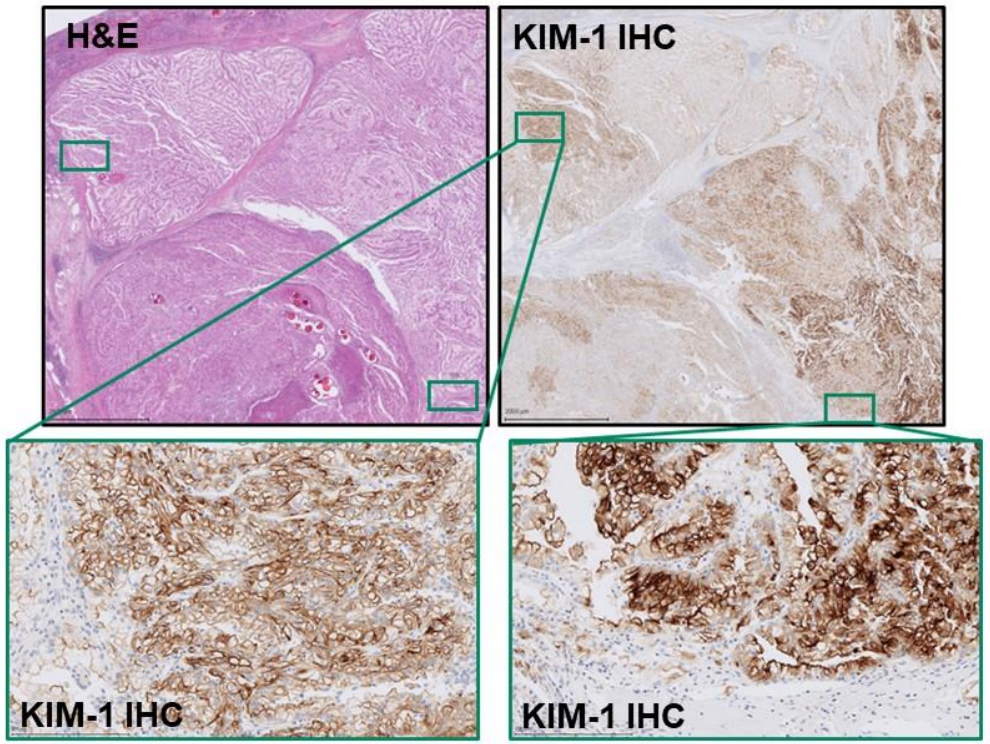
Ben-David et al: JCO Precision Oncology 2024

@ZakhariaYousef

KIM-1 (Kidney injury molecule-1) is a tumor associated protein and may be a useful circulating biomarker in RCC

- KIM-1, a type 1 membrane glycoprotein, has been identified as a marker of unresected clear-cell RCC and as a marker for early detection of RCC[1,2,3]
- In the ASSURE trial of adjuvant sunitinib, sorafenib, or placebo, higher levels of KIM-1 in post-nephrectomy, pre-treatment **plasma samples** were associated with worse DFS and OS[4]
- KIM-1 can be measured **in plasma or serum** and is stable under different storage conditions, suggesting suitability to serve as a **peripheral blood circulating biomarker**[5]

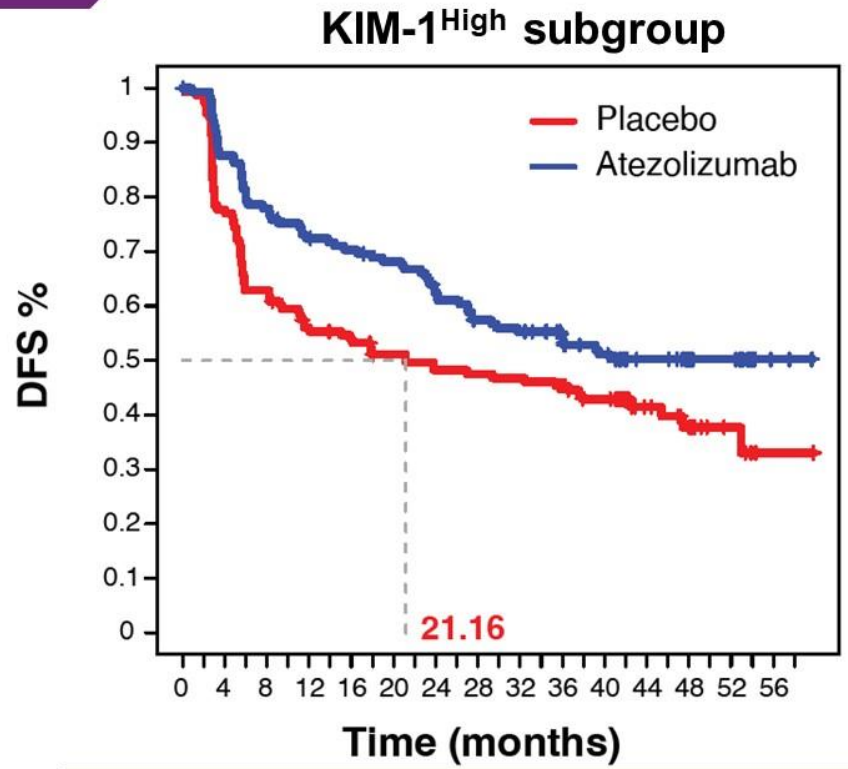
KIM-1 IHC analysis in RCC Primary Tumor



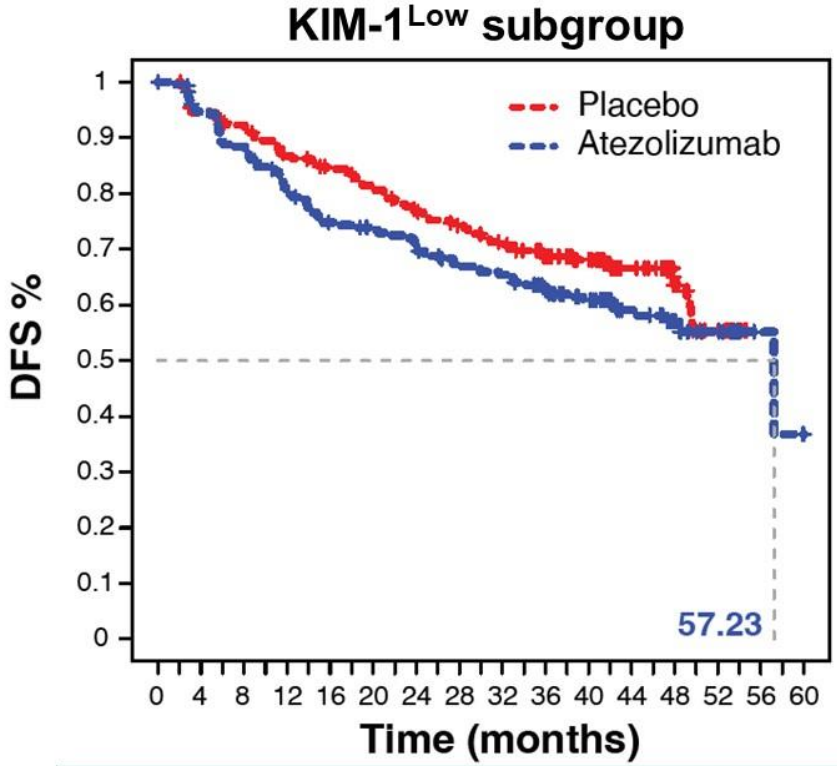
1. Kushlinskii NE, et al. Bull Exp Biol Med 2019; 167:388-92. 2. Scelo G, et al. Clin Cancer Res 2018;24:5594-601. 3. Xu W, et al. J Clin Oncol 2024; JCO2300699.
4. Xu W, et al. Clin Cancer Res 2021;27:3397-403. 5. Hou W, et al. Transpl Rev 2010; 24:143-6.

Atezolizumab improved DFS vs Placebo in the baseline KIM-1^{High} subgroup

Baseline



	n	Median DFS	HR[a] (95% CI)
Atezolizumab	151	NE	0.72 (0.52, 0.99)
Placebo	149	21.16	

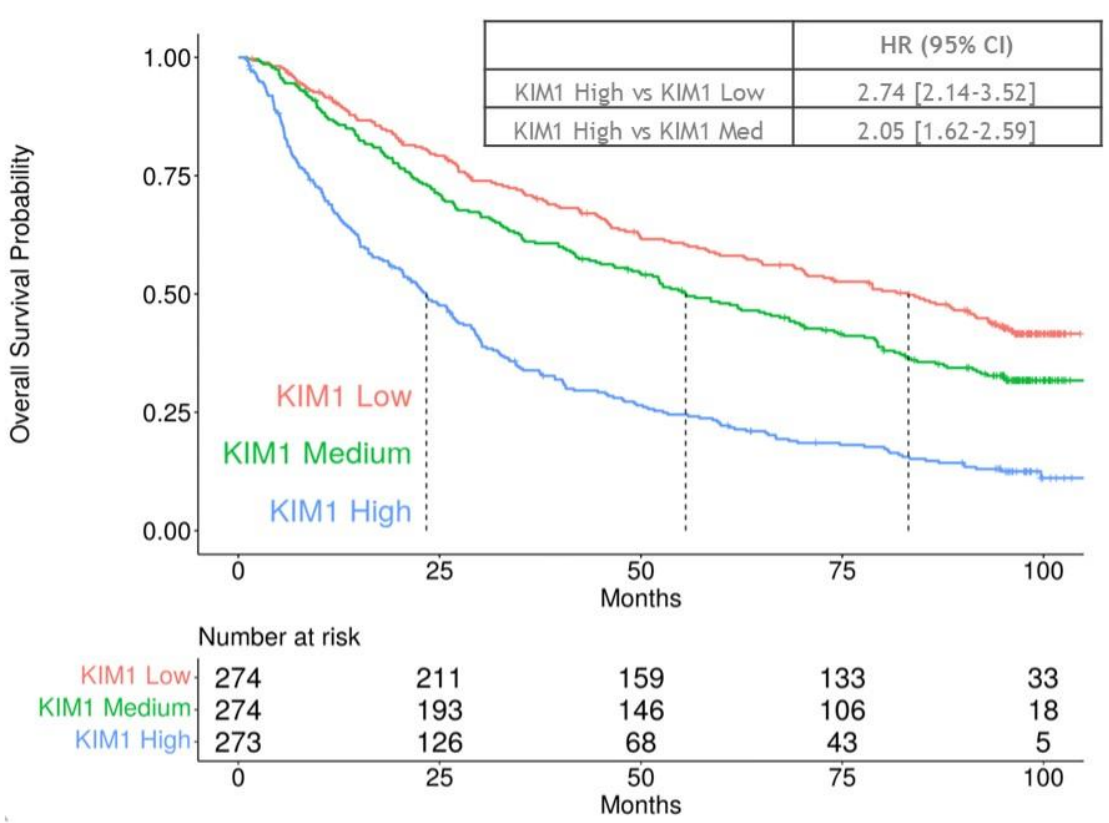


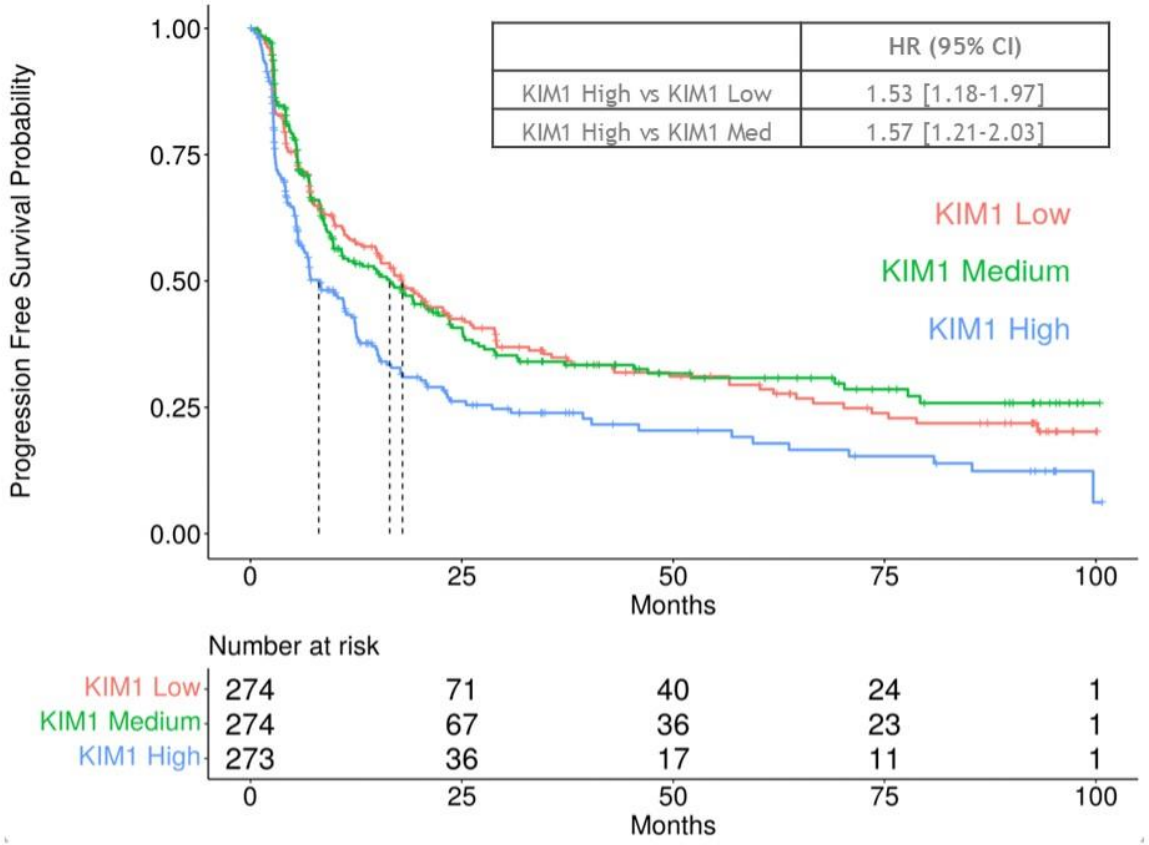
	n	Median DFS	HR[a] (95% CI)
Atezolizumab	229	57.23	1.12 (0.88, 1.63)
Placebo	223	NE	

[a] HR stratified by pathologic disease stage and geographic region.

Baseline KIM-1 levels and clinical outcomes

- Higher baseline KIM-1 was associated with worse overall and progression free survival





KIM-1 association with outcomes remains significant after adjustment for IMDC risk and baseline tumor burden in multivariable models

Xu W: GU ASCO 2025

KIM-1 decrease identifies responders to Nivo+Ipi

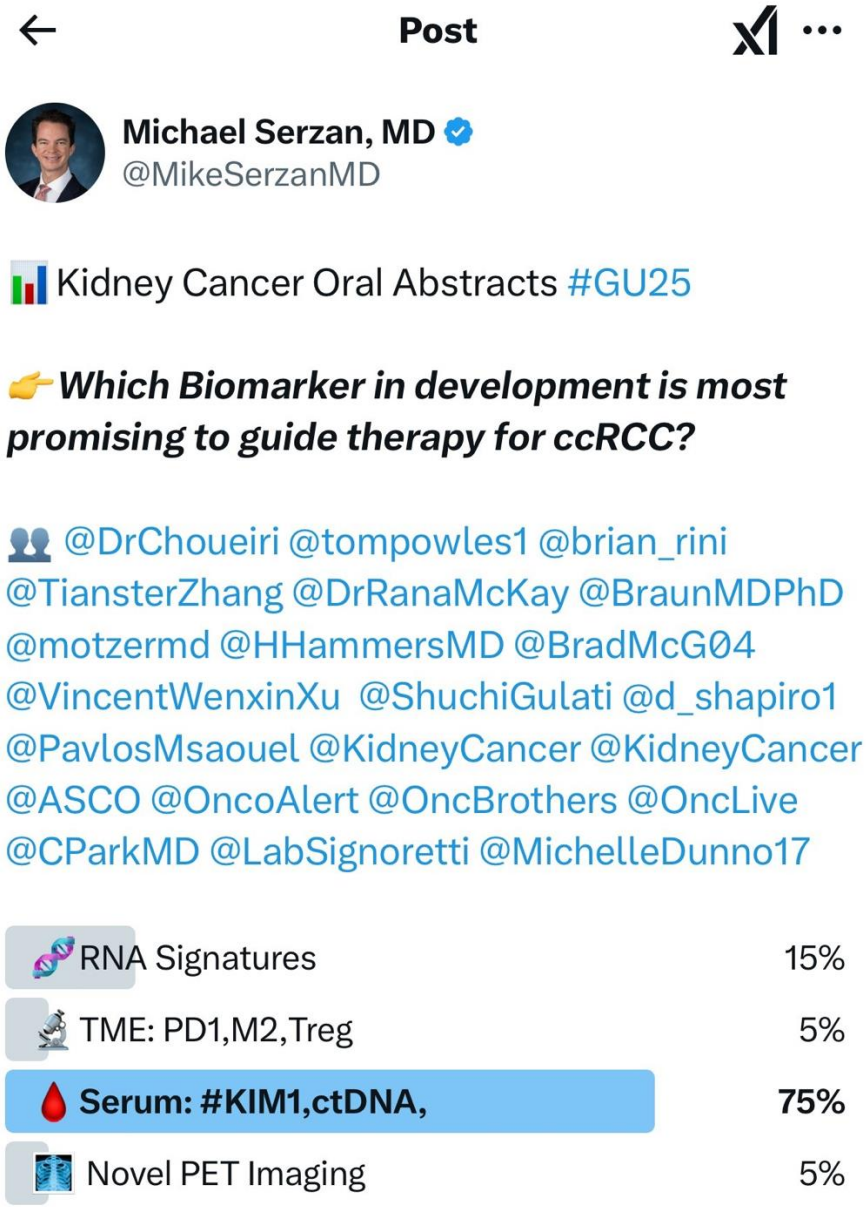
3 wks KIM-1 change	N (%)	ORR, % (95% CI)	mPFS, months	mOS, months
>30% Decrease	140 (31.7)	**69.3 (60.9-76.8)**	**70.8 (17.8- NR)**	**85.4 (63.1-NR)**
>10-30% Decrease	87 (19.7)	36.8 (26.4-47.8)	11.4 (6.3-18.2)	66.1 (40.4-80.1)
<10% Change	86 (19.5)	30.2 (20.8-41.1)	15.4 (10.3-20.7)	52.7 (30.3-70.7)
>10-30% Increase	56 (12.7)	23.2 (13.0-36.4)	7.1 (4.2-16.8)	40.3 (23.8-58.4)
>30% Increase	72 (16.3)	13.9 (6.9-24.1)	4.2 (3.0-8.1)	26.6 (18.8-38.4)

Patients with 30% decrease in KIM-1 after 3 weeks of treatment had over 3x longer median OS and 17x longer median PFS compared to those with 30% increase

Xu W: GU ASCO 2025

While NOT ready for clinical use, beyond sarcomatoid, it is exciting time.

While NOT ready for clinical use, beyond sarcomatoid, it is exciting time.



MAYO CLINIC

Thank you

NCI Designated Comprehensive Cancer Center

@ZakhariaYousef