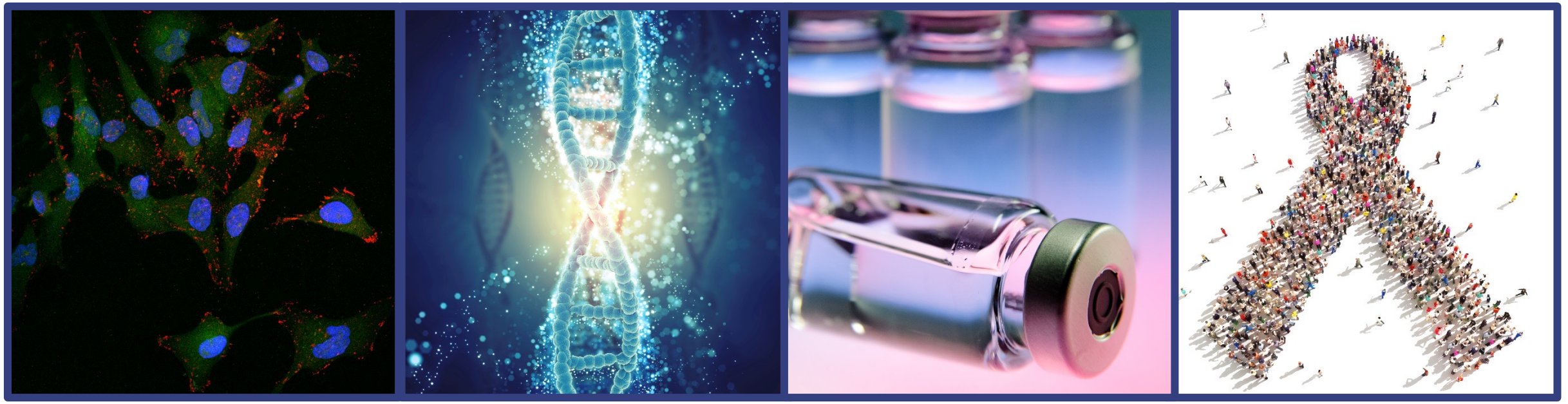

# Perioperative Treatment in RCC

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DDHO 2025

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

# Disclosures

- Institutional Grant: Merck, Bayer, Bristol-Myers Squibb, Genentech/Roche, SeaGen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, Pfizer, Xencor

# Scope of the problem

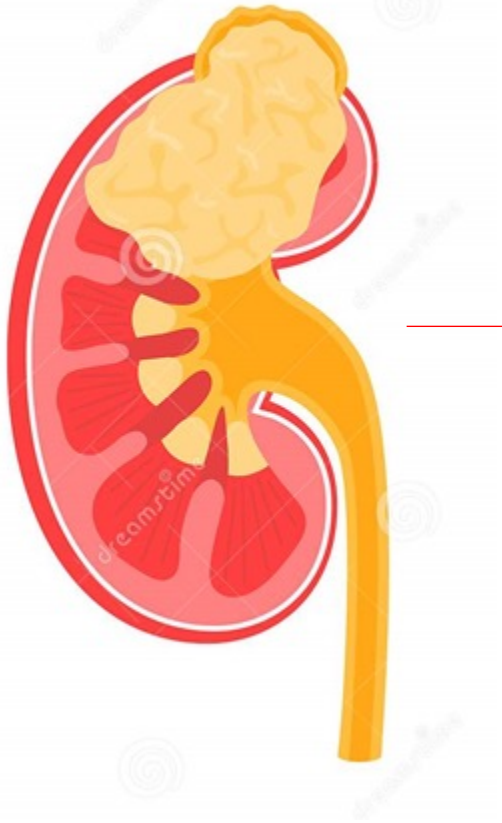
- Currently standard of care for locally advanced kidney cancer starts with surgery.

- However, ~50% of patients with Stage III kidney cancer will relapse.

- Our biomarkers  to predict outcome are highly imperfect.

# How can we treat locally advanced RCC?

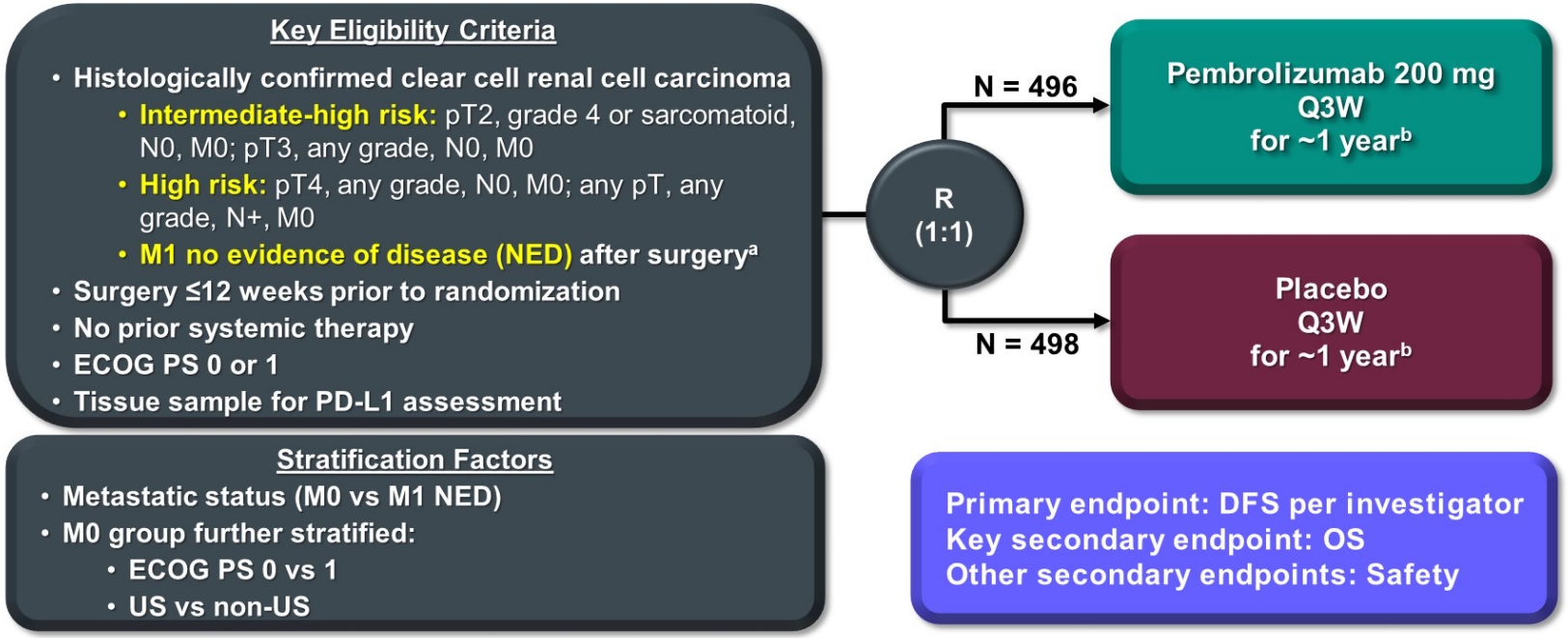
Surgery



Adjuvant treatment

# Evolving adjuvant landscape in RCC

## KEYNOTE-564 (NCT03142334) Study Design

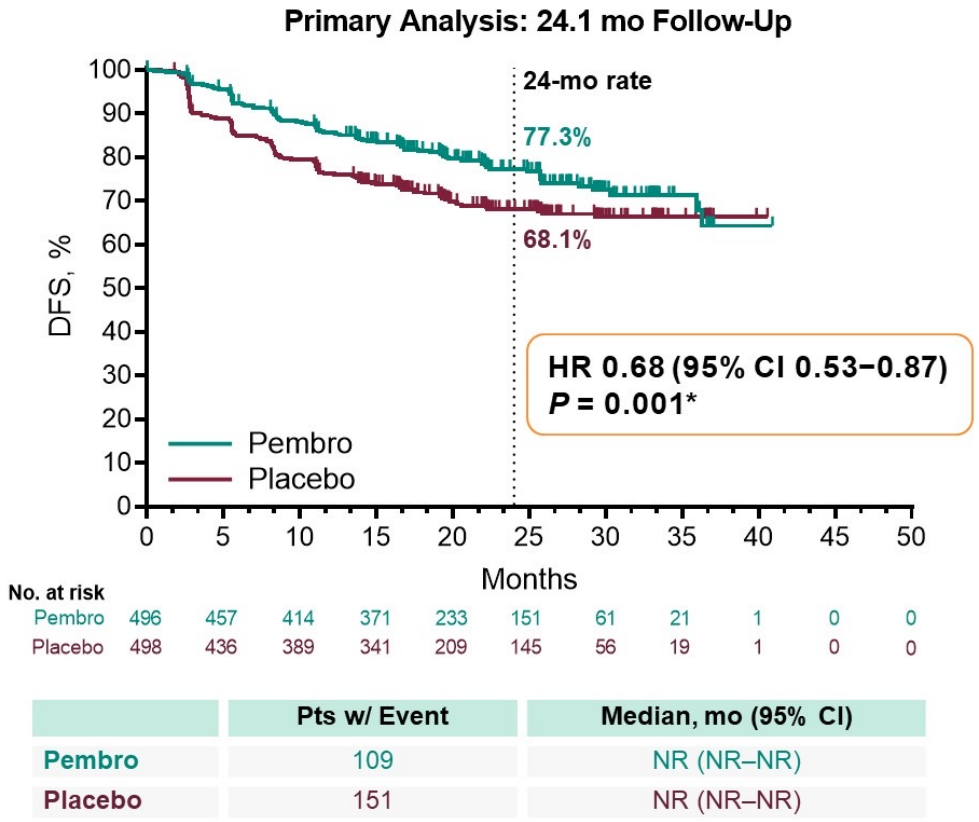



- Median (range) time from randomization to cutoff: 30.1 (20.8−47.5) months

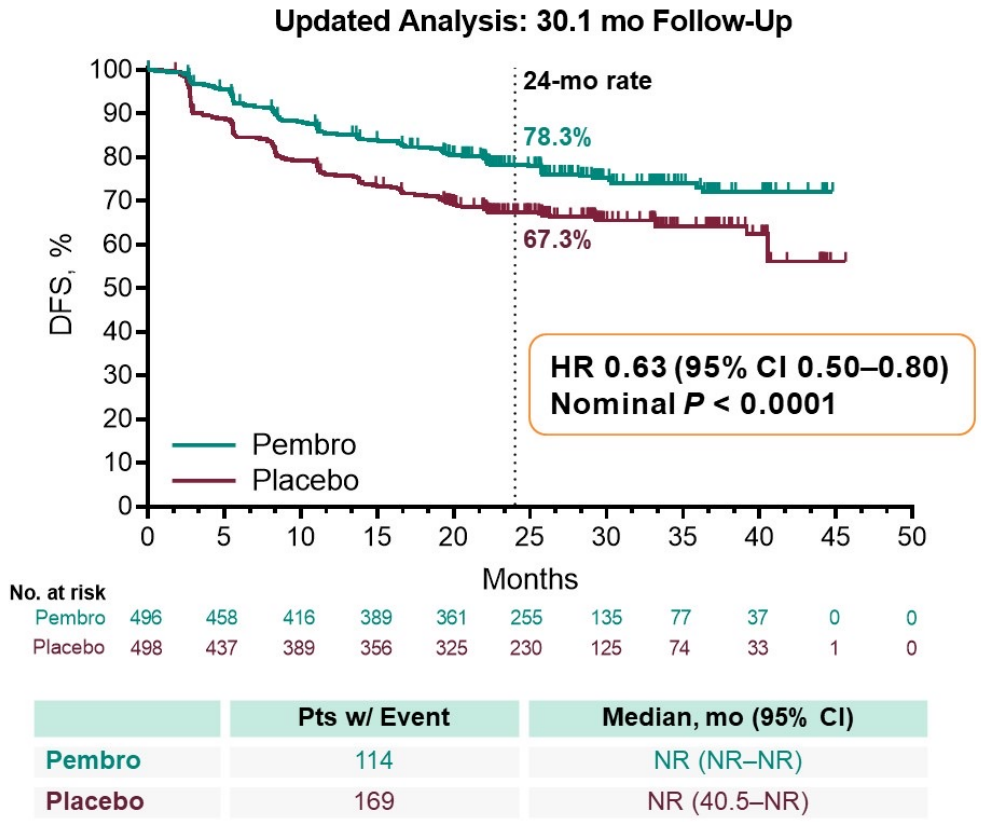
Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.
Data cutoff date: June 14, 2021.

Choueiri et al. NEJM 2021

# KEYNOTE-564 DFS by Investigator (ITT)—Primary Endpoint




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro | 109 | NR (NR–NR) |
| Placebo | 151 | NR (NR–NR) |




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro | 114 | NR (NR–NR) |
| Placebo | 169 | NR (40.5–NR) |

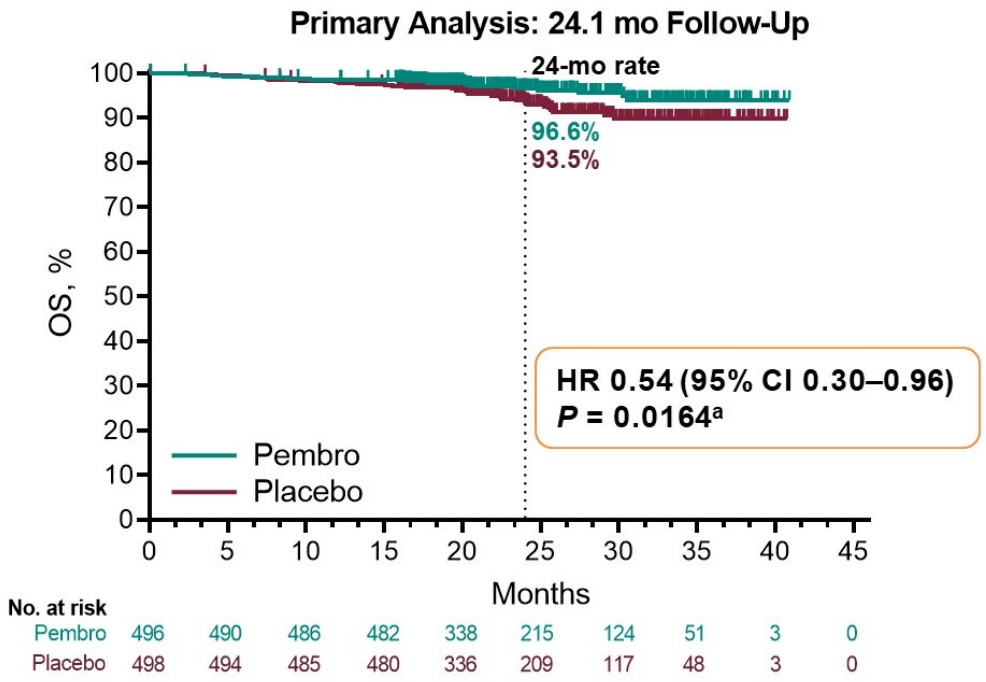
* denotes statistical significance.
ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Data cutoff at updated analysis: June 14, 2021.

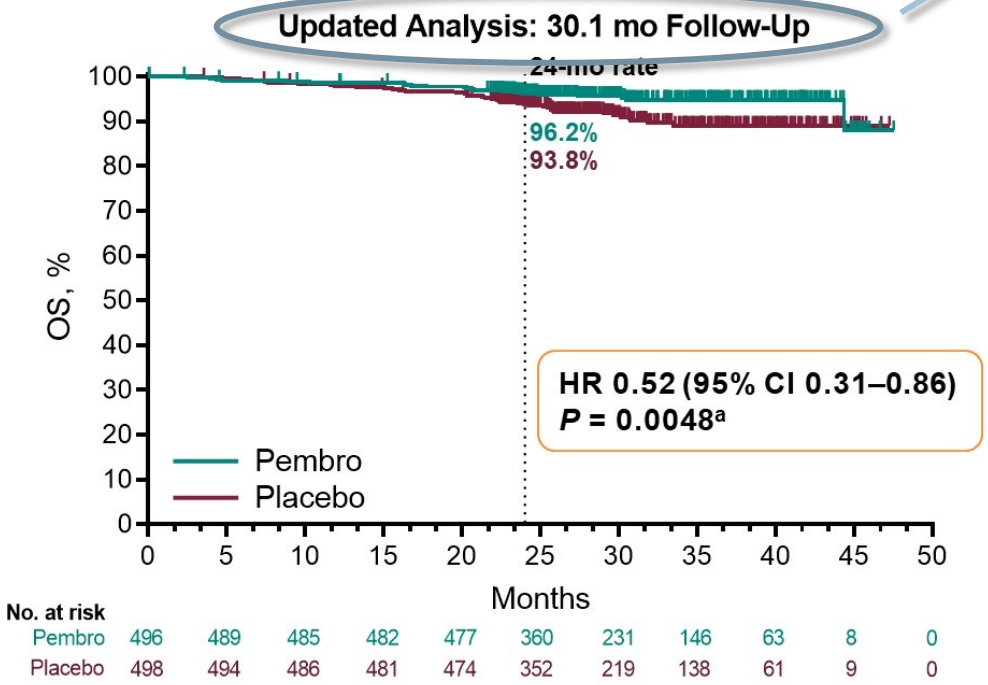
Powles T, et al. *Lancet Oncol*. 2022;23;1133-1144; Choueiri TK, et al. ASCO GU 2022. Abstract 290; Choueiri TK et al. *N Engl J Med*. 2021;385:683-694; Choueiri TK et al. 2021 ASCO Annual Meeting. Abstract LBA5.

# KEYNOTE-564: Interim OS (ITT)—Key Secondary Endpoint

Only 33% of deaths needed for final OS analysis had been accrued at data cutoff




| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro | 18 | NR (NR–NR) |
| Placebo | 33 | NR (NR–NR) |



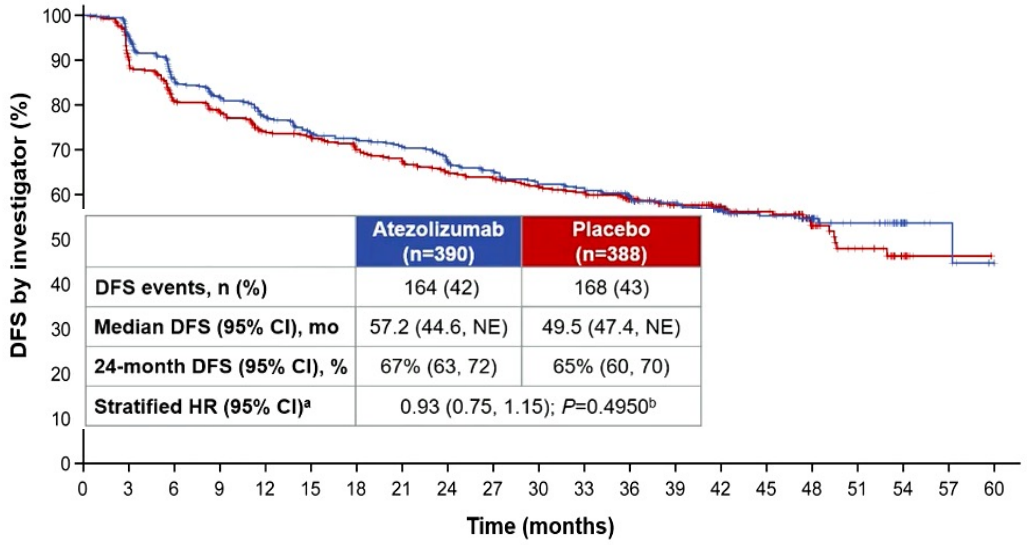

| | Pts w/ Event | Median, mo (95% CI) |
|---|---|---|
| Pembro | 23 | NR (NR–NR) |
| Placebo | 43 | NR (NR–NR) |

[a]Did not cross prespecified p-value boundary for statistical significance.
ITT population included all randomized participants. NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Data cutoff at updated analysis: June 14, 2021.


Powles T, et al. *Lancet Oncol.* 2022;23;1133-1144; Choueiri TK, et al. ASCO GU 2022. Abstract 290.
2. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694; Choueiri TK et al. 2021 ASCO LBA5.

# IMmotion010




| | Atezolizumab (n=390) | Placebo (n=388) |
|---|---|---|
| DFS events, n (%) | 164 (42) | 168 (43) |
| Median DFS (95% CI), mo | 57.2 (44.6, NE) | 49.5 (47.4, NE) |
| 24-month DFS (95% CI), % | 67% (63, 72) | 65% (60, 70) |
| Stratified HR (95% CI)[a] | 0.93 (0.75, 1.15); *P*=0.4950[b] | |

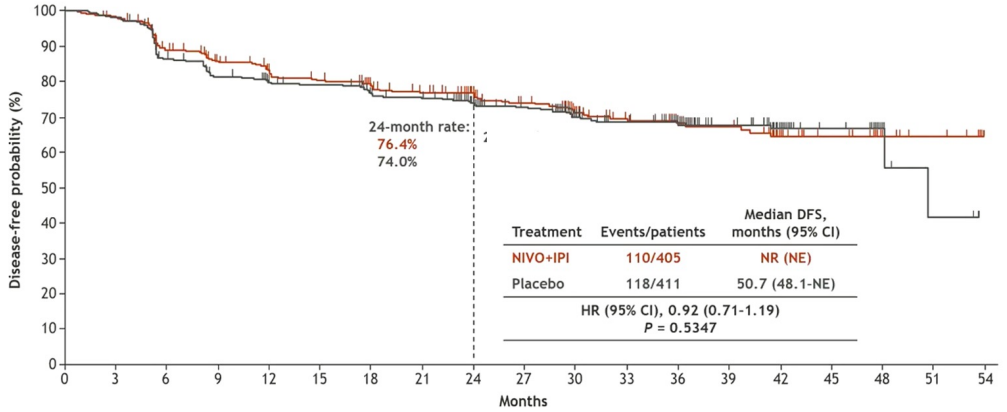
**Number at risk**

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 390 | 360 | 322 | 306 | 288 | 272 | 265 | 257 | 244 | 234 | 222 | 218 | 194 | 171 | 124 | 100 | 75 | 48 | 22 | 6 | 1 |
| Placebo | 388 | 343 | 305 | 294 | 275 | 268 | 254 | 243 | 232 | 226 | 216 | 209 | 187 | 161 | 121 | 91 | 56 | 33 | 15 | 3 | NE |

Data cutoff: 3 May 2022. Minimum follow-up, 38.6 months; Median follow-up, 44.7 months (range, 0-62.6).
NE, not estimable.
[a] Stratified for disease status and PD-L1 status. [b] Not significant at α=0.05.

Bex

# CheckMate-914




| Treatment | Events/patients | Median DFS, months (95% CI) |
|---|---|---|
| NIVO+IPI | 110/405 | NR (NE) |
| Placebo | 118/411 | 50.7 (48.1-NE) |

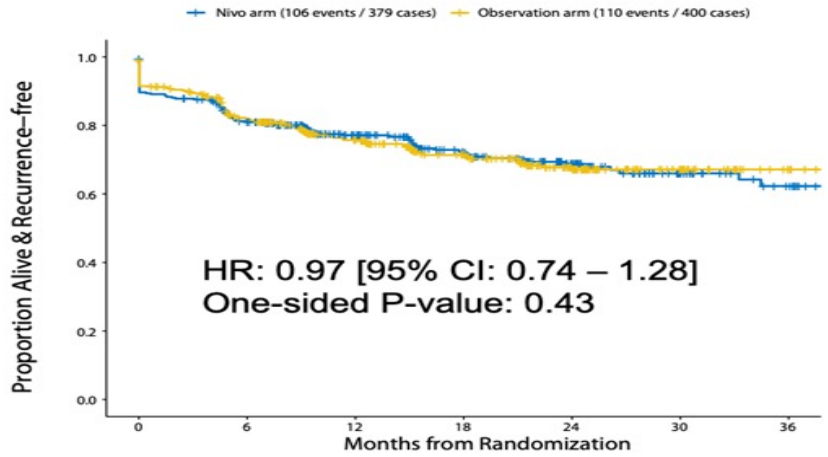
HR (95% CI), 0.92 (0.71-1.19)
*P* = 0.5347

**No. at risk**

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO+IPI | 405 | 378 | 337 | 316 | 299 | 289 | 270 | 259 | 224 | 203 | 150 | 125 | 89 | 73 | 42 | 34 | 13 | 9 | 0 |
| Placebo | 411 | 391 | 340 | 315 | 299 | 293 | 275 | 268 | 227 | 205 | 155 | 128 | 90 | 66 | 38 | 25 | 8 | 3 | 0 |

Median (range) follow-up, 37.0 (15.4-58.0) months.
As the DFS endpoint was not met, no formal analysis of OS was performed (in total, there were 33 deaths in the NIVO+IPI arm and 28 deaths in the placebo arm).

# PROSPER




**Number at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nivo arm | 379 | 291 | 208 | 151 | 99 | 50 | 30 |
| Observation arm | 400 | 300 | 214 | 161 | 100 | 47 | 22 |

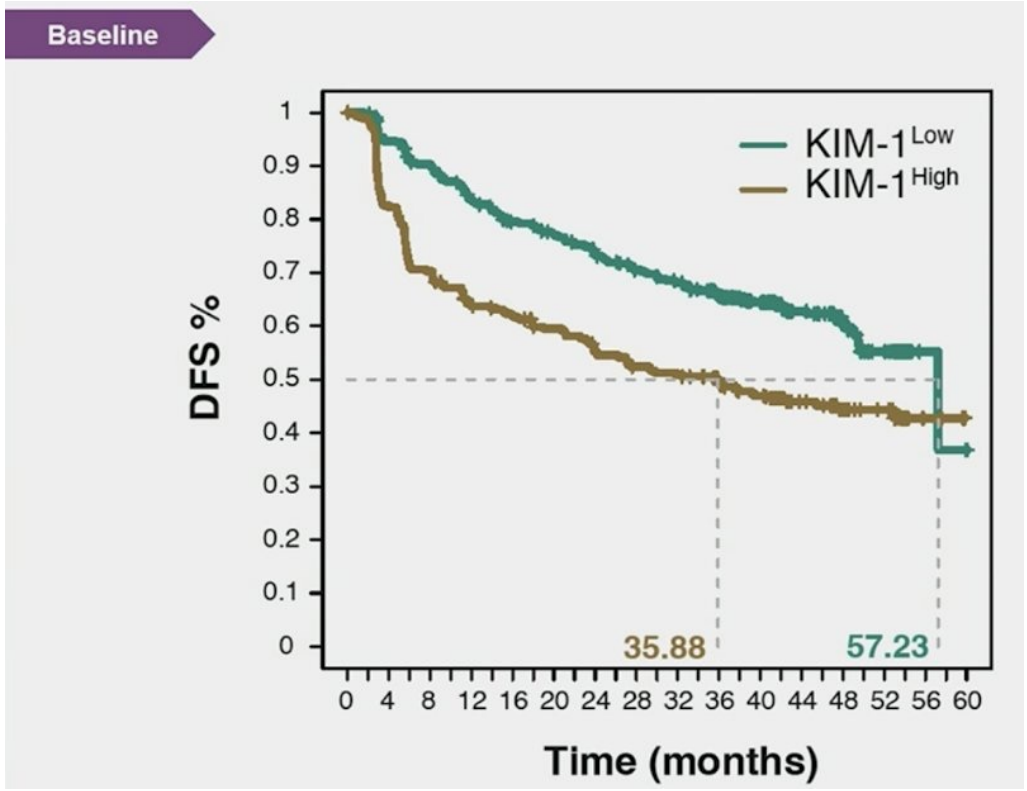

Allaf M, et al. ESMO 2022. Abstract LBA67.

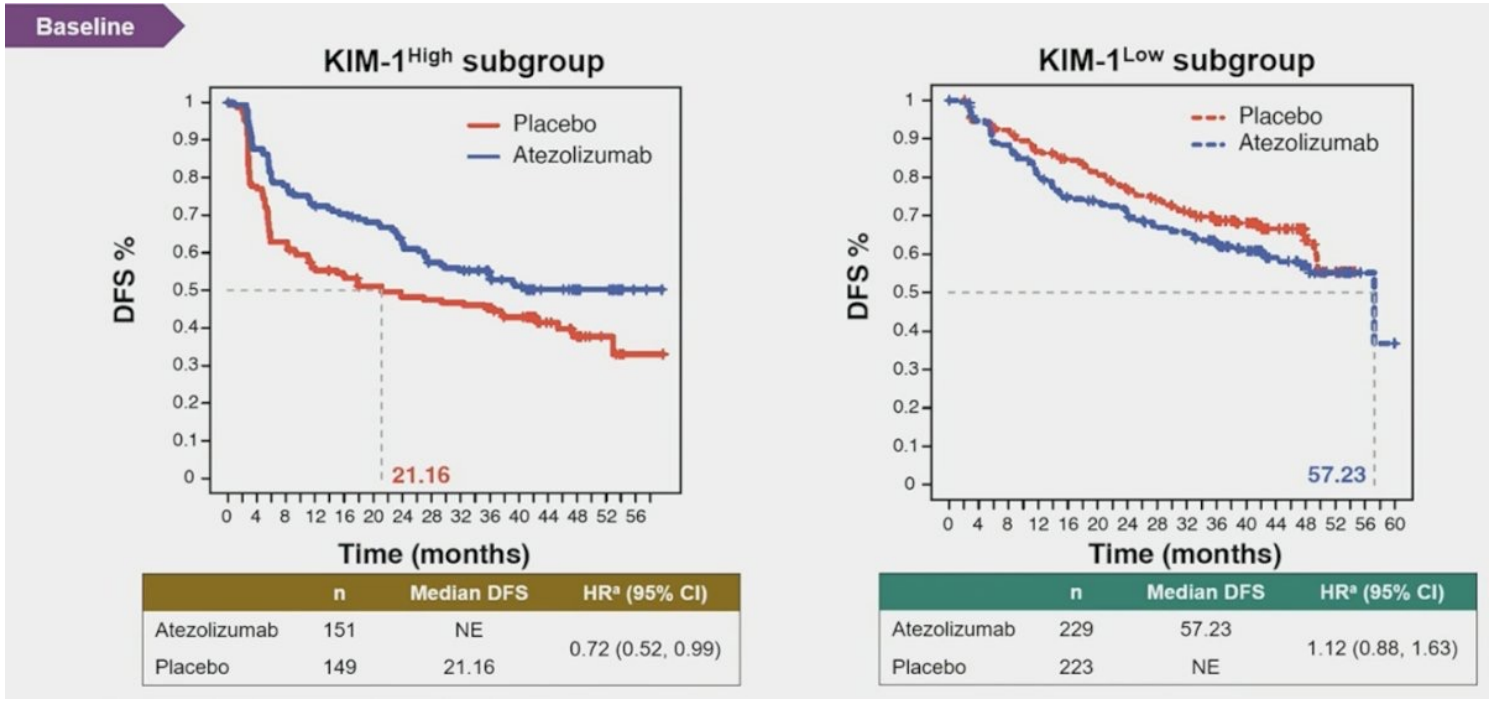
Motzer RJ, et al. ESMO2022. LBA4.

Pal SK, et al. *Lancet.* 2022 Oct 1;400(10358):1103-1116.

# Biomarker: Is KIM-1 next big thing?

## IMmotion010



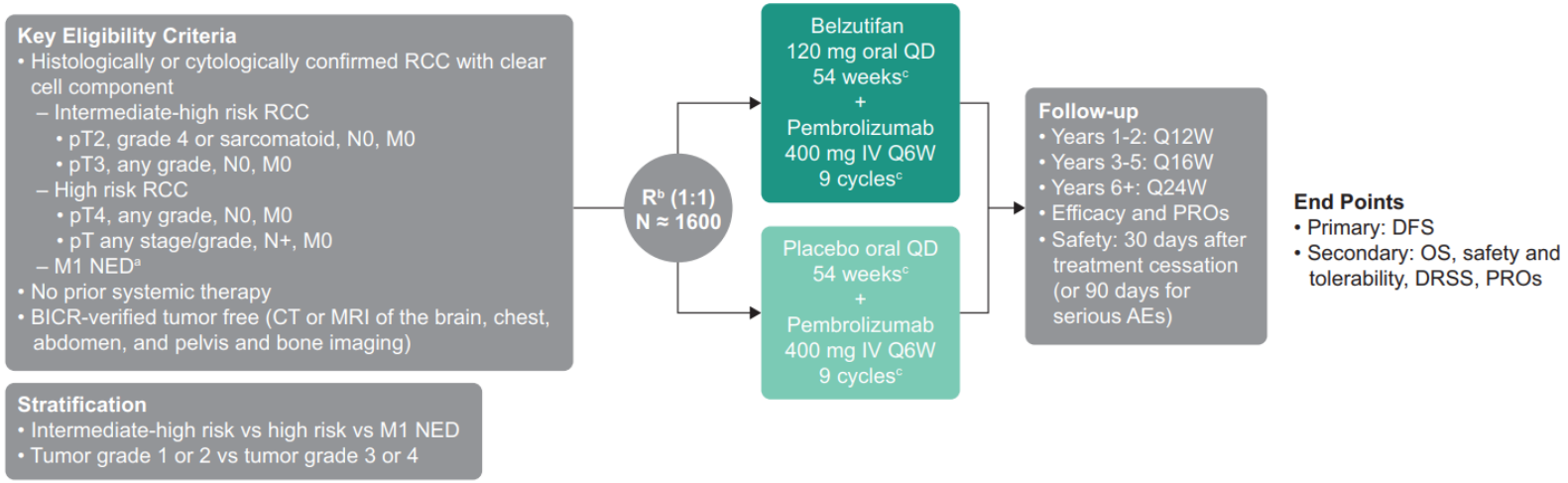

Rini et al. ASCO 2024

# Evolving adjuvant landscape in RCC

- Why we have 1 positive, and 3 negative trials?
- Is it due to design? Or pure luck?
- PD-1 vs PDL1?
  - ccRCC front line monotherapy response rate:
    - Pembrolizumab: 36.3%
    - Atezolizumab: 15%, 25%
    - Nivolumab: 28%, 29%
- With other combinations, can we make it better?
- Is it due to patient selection? Can ctDNA play a role or KIM-1, and others

# MK-6482-02 trial: LITESPARK-022

**Study design**




# A032201 (STRIKE) trial

## Testing the Addition of the Anti-Cancer Drug Tivozanib to Immunotherapy (Pembrolizumab) After Surgery to Remove All Known Sites of Kidney Cancer (STRIKE)

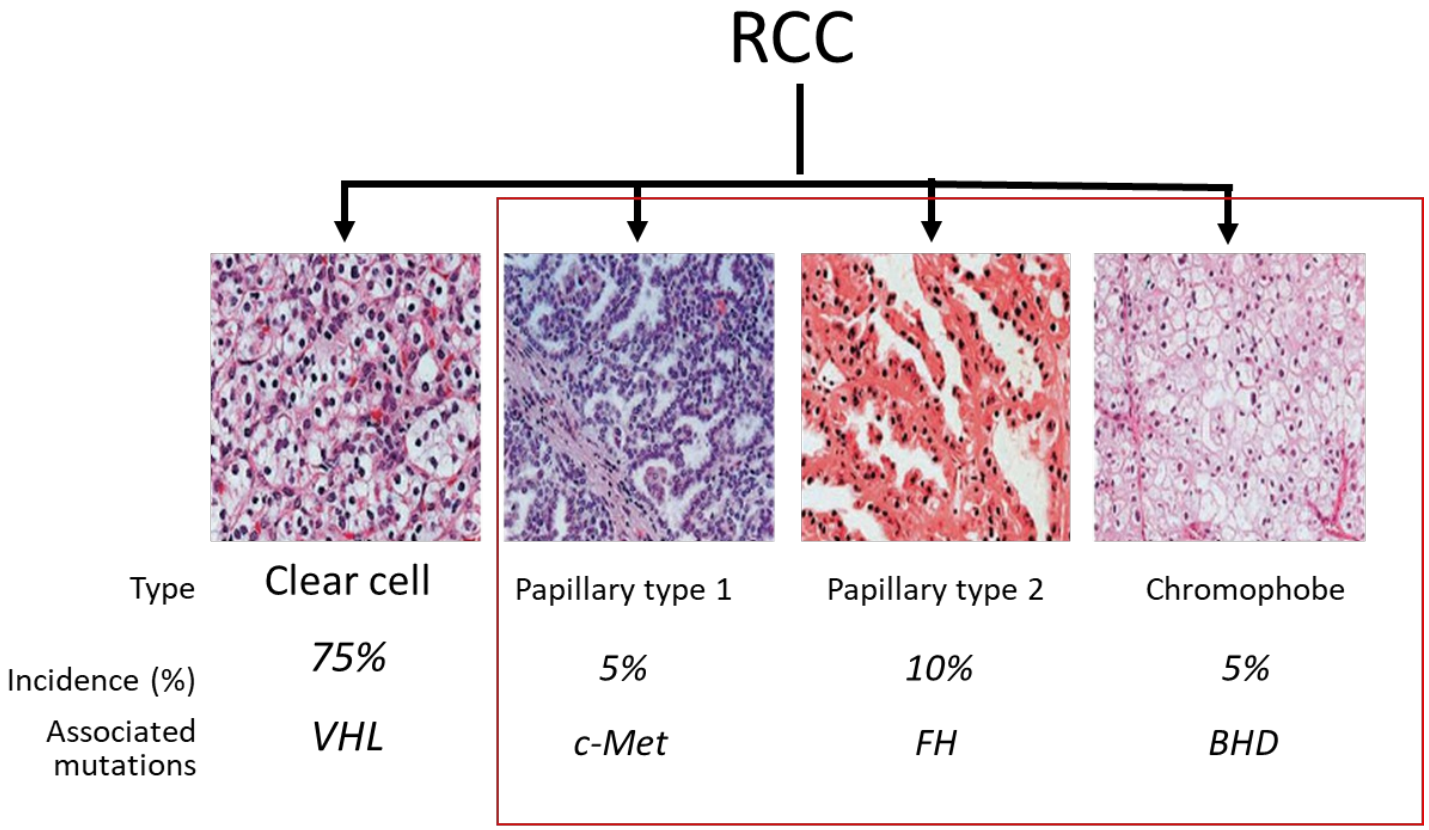
**ClinicalTrials.gov ID** NCT06661720

**Sponsor** Alliance for Clinical Trials in Oncology

**Information provided by** Alliance for Clinical Trials in Oncology (Responsible Party)

**Last Update Posted** 2025-04-02

# What about non-clear cell RCC?

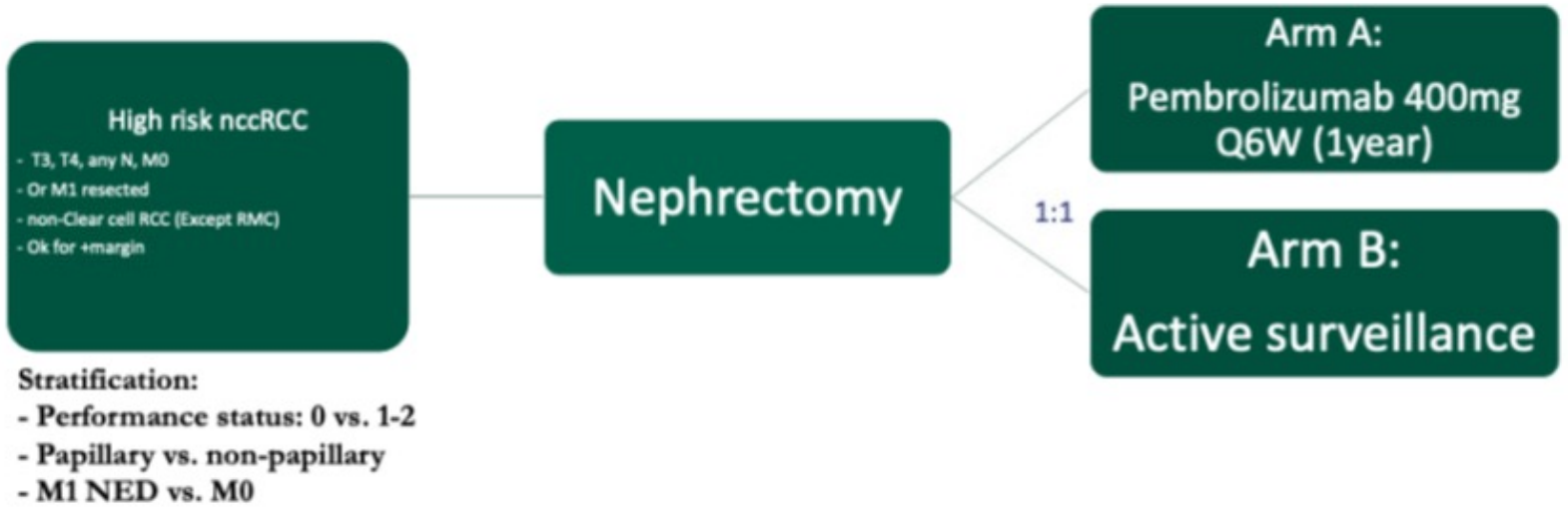



VHL=von Hippel-Lindau; FH=fumarate hydratase; BHD=Birt-Hogg-Dubé.

Modified from Linehan WM et al. *J Urol*. 2003;170:2163-2172.

No adjuvant data available for nccRCC

# Phase III study of adjuvant pembrolizumab vs active surveillance after nephrectomy in patients with non-clear cell renal-cell carcinoma (EA8252)




Phase 3, 1:1 randomization
Accrual rate: 6 per month
N: 360
**Primary endpoint:** Disease-free survival
2-yr DFS rates of 72% vs. 62% [Arm A vs. B; HR = 0.68]

**Secondary endpoints:** OS, Safety/tolerability

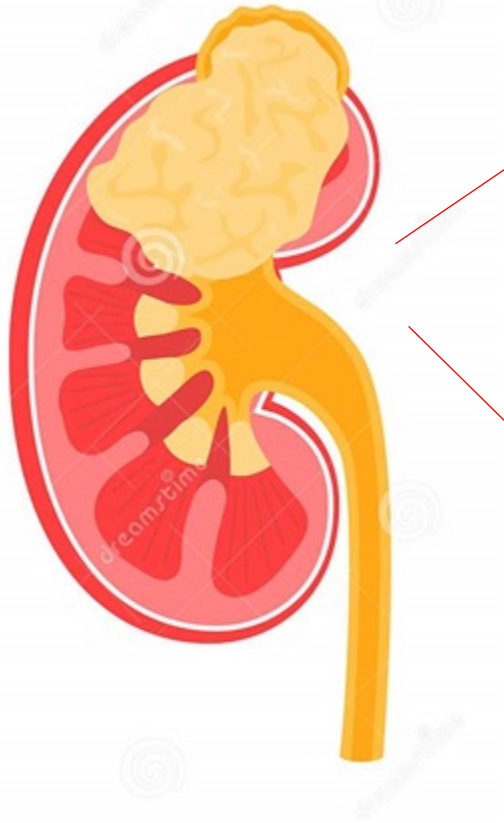
**Exploratory endpoints:** Correlatives, and additional DFS/OS

- Mehmet Asim Bilen (Study chair)
- Viraj Master (Urology co-PI)
- Naomi Haas (GU Committee Chair)
- Glenn Sykes (patient advocate)

# How can we treat locally advanced RCC?

Surgery

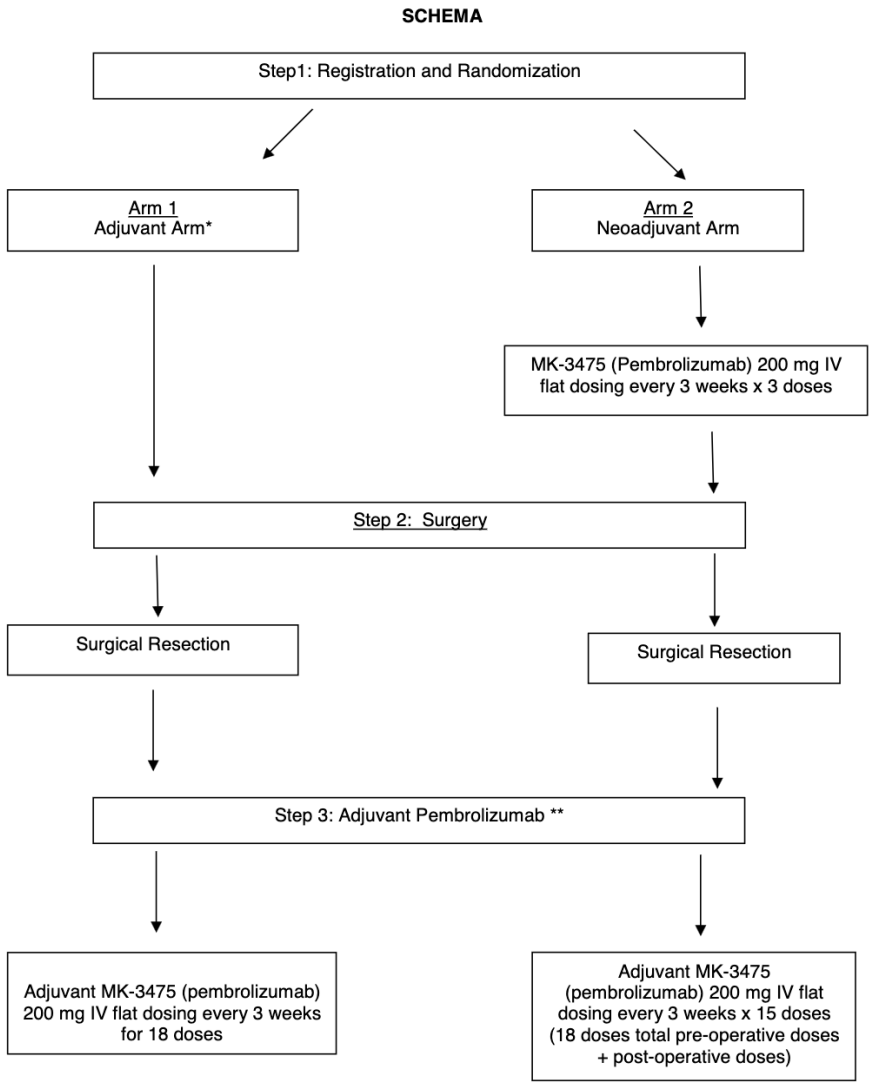
Neoadjuvant treatment

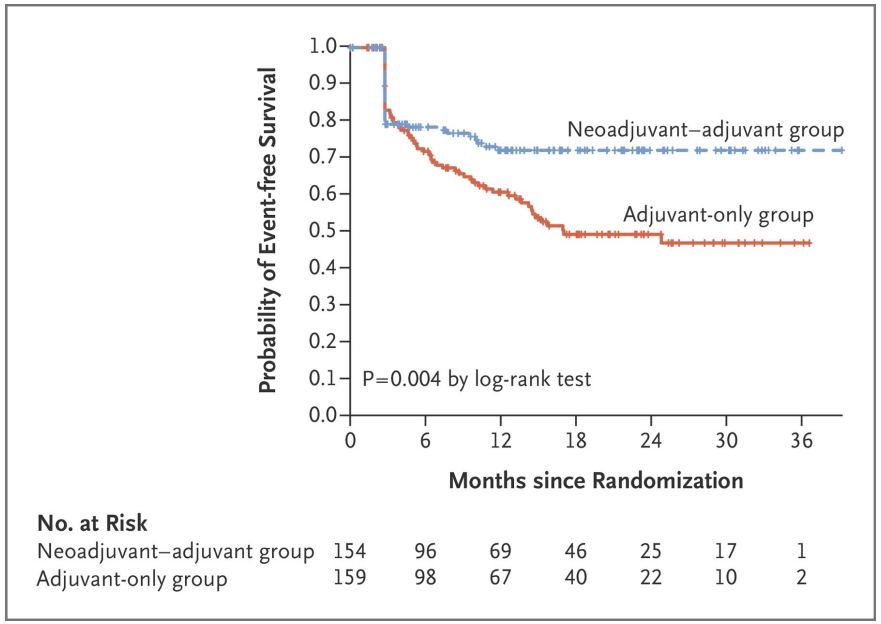


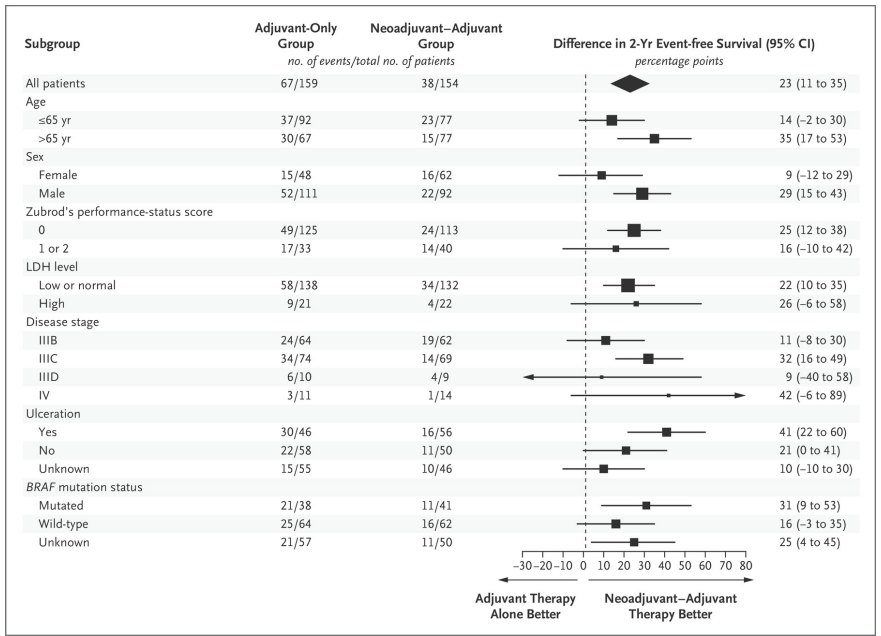
Observation

Adjuvant treatment

# Utility of neoadjuvant treatment in cancer: S1801



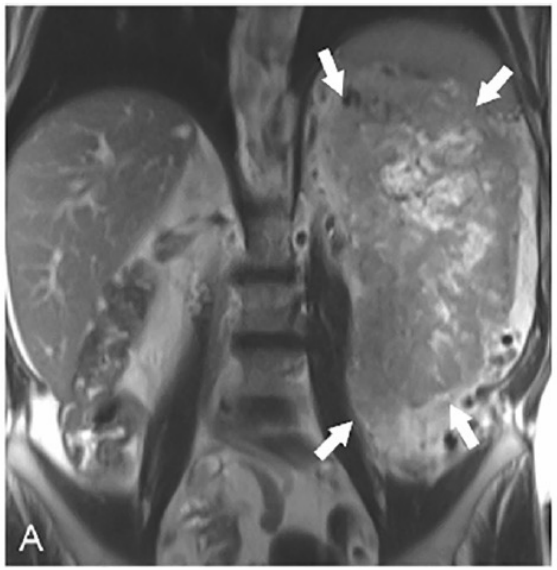
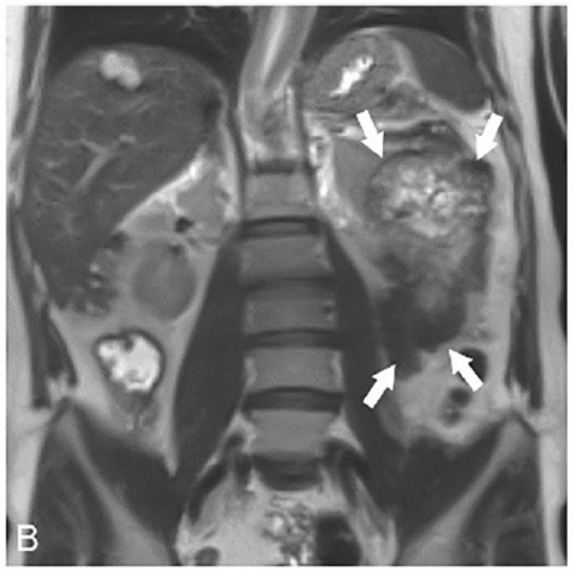
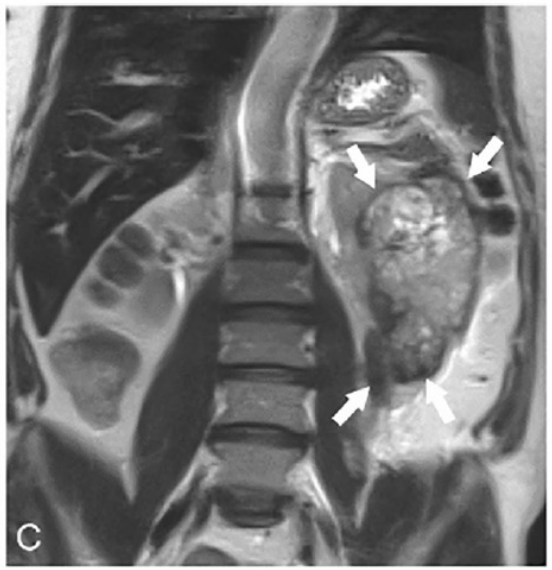

Patel et al. NEJM 2023

# Utility of perioperative treatment in renal cancer

- Localized RCC
  - Facilitate partial nephrectomy
- Locally advanced RCC  (?>cT2, ≥T3)
  - Makes surgery easier, potentially sparing organs
- Depends on treatment, it can cause systemic effect and immune induction
- Provide insight about biology of disease

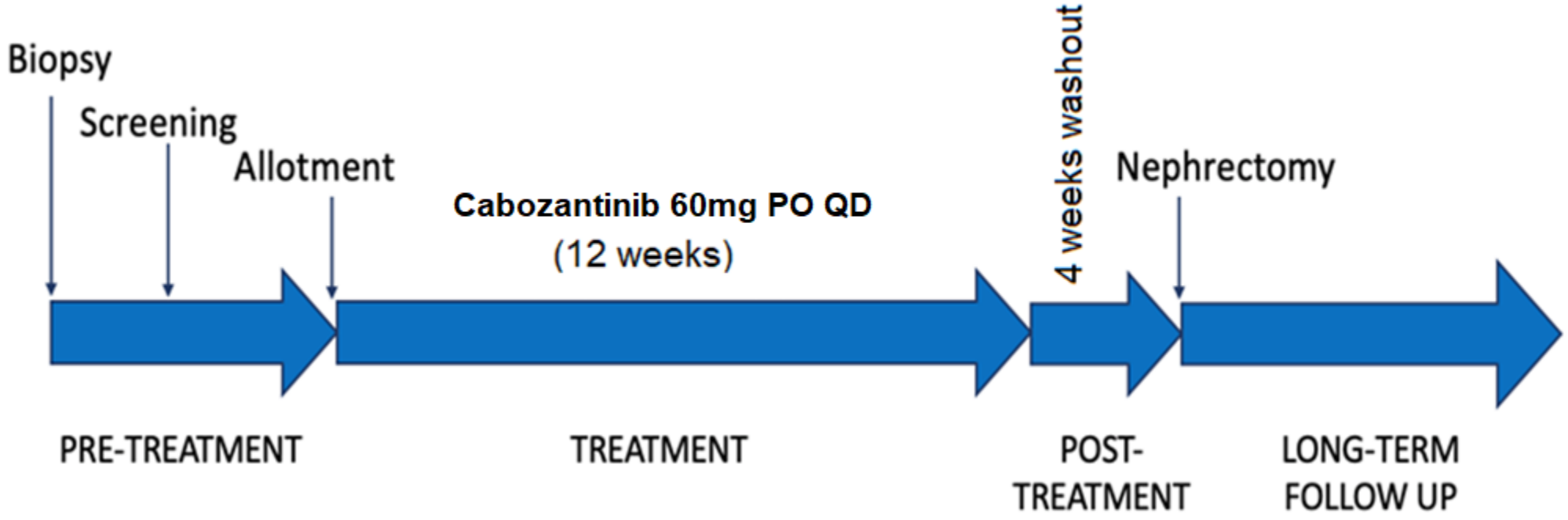
# Neoadjuvant therapy with cabozantinib: a case study

**Neoadjuvant therapy** is delivered before surgery with the goal of tumor size reduction or stopping the spread of cancer to make surgery less invasive and more effective.

| Baseline | 2 months | 1 year |
|---|---|---|
|  |  |  |
| April 2018 | June 2018 | April 2019 |
| 21.7 cm | 12.1 cm | Stable in size |

Bilen MA, et al. Front. Oncol. 2021

# Phase 2 Study of Neoadjuvant Cabozantinib in Patients with Locally Advanced Non-metastatic Clear Cell Renal Cell Carcinoma




- Patients with biopsy-proven clear cell RCC and clinical stage ≥ T3Nx or TanyN+ or deemed unresectable by the surgeon were eligible for this study.
- Primary endpoint: ORR

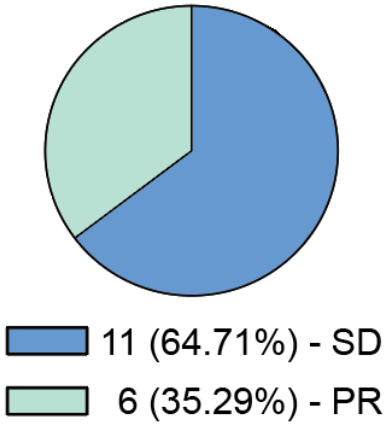
Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

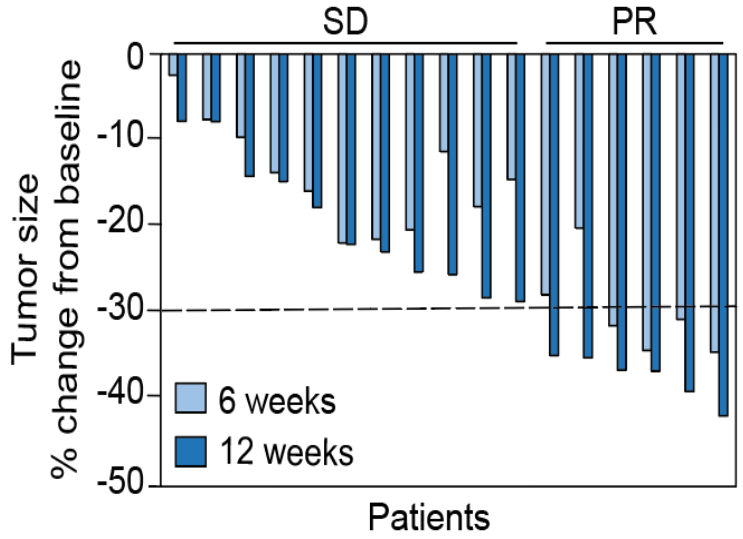
# Baseline Characteristics

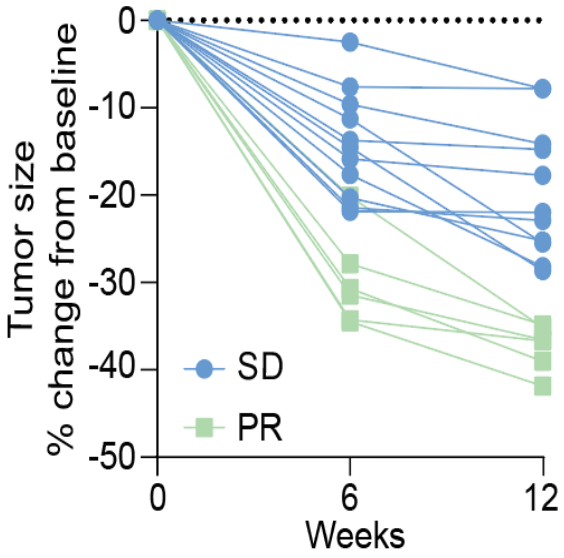
| Variable | N (%) = 17 |
|---|---|
| **Median Age** | 58 (range: 42-86) |
| **Gender** | |
| Male | 14 (82.4) |
| Female | 3 (17.6) |
| **Race** | |
| White | 14 (82.4) |
| Black | 2 (11.8) |
| Hispanic/Other | 1 (5.9) |
| **Clinical TNM stage** | |
| T3N0M0 | 15 (88.2) |
| T4N0M0 | 2 (11.8) |
| **Eastern Cooperative Oncology Group Performance Status** | |
| 0 | 9 (52.9) |
| 1 | 8 (47.1) |
| **Median baseline tumor size (mm)** | 90.2 [range: 30.8 – 151.6] |

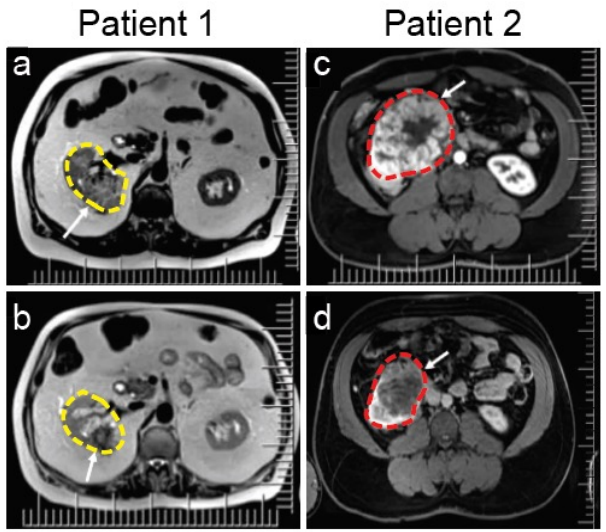
Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

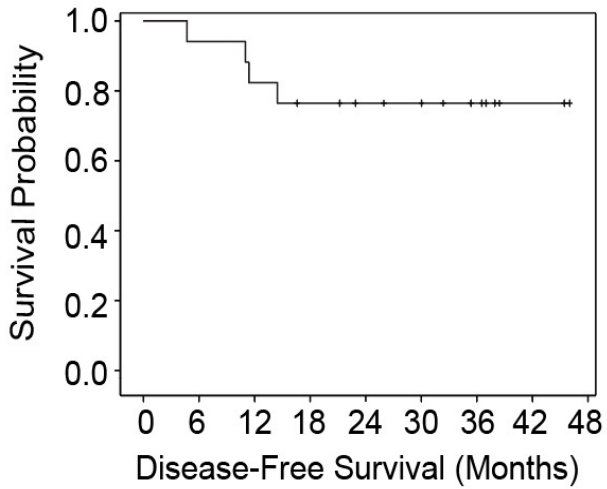
# Clinical outcomes of ccRCC patients receiving cabozantinib treatment

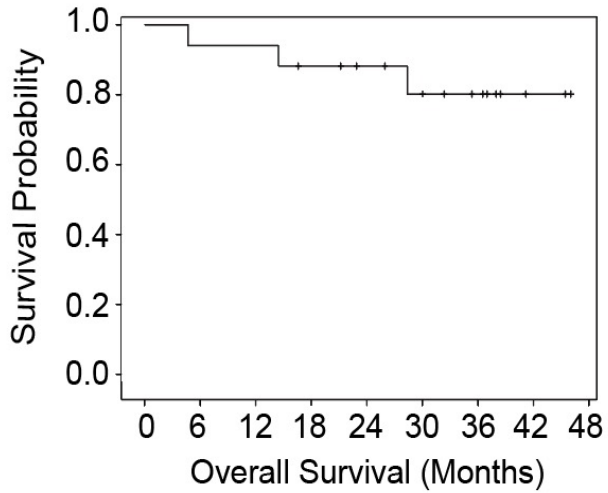


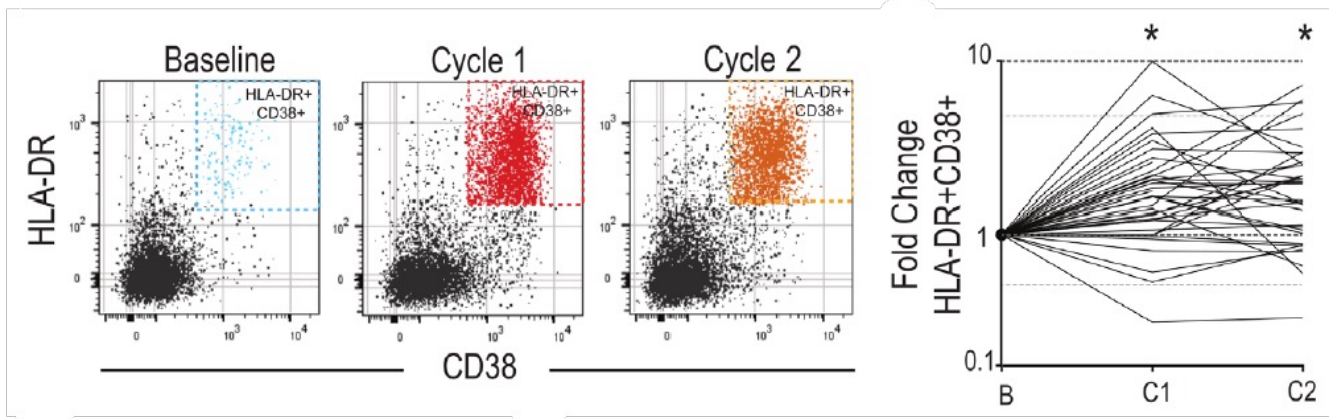



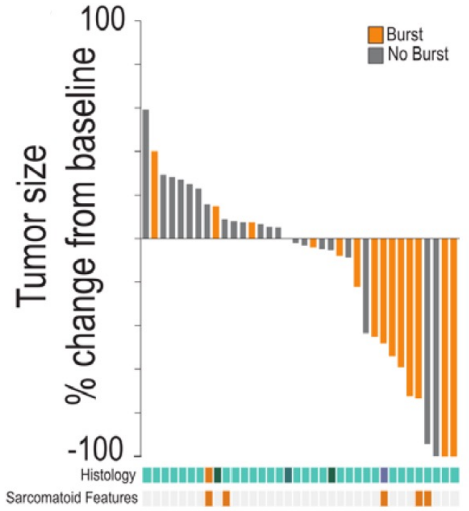

Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

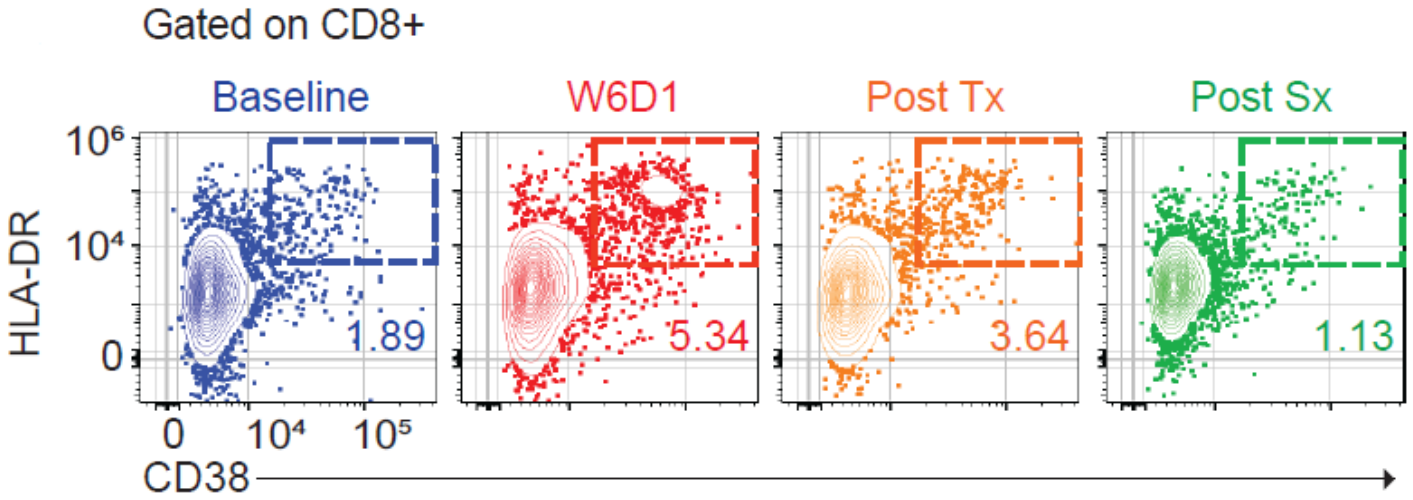
# How does cabozantinib alter patient immune responses?

# Cabozantinib activates CD8 T cells in the blood

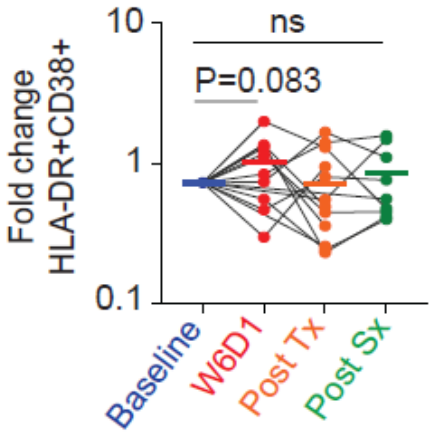
PD1 blockade in metastatic RCC patients – Carlisle et al., 2022




12/17 > 1.5-fold

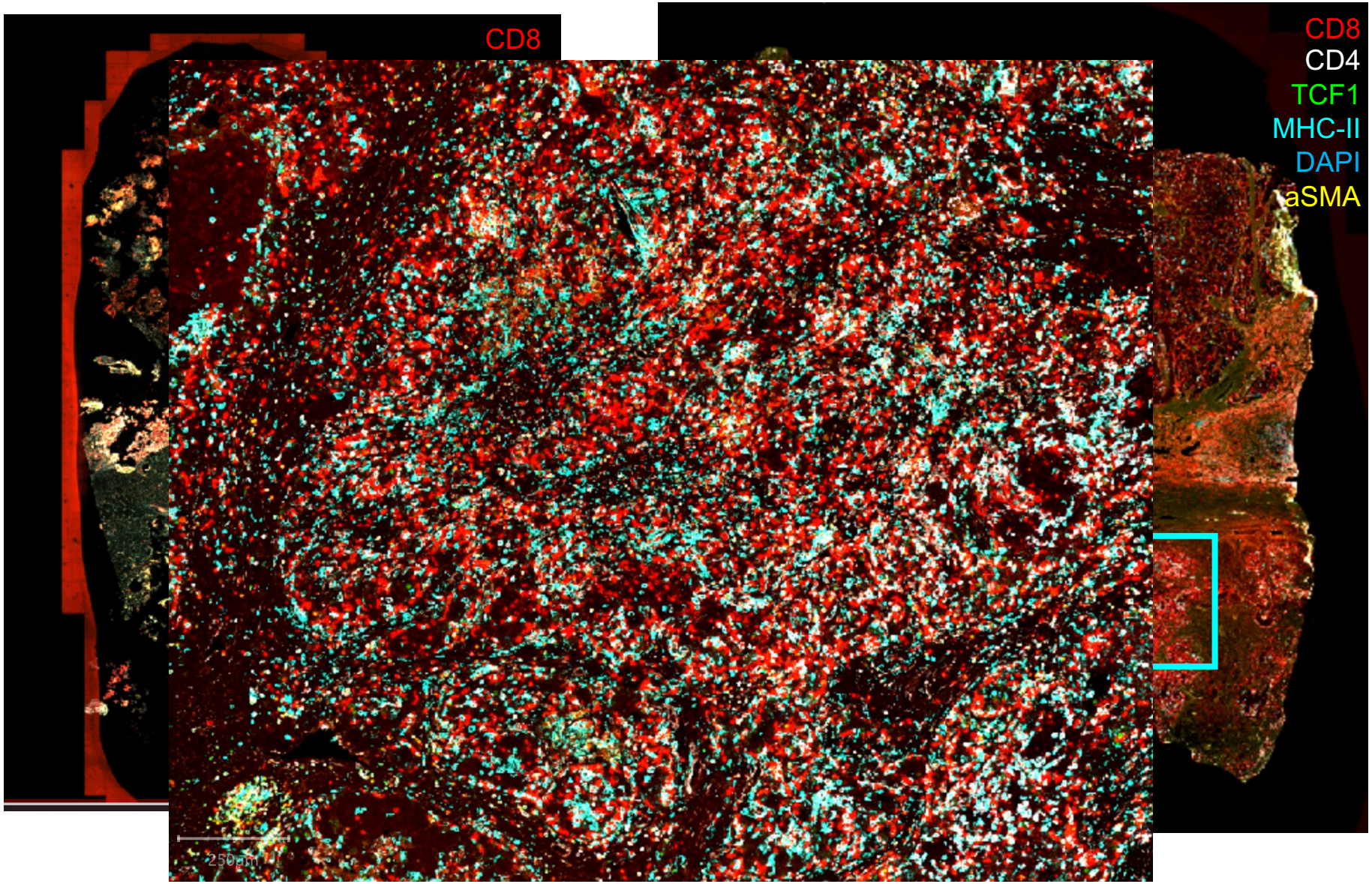



Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

# Cabozantinib activates CD8 T cells in tumors

Untreated Stage Matched ccRCC

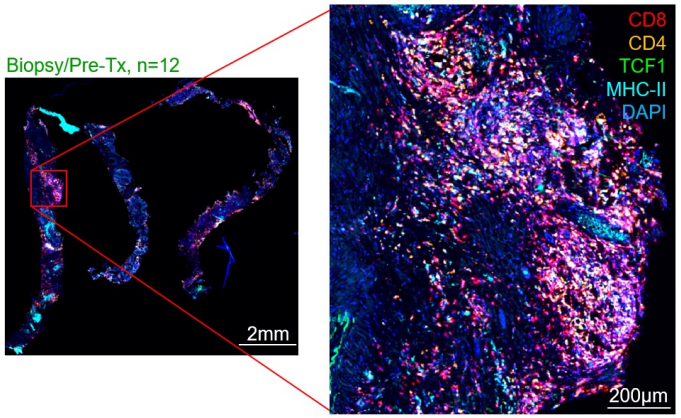
Cabozantinib treated ccRCC

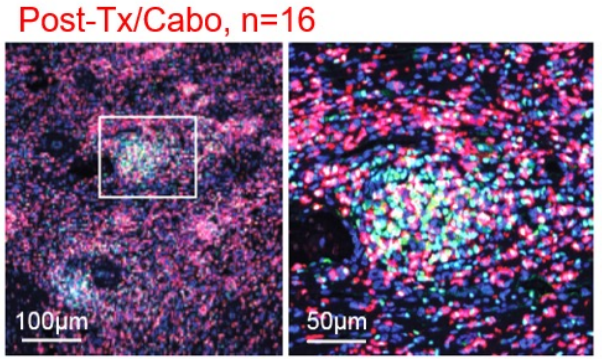


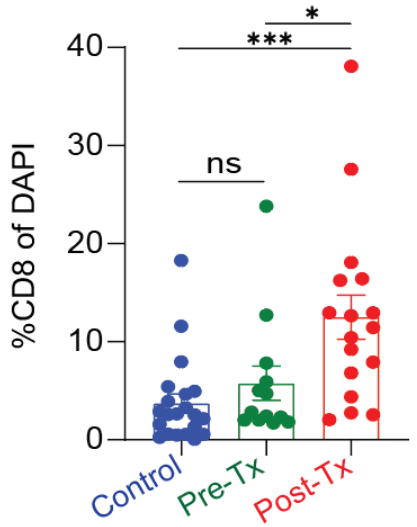

Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

# CD8 T cells activation in the tumor after cabozantinib treatment

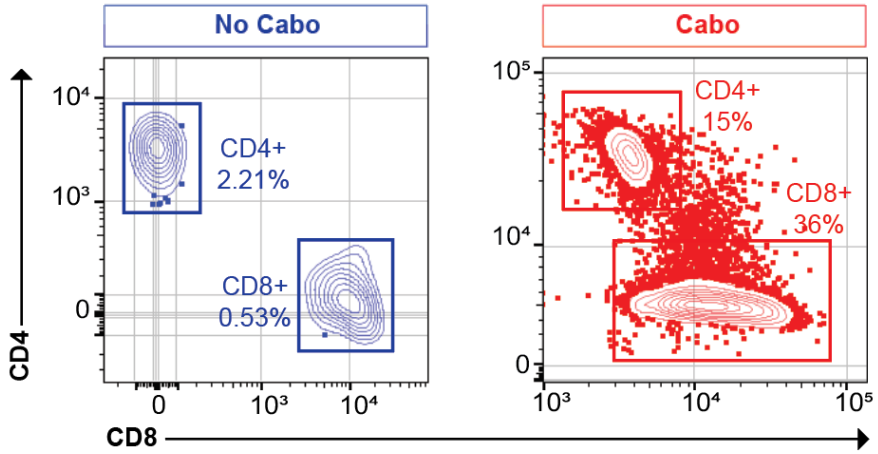
## IF

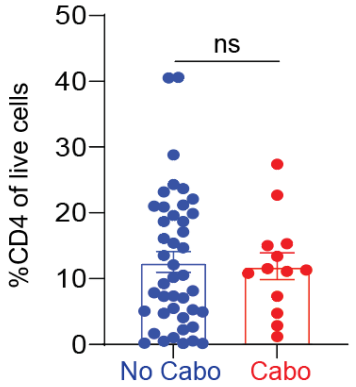


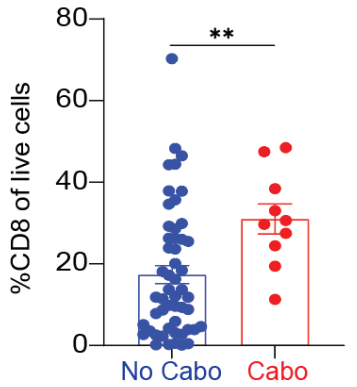




## FACS

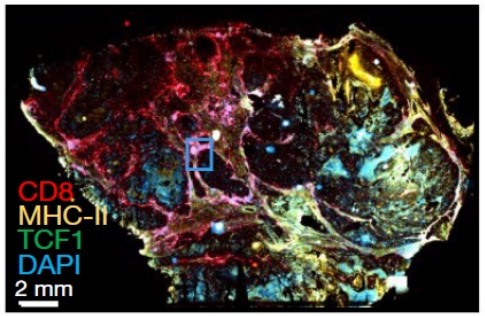


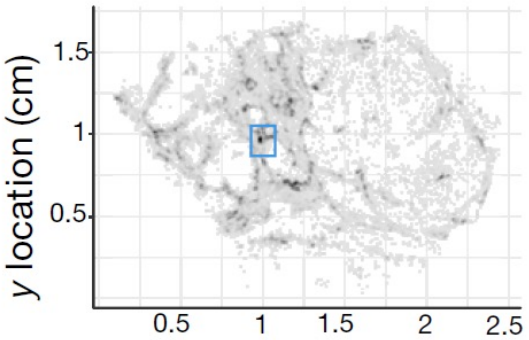



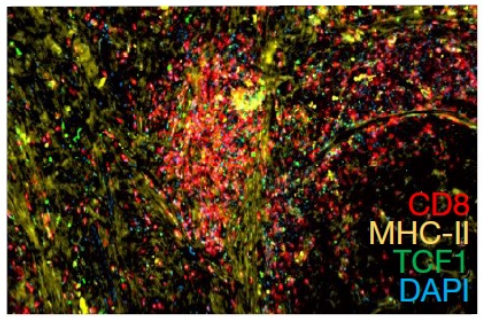




Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

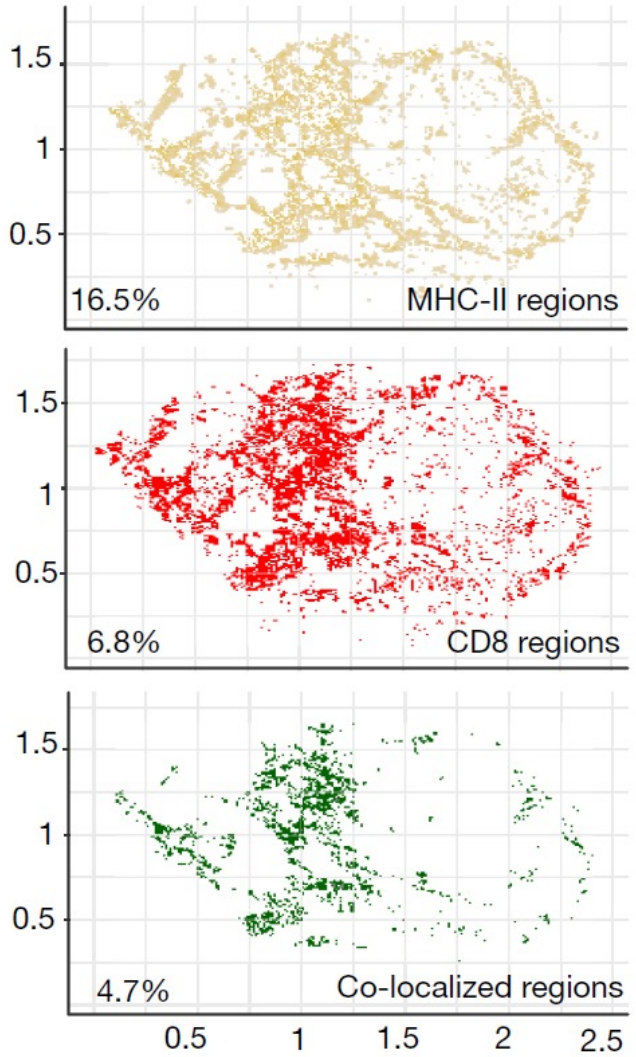
# Immune niches in ccRCC

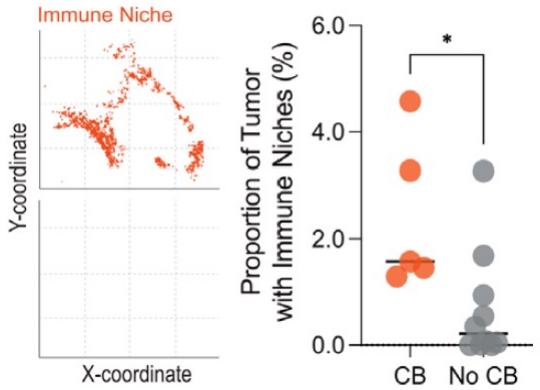


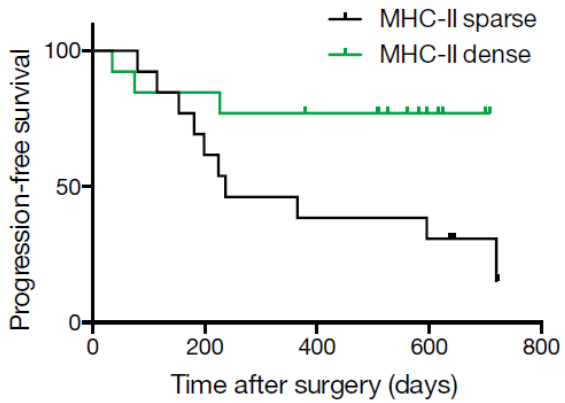




Jansen et al., 2019



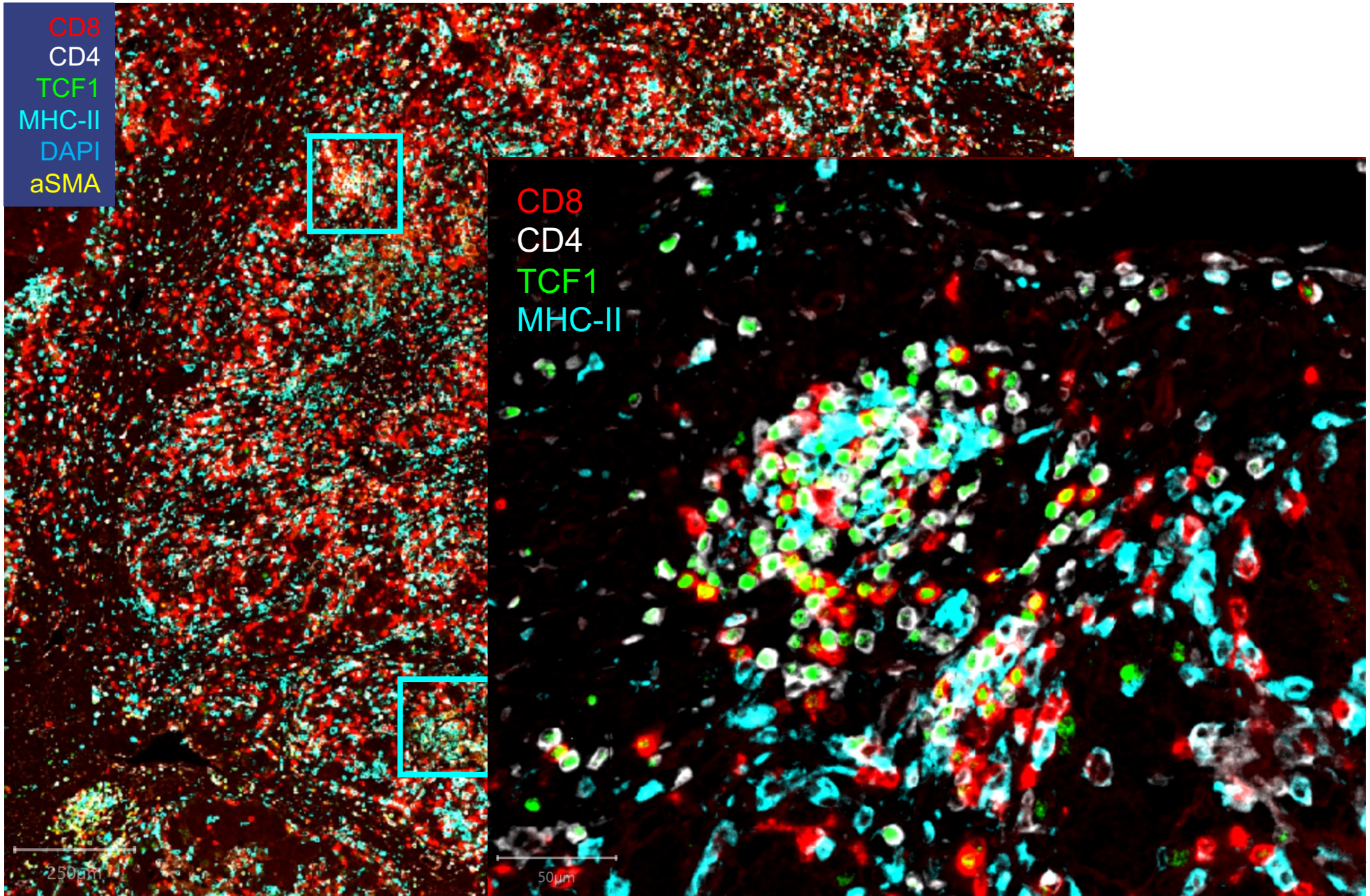




Carlisle et al., 2022

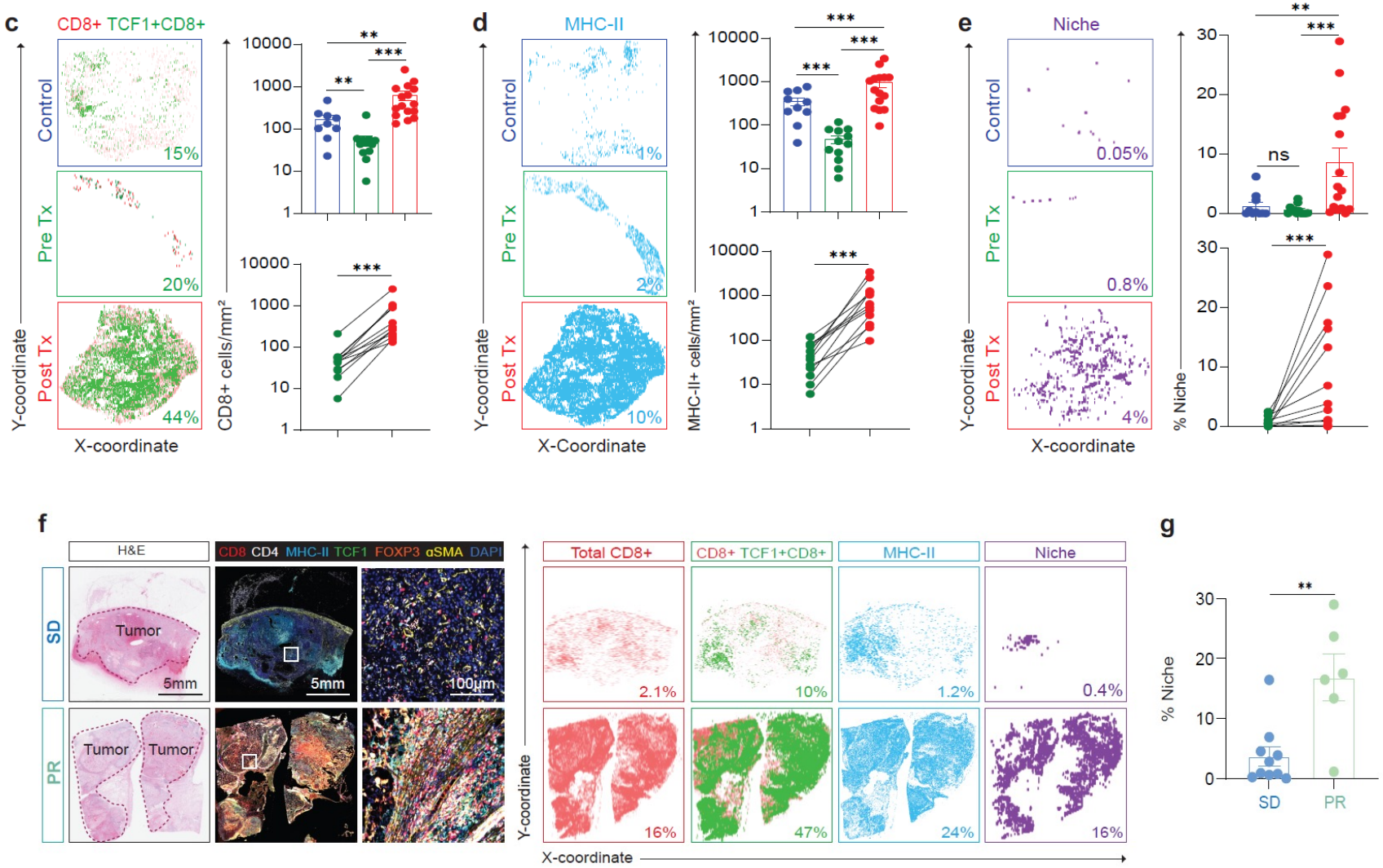



Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

# Cabozantinib regenerates immune niches in ccRCC



# CD8 T cells activation in the tumor after cabozantinib treatment

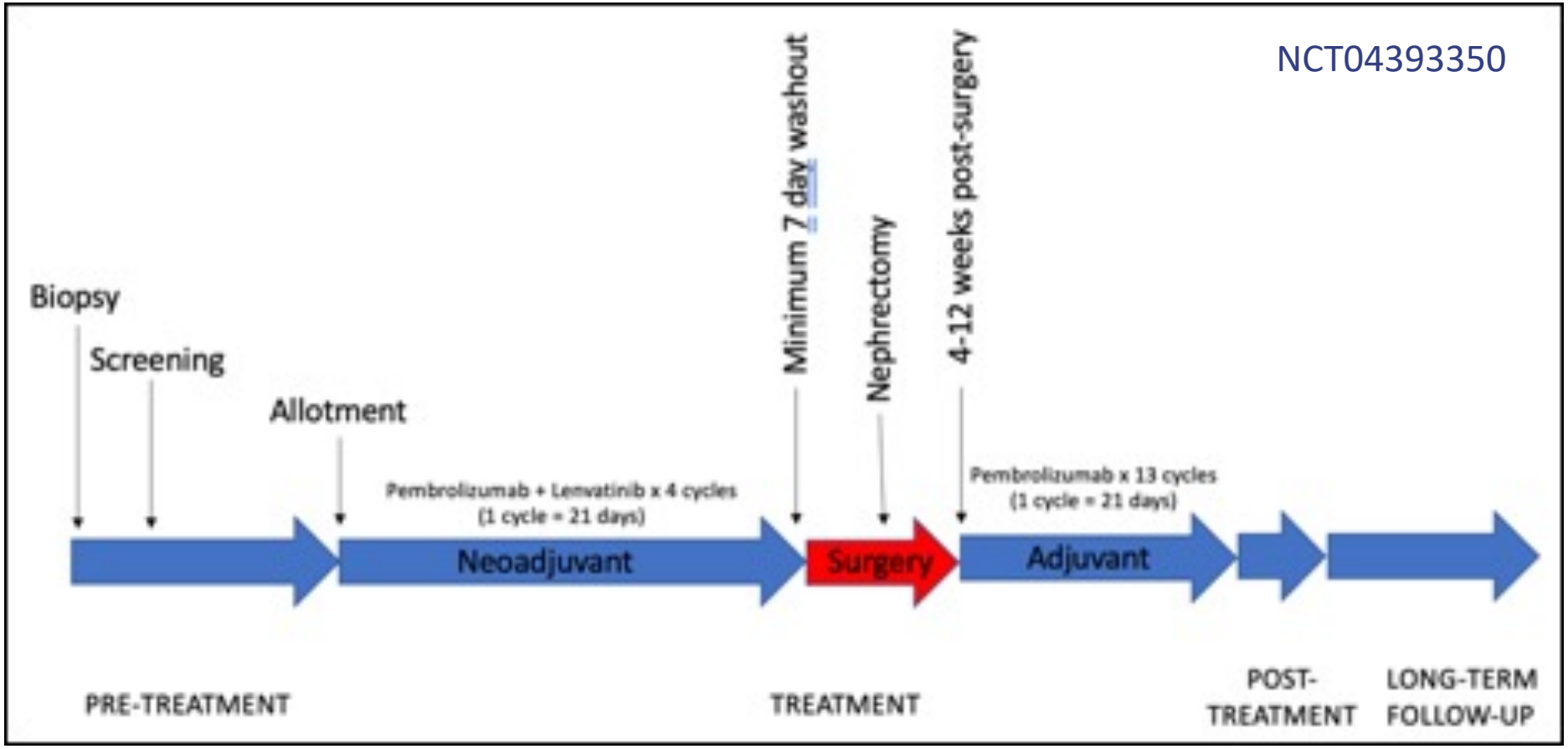



Bilen, Vo,..Kissick, Master et al. Nature Cancer 2025

## Summary and next steps

- Cabozantinib induces a large CD8 T cell response against the tumor, and helps generate immune-niches in the tumor with PD1 responsive TCF1+ CD8 T cells
- Implies a possibility to improve the proportion of patients who will respond to checkpoint immunotherapy
- Ongoing studies examining neo-adjuvant cabozantinib/other TKI + IO.

# Phase 2 Study of Perioperative Lenvatinib with Pembrolizumab in Patients with Locally Advanced Nonmetastatic Clear Cell Renal Cell Carcinoma




Bilen et al. GU ASCO 2025

# Baseline Characteristics

| Variable | N (%) = 18 |
|---|---|
| **Median Age** | 64.5 (range: 28-84) |
| **Gender** | |
| Male | 12 (66.7) |
| Female | 6 (33.3) |
| **Race** | |
| White | 12 (66.7) |
| Black | 4 (22.2) |
| Hispanic/Other | 2 (11.1) |
| **Clinical TNM stage** | |
| T3N0M0 | 17 (94.4) |
| T4N0M0 | 1 (5.56) |
| **Eastern Cooperative Oncology Group Performance Status** | |
| 0 | 7 (38.9) |
| 1 | 11 (61.1) |
| **Median baseline tumor size** | 77.3 [range: 50 – 180.1 mm] |

# Adverse events and dose reduction

| N (%) = 18 | | |
|---|---|---|
| **Treatment – Related AEs** | | |
| **Event** | **Any Grade** | **≥Grade 3** |
| Fatigue | 15 (83.3) | 0 (0) |
| Hypertension | 10 (55.6) | 7 (38.9) |
| Hypothyroidism | 10 (55.6) | 0 (0) |
| Palmar-Plantar Erythrodysesthesia Syndrome | 9 (50.0) | 0 (0) |
| Diarrhea | 8 (44.4) | 0 (0) |
| Anorexia | 7 (38.9) | 0 (0) |
| Mucositis Oral | 7 (38.9) | 0 (0) |
| Nausea | 7 (38.9) | 2 (11.1) |
| Proteinuria | 7 (38.9) | 2 (11.1) |
| **Treatment – Related SAEs** | | |
| Thromboembolic event | 1 (5.6) | |
| CPK Increased (Autoimmune Rhabdomyolysis) | 1 (5.6) | |
| **Lenvatinib Dose Reductions Due to Treatment – Related AEs** | | |
| 14 mg | 9 (50) | |

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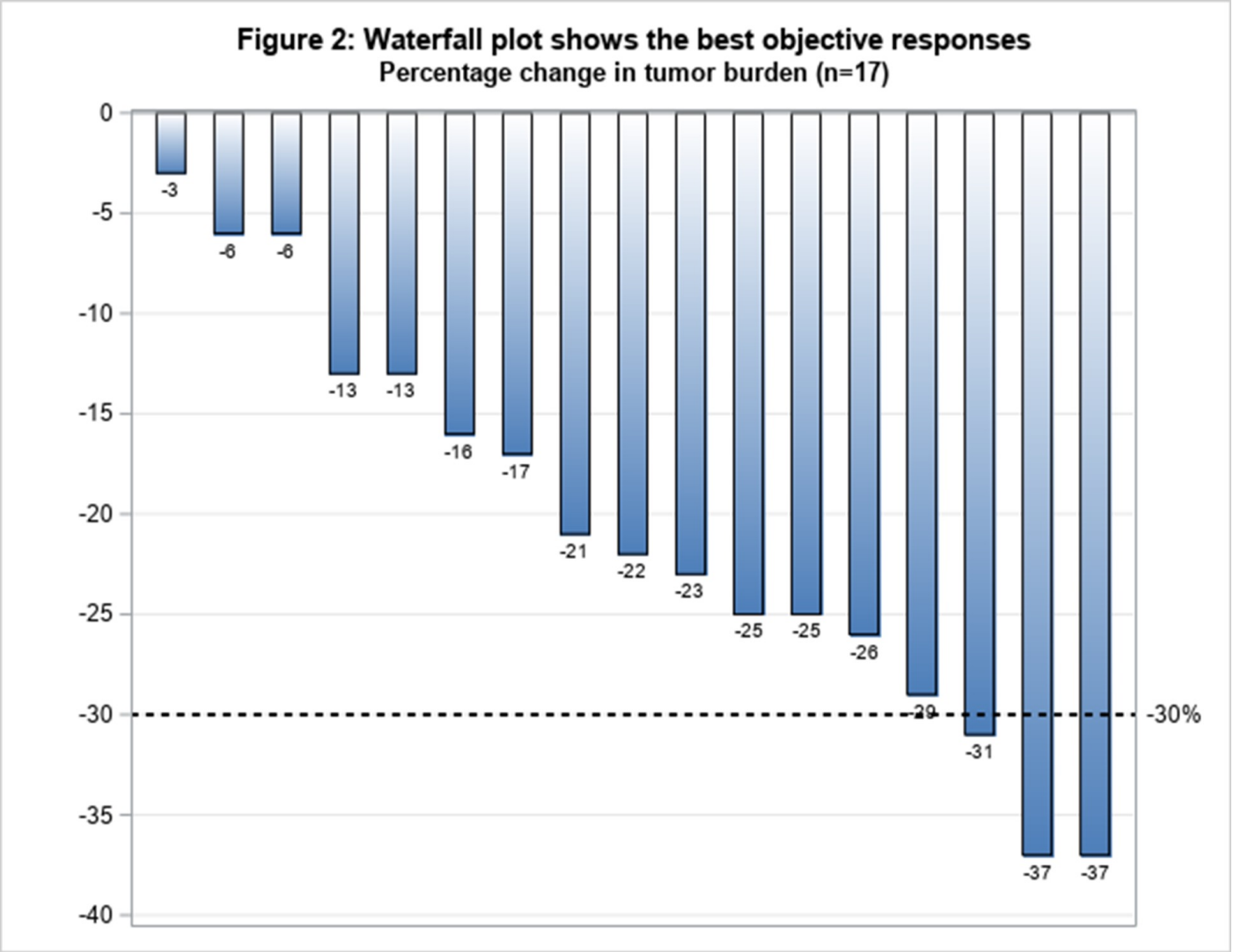
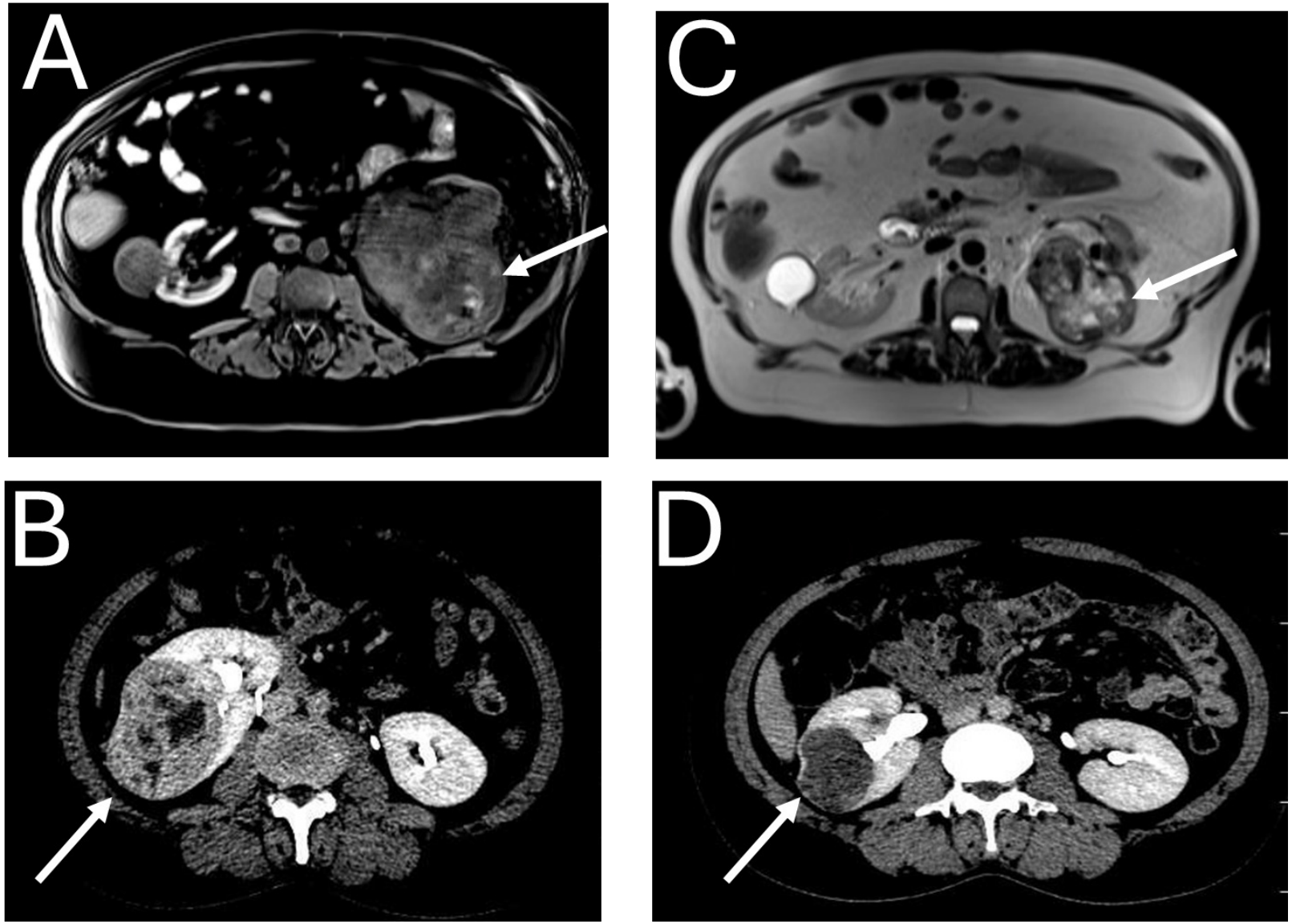
# Efficacy




Bilen et al. GU ASCO 2025

# Efficacy




Bilen et al. GU ASCO 2025

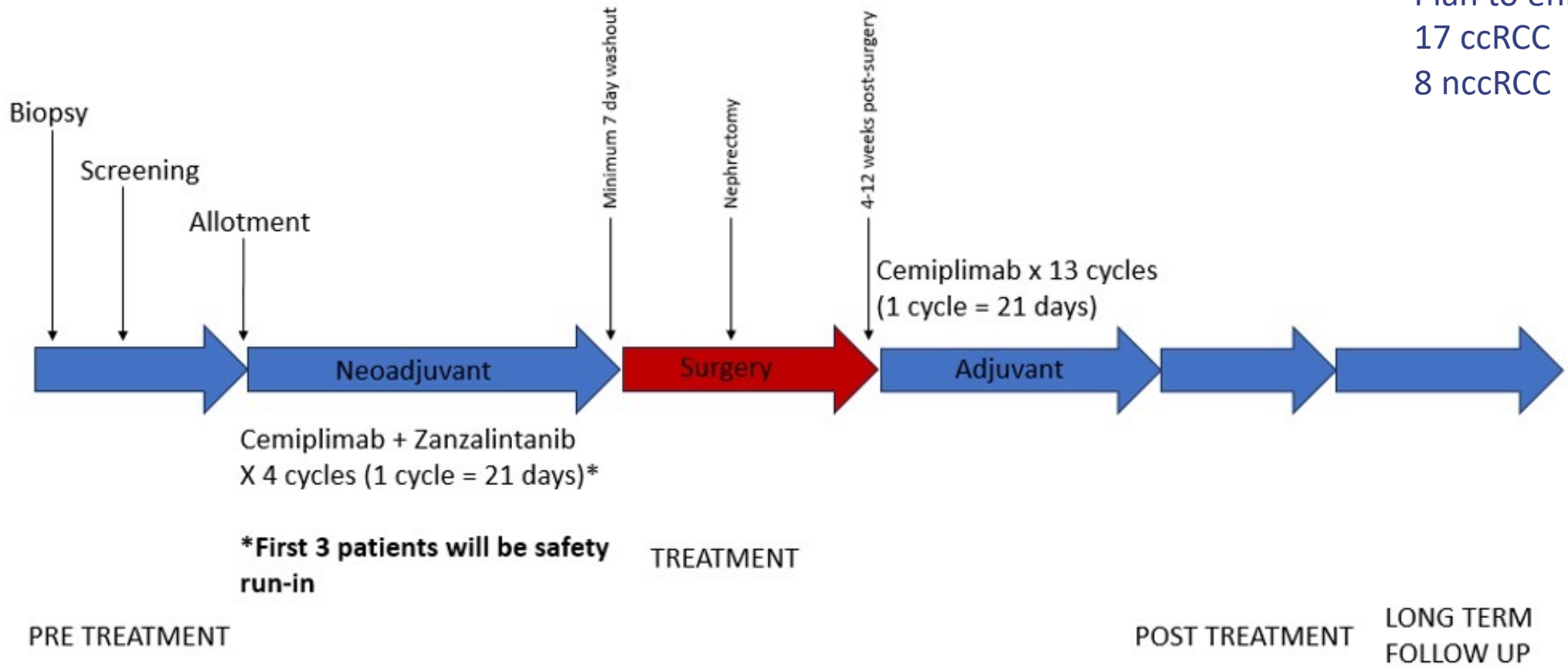
# Pending items

- Long term clinical outcome
  - DFS, OS
- Pathological response rate
- Correlative analysis
  - Tissue and blood based IO markers
  - ctDNA
  - Microbiome samples
  - Body composition and PRO

| NCT Trial # | Phase | Arm | Drug | Dose | Duration | Goal N | Inclusion criteria | | Primary endpoint | Status |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Stage | Histology | | |
| **Immunotherapy or Immunotherapy Combinations** | | | | | | | | | | |
| NCT04393350 | II | single | Lenvatinib and pembrolizumab | Len:18 mg daily<br>Pembro: 200 mg q3w | 12 weeks | 17 | ≥cT3Nx or TanyN+[f] | cc[d] | ORR | Recruiting |
| NCT03680521 | II | Single | Sitravatinib and nivolumab | Sitravitinib: oral capsule daily<br>Nivolumab: 24 mg IV q2w | Sitravatinib: 6-8 weeks[e]<br>Nivolumab: 4-6 weeks | 25 | Locally advanced RCC | cc | ORR and point in treatment course of ORR | Active, not recruiting |
| NCT04385654 | II | Single | Toripalimab and axitinib | Toripalimab: 240 mg IV q3w<br>Axitinib: 5 mg PO BID | 6 weeks | 40 | cT ≥ 2 or cN+ | non-cc | Major pathologic response (MPR); pathologic complete response (pCR); pathologic no response (pNR) | Not yet recruiting |
| NCT04118855 | II | Single | Toripalimab and axitinib | Toripalimab: 240 mg IV q3w<br>Axitinib: 5 mg PO BID | Up to 12 weeks | 30 | T2-3, N0, M0 | cc | ORR | Not yet recruiting |
| NCT04995016 PANDORA | II | Single | Pembrolizumab and axitinib | Pembrolizumab: 200 mg q3w<br>Axitinib: 5 mg PO BID | 12 weeks | 18 | ≥T3Nx or TanyN+[f] | cc[d] | MPR | Not yet recruiting |
| NCT05024318 NAPSTER | II | Randomized | Stereotactic ablative radiotherapy (SABR) (arm 1) vs pembrolizumab and SABR (arm 2) | Arm 1:<br>SABR: 42Gy in 3 fractions<br>Arm 2:<br>Pembrolizumab 200 mg q3w x 3 cycles with SABR administered after cycle 1 | 9 weeks | 26 | T1b-3, N0-1, M0 or low volume M1 planned for nephrectomy | cc[i] | MPR | Not yet recruiting |
| NCT03341845 NeoAvAx | II | Single | Axitinib and avelumab | Axitinib: 5mg BID<br>Avelumab: 10mg/kg q2w | 12 weeks | 40 | "non metastatic, completely resectable primary tumour of int to high risk" | cc | Rate of PR | Recruiting |
| NCT04028245 SPARC-1 | II | Single | Spartalizumab and canakinumab | Spartalizumab: 400 mg q4w<br>Canakinumab: 300 mg q4w | 8 weeks | 14 | ≥ cT2Nx or cTanyN1 | cc[c] | % of patients who proceed to radical nephrectomy[h] | Recruiting |
| NCT04322955 Cyto-KIK | II | Single arm | Preoperative nivolumab and cabozantinib | Nivolumab: 480 mg every 4 weeks<br>Cabozantinib: 40 mg daily | Up to 12 weeks[g] | 45 | Metastatic | cc[d] | CR rate | Recruiting |

# Pending trial (Zanza+cemiplimab)

Plan to enroll:
17 ccRCC
8 nccRCC



# NEOSHIFT

## NEOadjuvant Sandwich Immunotherapy with HIF inhibiTion in RCC

No neoadjuvant = SOC

*Merck and Arcus both posses HIF2 inh and PD1 inh with single agent
HIF2 inh and combo with PD1 MTD either established or ongoing

**Eligibility**

- ccRCC on biopsy
- T2b,T3, T4, N+
- Tumor ≥ 7 cm on imaging
- PS 0-1

Exp. Arm 1

HIF2α for 9 weeks

Exp. Arm 2

PD-1 Q3w x4
+ HIF2α for 9 weeks

**Surgery**

1-4 weeks
post PD-1

**Pembrolizumab**

- 1 year if applicable (per KYN-564 ELIG) on SOC
- 9 months on Exp. arms 1 & 2

# Perioperative treatment in renal cancer

- What is ideal end point?
  - ORR or DFS or OS
- pCR is rare in primary renal tumor, why?
- What is ideal duration for neoadjuvant treatment?
  - 3 months, more or less
- How much AEs can be tolerated?

# Team Effort

**Medical Oncology:**

- Omer Kucuk
- Bradley Carthon
- Bassel Nazha
- Jackie Brown
- Wayne Harris
- Jordan Ciuro
- Shahid Ahmed
- Jake Berchuck
- Ravi Parikh

**Urology**

- **Viraj Master**
- **Haydn Kissick**
- **BaoHan Thi Vo**
- Martin Sanda
- John Petros
- Ken Ogan
- Shreyas Joshi
- Aaron Lay
- Vikram Narayan

**Biostatistics**

- Yuan Liu

**Nuclear Medicine**

- David Schuster
- Saima Muzahir

**Pathology**

- **Adeboye Osunkoya**
- Lara Harik