



KCRS22 Kidney Cancer Research Summit

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

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Conflict of Interest

Advisory board: Exelixis, Bayer, BMS, Eisai, Pfizer, AstraZeneca, Janssen, Calithera Biosciences, Genomic Health, Nektar, EMD Serono, SeaGen, and Sanofi

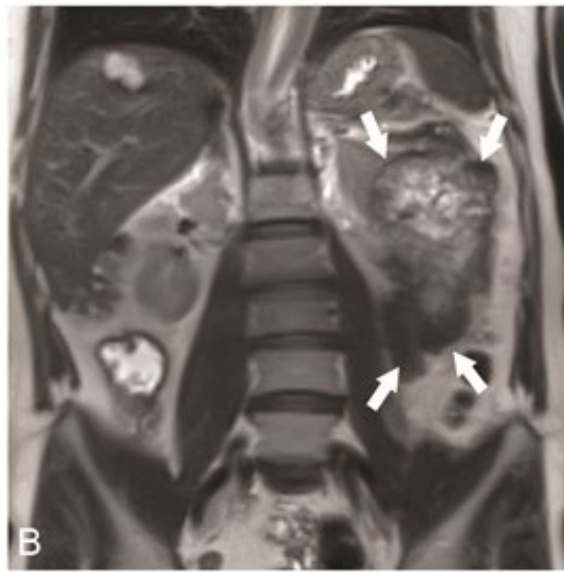
Research: Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, SeaGen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer

Utility of presurgical treatment in renal cancer

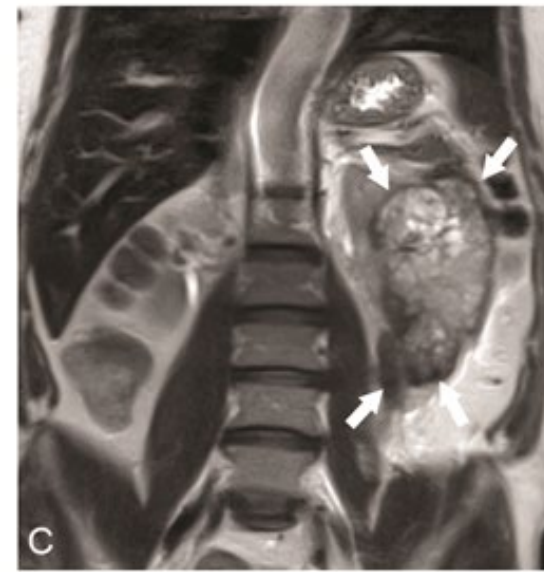
- Localized RCC
 - Facilitate partial nephrectomy
- Locally advanced RCC ($>cT2, \geq T3$)
 - Makes surgery easier, potentially sparing organs
- Depends on treatment, it can cause systemic effect and immune induction
- Provide insight about biology of disease



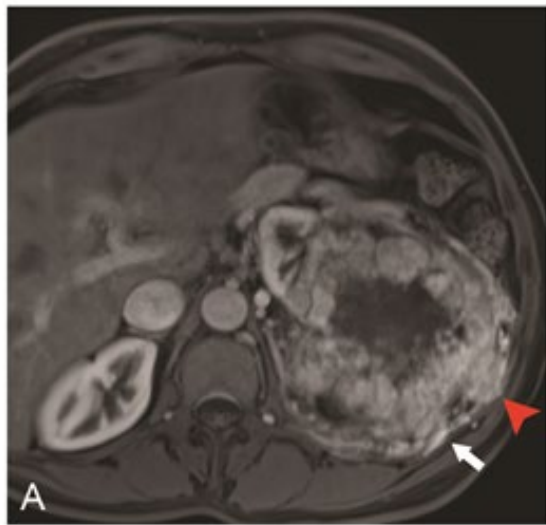
April 2018



June 2018



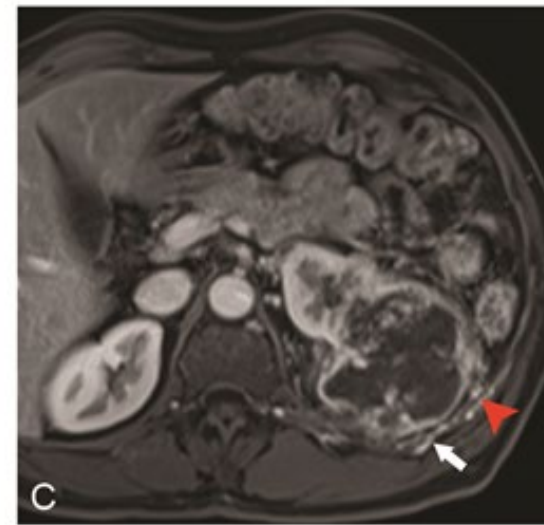
April 2019



April 2018



June 2018



April 2019

Bilen et al. Front Oncol. 2021
2022 Kidney Cancer Research Summit

Background

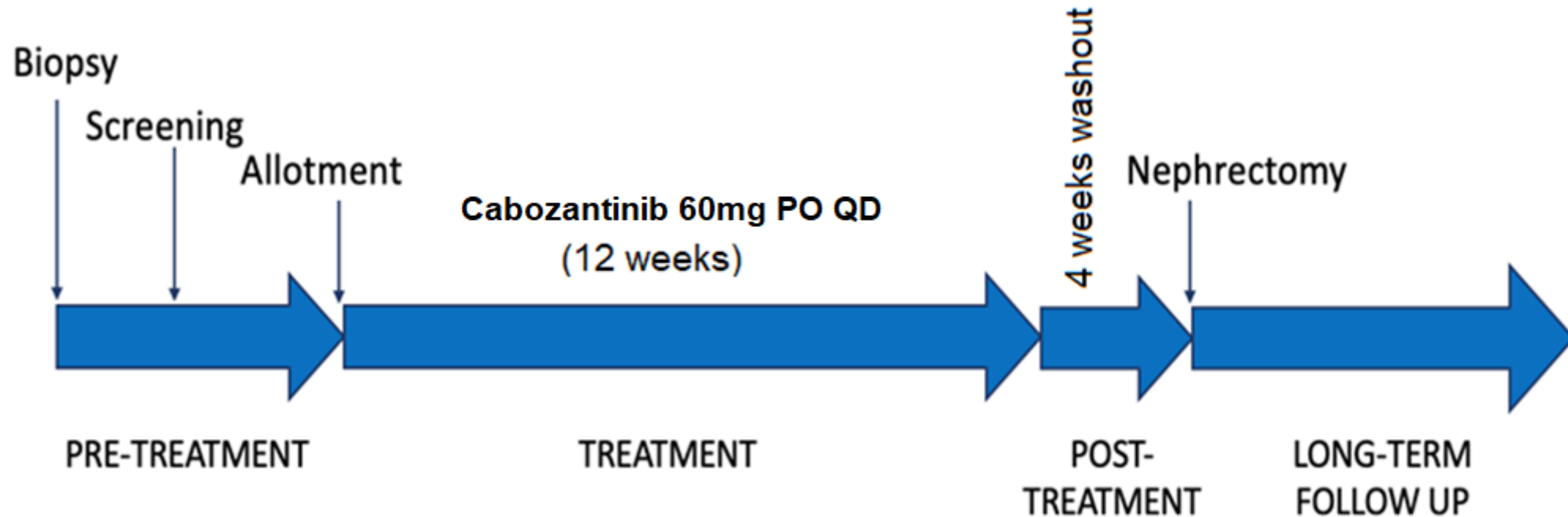
- The multi-targeted tyrosine kinase inhibitor cabozantinib is a standard of care for metastatic renal cell carcinoma as a single agent and in combination.^{1,2,3}
- The increased response rates with cabozantinib, along with the other neoadjuvant TKI data, support an expanded role for cabozantinib in the neoadjuvant setting.
- We present the analysis of a Phase 2 study of neoadjuvant cabozantinib for locally advanced non-metastatic clear cell RCC (NCT04022343).

¹Choueiri et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med . 2015 Nov 5;373(19):1814-23.

²Choueiri et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial

³Choueiri et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med . 2021 Mar 4;384(9):829-841.

Study design



- Patients with biopsy-proven clear cell RCC and clinical stage \geq T3Nx or TanyN+ or deemed unresectable by the surgeon were eligible for this study.

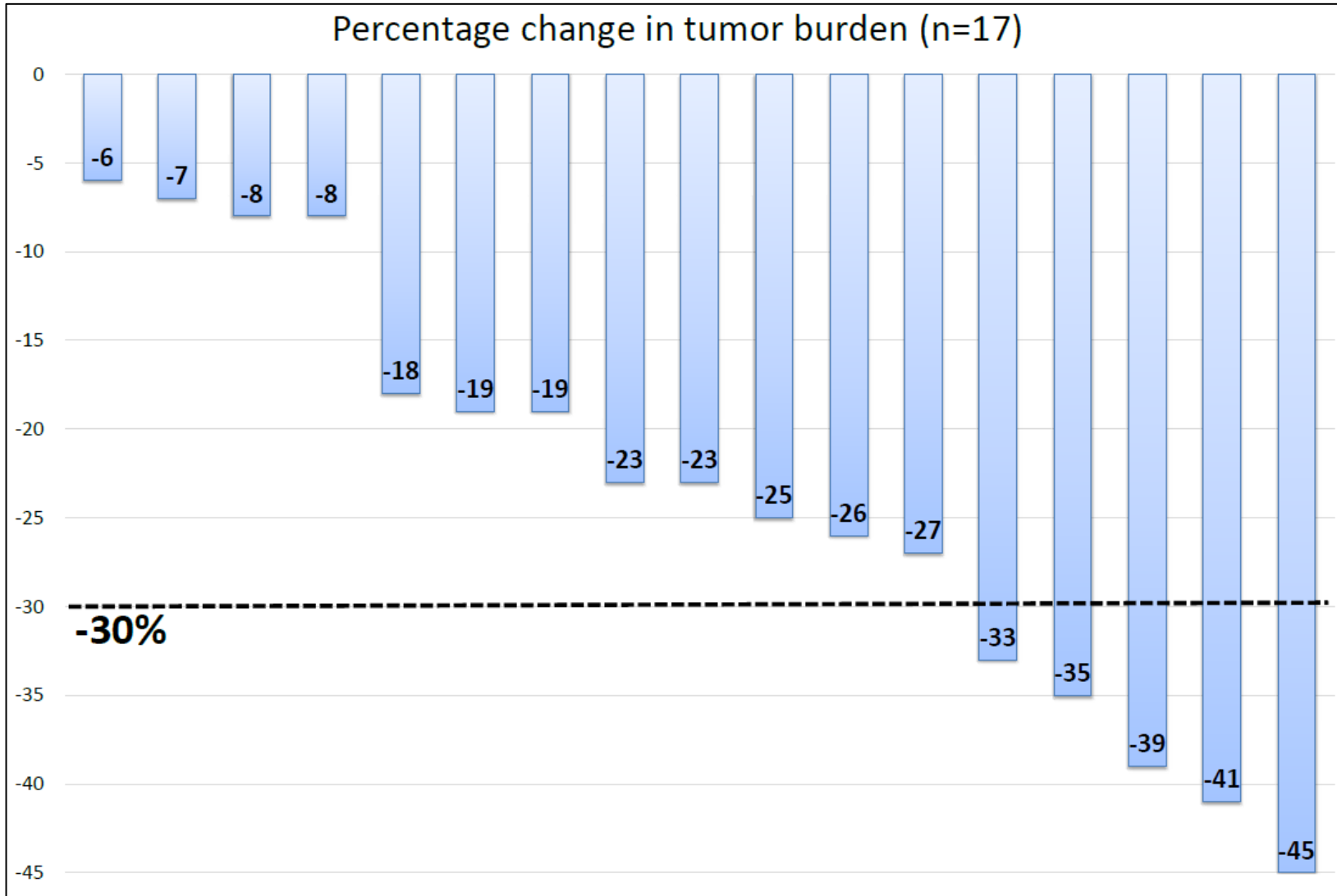
Study Endpoints and Statistical design

- **Primary endpoint:** Objective response rate per RECIST v1.1 at week 12.
- **Design:** The Simon's two-stage design was used to test null hypothesis of ORR = 0.05. At the first stage, if 0 out of 9 patients achieve ORR, then stop the trial, otherwise, additional 8 patients are enrolled in the second stage, and if ≥ 3 ORR out of total 17 patients, then reject null hypothesis. The design yields a type I error rate of 0.05 and power of 80% when the true response rate is 25%.
- **Secondary endpoints:** Safety, tolerability, clinical outcome (DFS, OS), surgical outcome and quality of life.

Baseline Characteristics

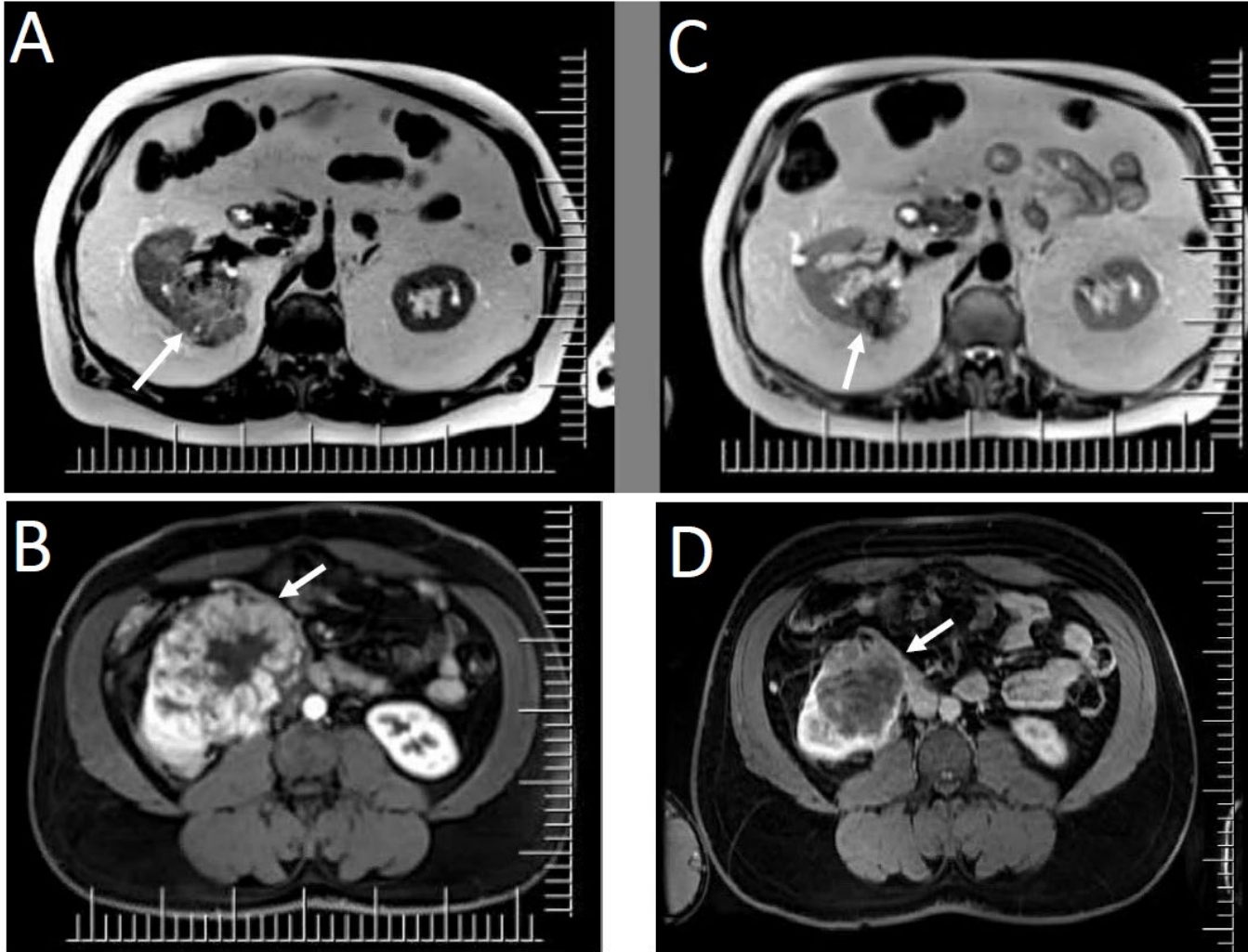
Variable	N (%) = 17
Median Age	58 (range: 42-86)
Gender	
Male	14 (82.4)
Female	3 (17.6)
Race	
White	14 (82.4)
Black	2 (11.8)
Hispanic/Other	1 (5.9)
Clinical TNM stage	
T3N0M0	15 (88.2)
T4N0M0	2 (11.8)
Eastern Cooperative Oncology Group Performance Status	
0	9 (52.9)
1	8 (47.1)
Median baseline tumor size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

Tumor response



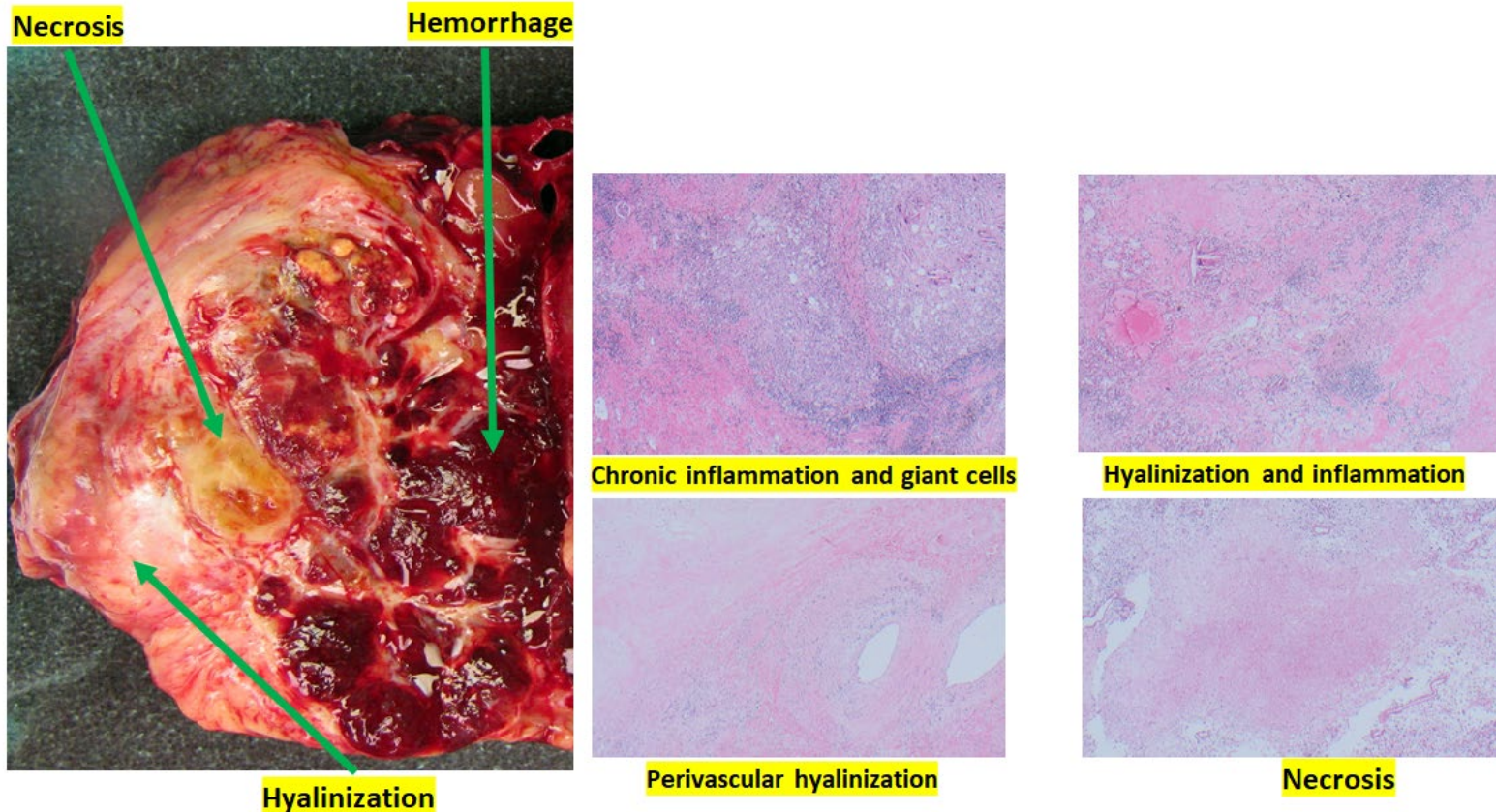
- All patients had tumor reduction after treatment, and no disease progression.
- **5 patients (29.4%)** had partial response [ORR = 0.29, 95% CI = (0.10, 0.56)], and 12 patients had stable disease.
- Median reduction of primary renal tumor size was **23%** (range: 6-45%).

Tumor response



- All patients completed 12 weeks of treatment, and 16 of them underwent surgery as planned without any delay.
- One patient refused to undergo surgery due to personal reasons and received further systemic treatment.
- One patient who was deemed to be unresectable became resectable at the end of treatment.
- Two patients were converted from radical to partial nephrectomy.

Histopathological findings

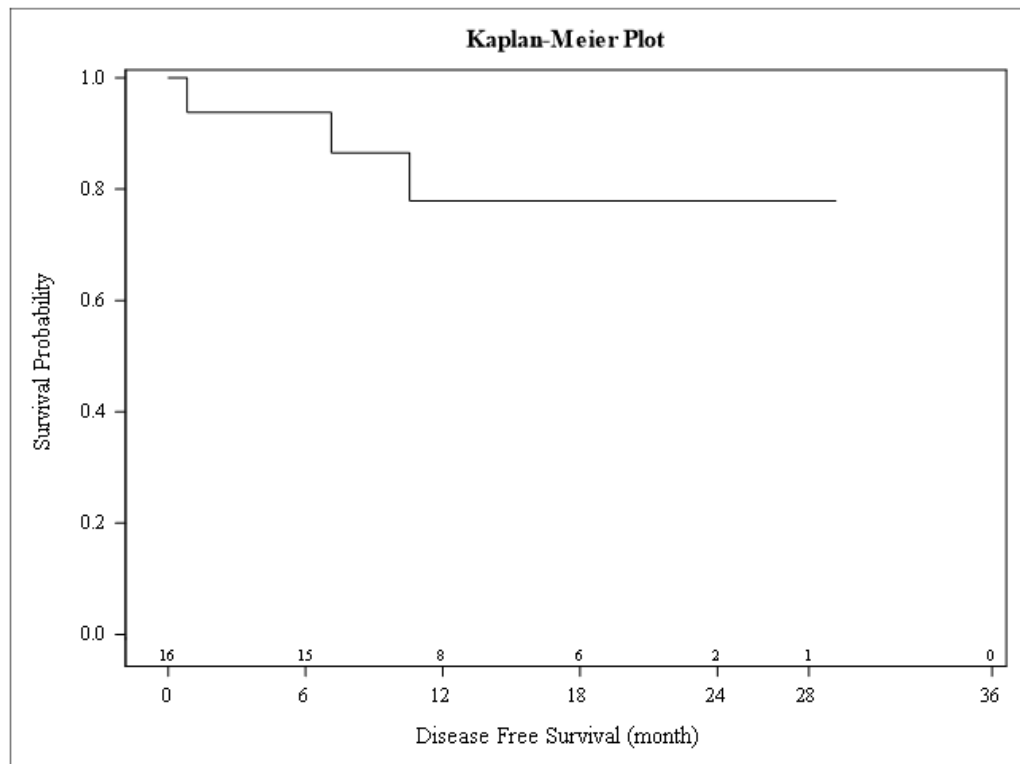


Surgical T stage	N (%)
ypT1a	1 (6.2%)
ypT1b	1 (6.2%)
ypT3a	11 (69%)
ypT3b	1 (6.2%)
ypT3c	1 (6.2%)
ypT4	1 (6.2%)

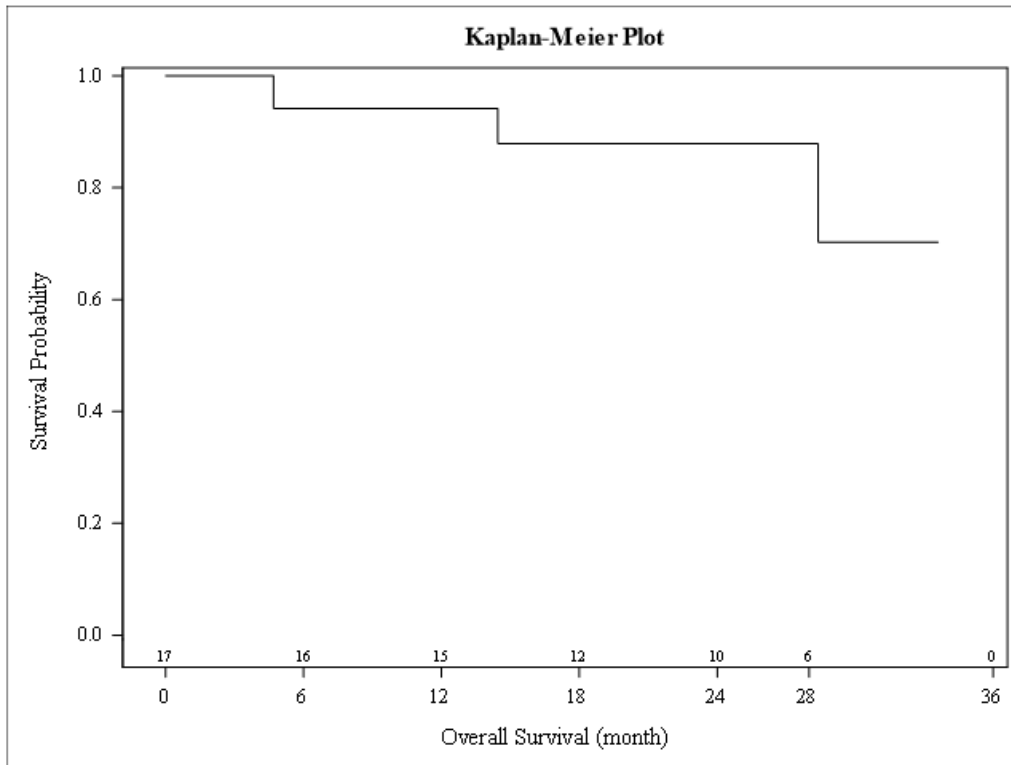
WHO/ISUP grades	N (%)
Grade 2	3 (19%)
Grade 3	7 (44%)
Grade 4	6 (37%)

- Surgical resection margins were negative in all patients
- Sarcomatoid differentiation was present in 3 tumors.

DFS and OS



No. of Subject	Event	Censored	Median Survival (95% CI)	6 Month Survival	12 Month Survival
16	3 (19%)	13 (81%)	NA (10.5, NA)	93.8% (63.2%, 99.1%)	77.9% (45.2%, 92.4%)



No. of Subject	Event	Censored	Median Survival (95% CI)	6 Month Survival	12 Month Survival
17	3 (18%)	14 (82%)	NA (28.4, NA)	94.1% (65.0%, 99.1%)	94.1% (65.0%, 99.1%)

Median follow-up is 25 months.

One patient had disease recurrence after nephrectomy. Three patients have died since start of clinical trial (1 disease progression, 1 COVID-19 complications, and 1 unknown cause).



Summary of Adverse Events

N (%) = 17

Treatment – Related AEs

Event	Any Grade	≥Grade 3
Diarrhea	12 (70.6)	0 (0)
Anorexia	10 (58.8)	1 (5.9)
Fatigue	10 (58.8)	2 (11.8)
Hypertension	10 (58.8)	4 (23.5)
Nausea	9 (52.9)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	9 (52.9)	5 (29.4)
Mouth sores	8 (47.1)	2 (11.8)
Alanine aminotransferase increased	6 (35.3)	0 (0)
Hypomagnesemia	4 (23.5)	0 (0)

Treatment – Related SAEs

Pulmonary embolism	1 (5.9)
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Dose Reductions Due to Treatment – Related AEs

40 mg	5 (29.4)
20 mg	2 (11.8)

- No treatment related grade 4 or 5 AEs related to cabozantinib or surgery occurred.
- We did not experience any immediate intraoperative or postoperative complications.

Conclusions

- Cabozantinib was clinically active and safe in the neoadjuvant setting in patients with locally advanced non-metastatic clear cell RCC.
- Additional data will be reported including additional long term outcomes, correlative studies, quality of life, and frailty/sarcopenia indices.
- Future trials should explore this space.
 - Pem/len→surgery-->pem NCT04393350
 - Unmet need for non-clear cell RCC adj

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