Update on Role of Cytoreductive Nephrectomy in Metastatic Clear Cell Renal Cancer

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Objectives

- Describe why cytoreductive nephrectomy (CN) was established as standard of care in metastatic Renal cell carcinoma (mRCC)
- Explore the trials leading to the paradigm shift away from CN for mRCC
- Describe the role of new check point inhibitors

RCC

- 2-3% of all cancers yearly
- 3rd most common urologic tumor
- Clear cell most common histological subtype (75-80%)
- 30% of patients will present with mRCC
- Up to 40% will progress to mRCC after initial localized treatment
- Systemic therapy +/- CN

Khanna et al. Contemporary management of advanced renal cell carcinoma. Clin Adv Hematol Oncol. 2018 Jun; 16(6):438-446

Risk Stratification

Motzer (MSKCC Criteria)

Time from diagnosis to systemic treatment <1 year Measured ~1 month after stopping anticoagulation	No 0	Yes +1
Hemoglobin < Lower Limit of Normal • Men (Normal): 13.5-17.5 g/dL • Women (Normal): 12.0-15.5 g/dL	No 0	Yes +1
Calcium >10mg/dL (>2.5 mmol/L)	No 0	Yes +1
LDH > 1.5x Upper Limit of Normal Normal: 140 U/L	No 0	Yes +1
Performance status <80% (Karnofsky)	No 0	Yes +1

Interpretation:

Score	Risk	Median survival
0	Good	20 months
1 - 2	Intermediate	10 months
≥3	High	4 months

IMDC Criteria

<1 year from time of diagnosis to systemic therapy	No 0	Yes +1
Karnofsky Performance Status <80%	No 0	Yes +1
Hemoglobin < lower limit of normal Usually ~120 g/L or 12 g/dL	No 0	Yes +1
Corrected calcium > upper limit of normal Usually ~8.5-10.2 mg/dL	No 0	Yes +1
Neutrophils > upper limit of normal Usually ~2.0-7.0×10^9/L	No 0	Yes +1
Platelets > upper limit of normal Usually ~150,000-400,000 cells/µL	No 0	Yes +1

Interpretation:

IMDC Risk Score	Risk group	Median survival
0	Favorable	43.2 months
1-2	Intermediate	22.5 months
≥3	Poor	7.8 months

Heng et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population based study. Lancet Oncol 2013 Feb; 14 (2):141-148

Motzer RJ et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced RCC. J Clin Oncol 2002. Jan 1;20(1):289-96

Cytoreductive nephrectomy

- CN established during an era when mRCC was treated w/ cytokines with low survival rate
  - IFN: 12% response rate; complete responses rare, fever/chills/myalgias
  - IL-2: 9% CR rate, durable; bad side effects.
  - Small series from the 90s reported that pts who required CN due to severe bleeding post RX appeared to do better.

Koneru R. Role of cytokine therapy for RCC in the era of targeted agents. Curr Oncol. 2009 May; 16(Suppl 1_:S40-44

CN in addition to cytokines

- EORTC 30947 (2001 Lancet)
  - 83 patients w/ good performance status randomized to CN+IFN vs IFN alone
  - OS 17 mos CN+IFN vs 7 mos IFN
  - Time to progression 5 mos CN+IFN vs 3 mos IFN
  - 5 CR with CN+IFN VS 1 with IFN

Mickisch GH, et al. "Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial". *The Lancet*. 2001. 358(9286):966-970.

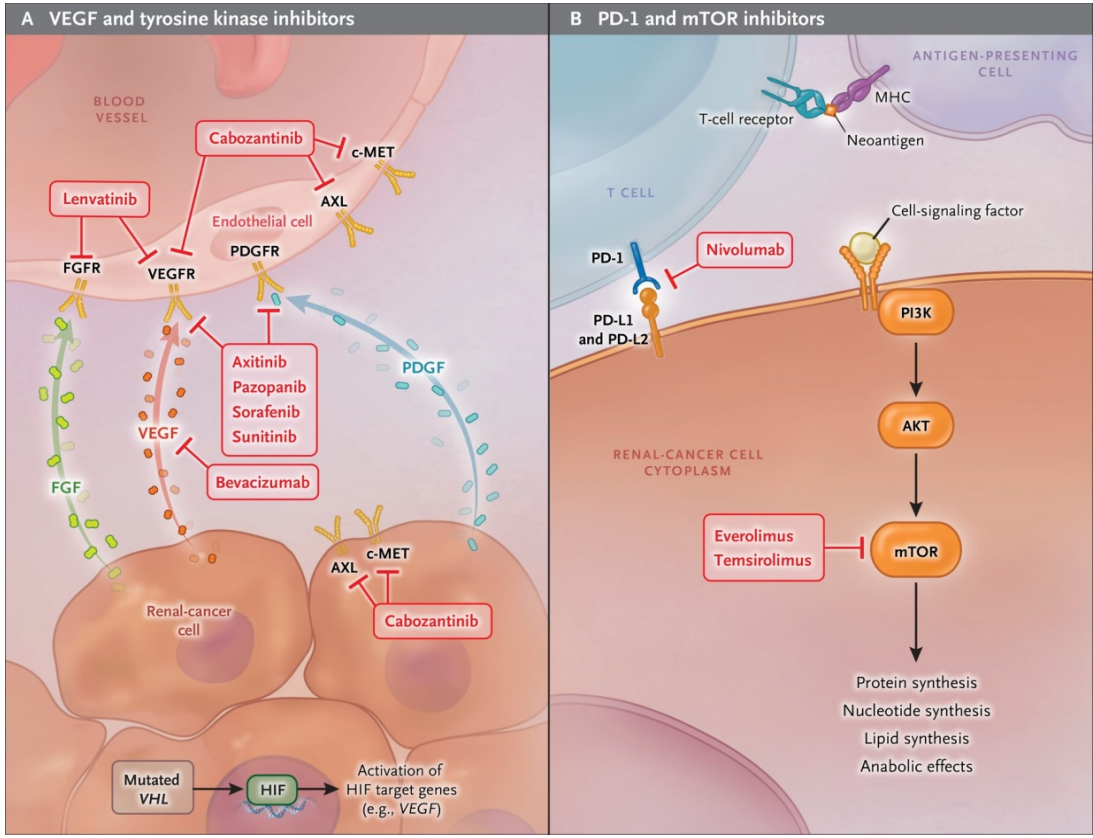
CN in addition to cytokines

- SWOG 8949 (2001 NE Journal of Medicine)
  - 246 patients w/ mRCC and ECOG 0-1 randomized to CN+IFN vs IFN alone
  - Median FU 1y
  - OS 11.1 mos in CN+IFN group vs 8.1 mos
  - 1y survival 49.7% CN+IFN vs 36.8% IFN
- Combined analysis
  - 331 patients
  - Survival benefit 13.6 mos vs 7.8 mos
- Standard of care recommended by NCCN

Flanigan RC, et al. "Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer". The New England Journal of Medicine. 2001. 345(23):1655-9

Era of Targeted Therapy

- Background
  - Discovery - inactivation of the VHL tumor supressor gene led to increased HIF-1α and then increased VEGF and PDGF which promote tumor angiogenesis. These pathways became backbone for modern targeted therapies .
  - FDA approved 2005
  - 10 TKI/mTORi on market

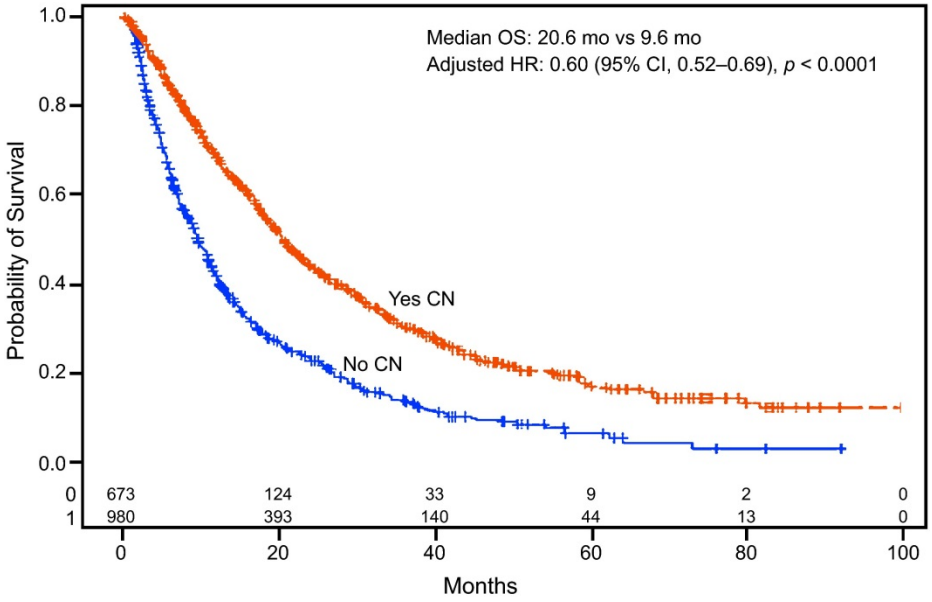


Trials

- Sunitinib
  - Motzer et al. 2007 (N Engl J Med)
    - Phase III RTC demonstrating superiority over IFN
    - (PFS 11mos vs 5mos; OS 26.4mos vs 21.8mos)
    - Pivotal trial→ resulted in Sunitinib being first line over cytokines for good/intermediate risk disease

CN w/ targeted therapy?

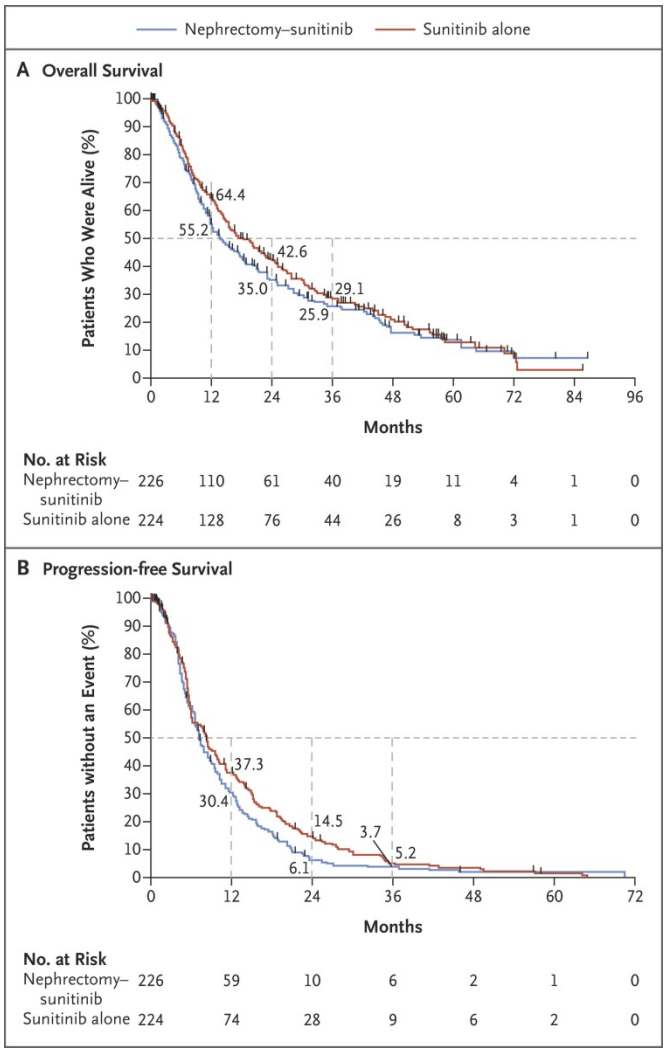
- Heng et al. 2014
  - Retrospective review of pts with synchronous mRCC
  - 1658 patients all w/ Suntinib exposure
    - 982 pts w/ CN- 9% favorable, 63% intermediate (IMDC criteria)
      - OS benefit (20.6 vs 9.6 mos) and longer PFS (7.5 vs 4.5 mos)
      - Too small numbers to compare between good risk but OS suvival advantage seen with CN in intermediate risk



CN w/ targeted therapy?

CARMENA (2018 NE Journal of Medicine)

- Phase 111 RTC
- 450 patients intermediate/poor risk mRCC randomized to CN + sunitinib vs suntinib alone
- Similar OS between groups
  - Median OS 18.4 mos vs 13.9 mos
- No difference in progression free survival

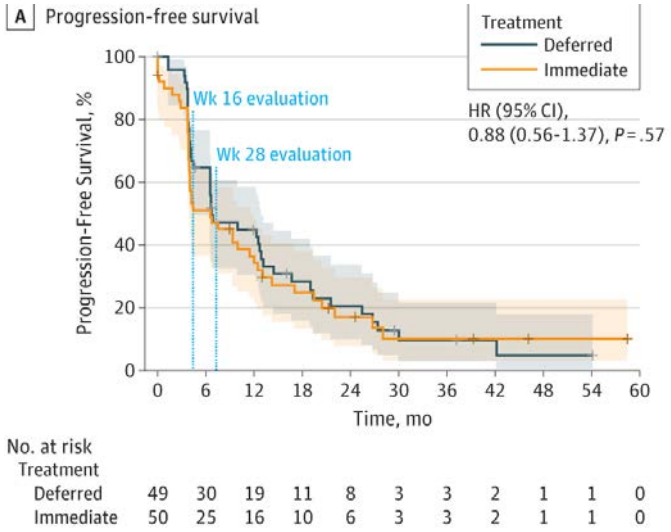


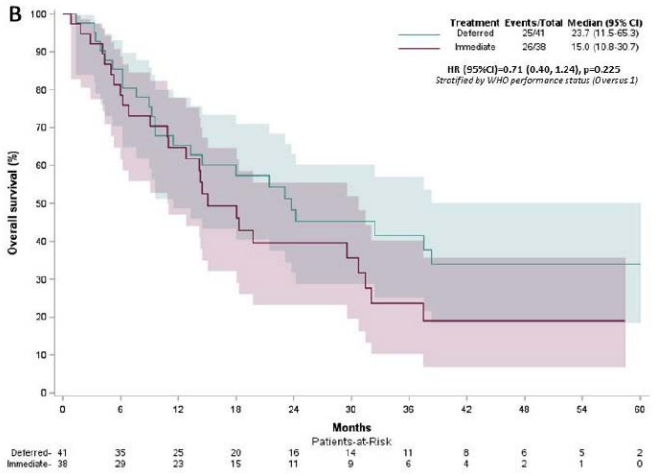
CARMINA had Problems !

- Closed before original endpoints at the second interim analysis based on the results observed after IMDC report and slow accrual. Trial was enriched with poor risk pts who are not known to benefit from CN (inclusion criteria required a PS of 0-1 and eligibility for both CN and ST . It is unknown whether the study population was representative of pts believed to benefit most from CN given that CARMINA focused on pts requiring up front ST and did not enroll pts eligible for up -front surveillance or a delayed ST strategy.)
- Significant crossover also occurred in the two arms - 17% of pts randomized to Sunitinib-alone underwent subsequent CN, and 7% of pts in the upfront CN arm did not undergo CN. All pts were at least intermediate risk.

CN w/ targeted therapy?

- SURTIME (JAMA 2018)
  - Phase 3 RTC
  - 99 patients randomized to **immediate CN + suntinib vs suntinib + delayed CN**
    - 88% MSKCC intermediate risk disease
    - **14 pts in delayed arm had disease progression before CN**
    - 80% vs 98% received suntinib
    - Similar progression free survival rates (42% vs 43%)
    - Median overall survival 15 mos vs 23 mos (p=0.23)
  - Authors argue that delaying exposure to sunitinib may be risk





- **CARMENA and SURTIME** - tempered enthusiasm for the initial treatment of de novo mRCC with CN, (which was generated from retrospective data and pre-TT era randomized trials). **ST - the priority for management of mRCC in the TT era and beyond** - 13-30% of pts do not receive ST after CN due to rapid progression or complications.
- **CN should not be upfront management for pts with poor performance status, poor IMDC/MSKCC risk pts, other poor prognostic features or intermediate IMDC/MSKCC who require ST.**
- **CN still has a role in mRCC pts with** :

limited mets ameniable to surveillance or metastasectomy, pts requiring palliation and potentially in pts with favorable response or stable disease after initial ST.

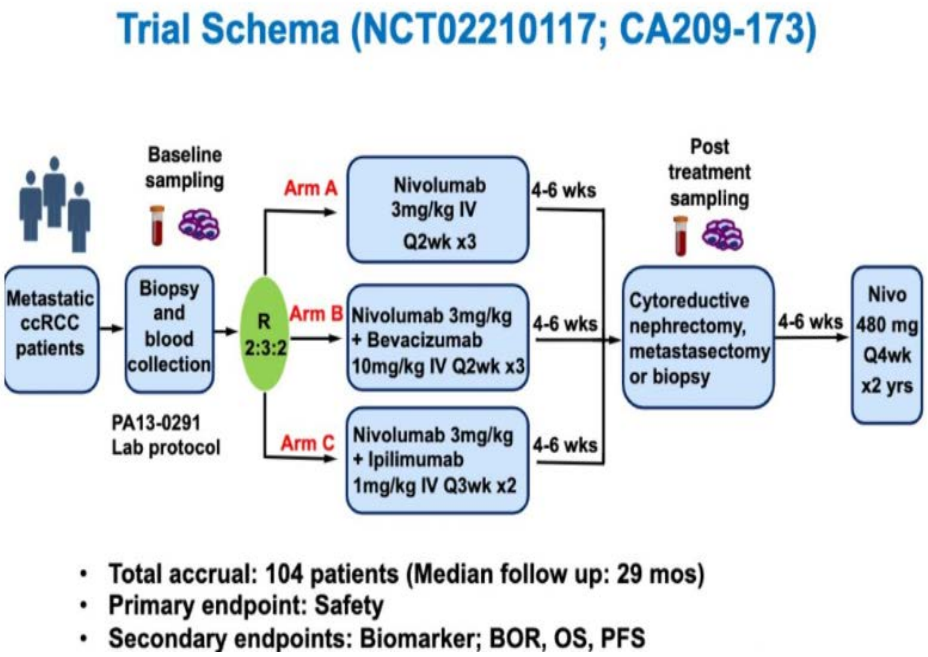
Check point inhibitors

- Some RCC tumors- inherently resistant to TKI's, most acquire resistance over time.
- **Anti-PD1 or PD-L1, anti-CTLA-4 new kids on the block**
- **Checkmate 025** – phase 111 study (randomized 821 pts –previously Rxed by 1 or 2 lines of antiangiogenic agents to **nivolumab 3mg/kg iv 2 weekly vs everolimus 10 mg daily)**
    - **Improved OS survival (25mos vs 19.6 mos), less toxicity and better quality of life**
- Approved currently for poor risk and TKI refractory disease
- Studies ongoing on combination immunotherapy but results promising

Atkins et al. Immune checkpoint inhibitors in advanced renal cell carcinoma: experience to date and future directions. Annals of Oncology, July 2017; 28(7):1484-94

Checkpoint Inhibitors + CN?

- NCT02210117 (MD Anderson)
  - 100 patients w/o prior immune checkpoint therapy or TKI therapy randomized to **nivo, nivo+bev or nivo+ipi followed by surgery (CN, metastectomy) followed by nivo x2y post op**
    - Patient's not randomized to surgery



Gao J, Karam JA, Tannir NM, et al. A pilot randomized study evaluating nivolumab (nivo) or nivo+ bevacizumab (bev) or nivo+ ipilimumab (ipi) in patients with metastatic renal cell carcinoma (MRCC) eligible for cytoreductive nephrectomy (CN), metastasectomy (MS) or post-treatment biopsy (Bx). American Society of Clinical Oncology; 2018

PRELIMINARY RESULTS

Response to drug only:

50% nivo, 48% nivo+bev, 39% nivo+ipi

Response to drugs/surgery:

77% nivo, 93% nivo+bev, 57% nivo-ipi

Characteristics	Nivolumab (N=29)	Nivolumab + Bevacizumab (N=45)	Nivolumab + Ipilimumab (N=30)
Age			
Mean	57	62	61
Range	40-74	38-84	46-78
sex - no. (%)			
Male	22 (76)	32 (71)	28 (93)
Female	7 (24)	13 (29)	2 (7)
KPS - no. (%)			
100	15 (52)	20 (44)	20 (67)
90	0 (0)	1 (2)	
80	14 (48)	22 (49)	10 (33)
60	0	2 (4)	0
Number of Previous Regimens no. (%)			
0	27 (93)	38 (84)	28 (93)
1	2 (7)	5 (11)	1 (7)
>2	0	2 (4)	0
IMDC prognostic risk no. (%)			
Favorable	1 (3)	3 (7)	3 (10)
Intermediate	24 (83)	30 (67)	21 (70)
Poor	4 (14)	12 (27)	6 (20)

Clinical Response	Nivo N=29	Nivo + Bev N=45	Nivo + Ipi N=30
BOR (95% CI)	**59%** (41, 75%)	**44%** (31, 59%)	**43%** (27, 61%)
CR	2 (6.9%)	1 (2.2%)	1 (3.3%)
PR	15 (51.7%)	19 (42.2%)	12 (40.0%)
SD	3 (10.2%)	7 (15.6%)	2 (6.7%)
PD	8 (27.6%)	12 (26.7%)	12 (40.0%)
Withdraw	1 (3.5%)	6 (13.3%)	3 (10%)

- Baseline demographics- most Pts had intermediate or high risk disease

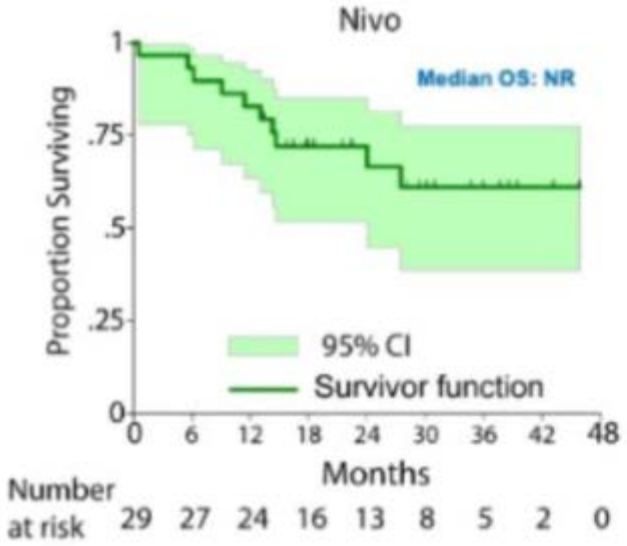
- Overall survival (OS) at one year was 86% for nivo, 73% for nivo/bev, and 83% for ipi/nivo

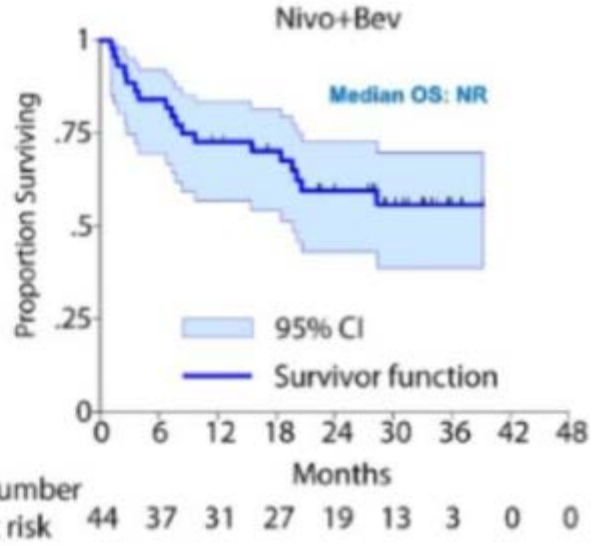
For patients who received cytoreductive surgery, the overall survival at 1 year was:
100% - nivo, 94% - nivo/bev and 92% - ipi/nivo.

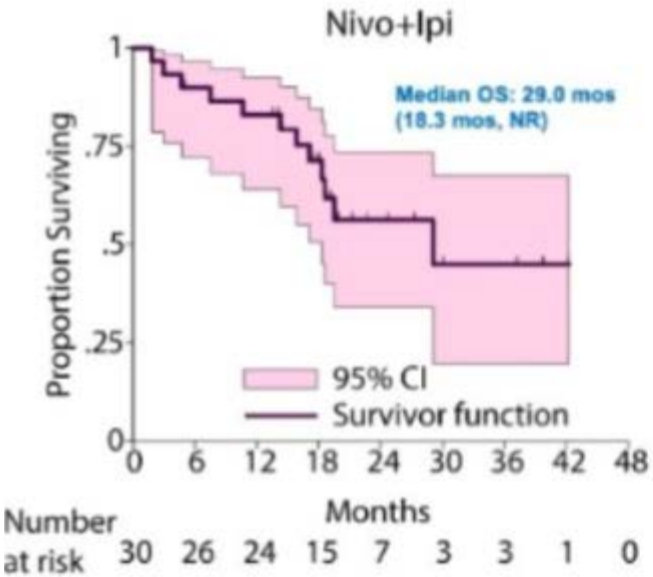
Median OS has not yet been reached after a follow up of 24.6 months. Two year OS data is shown below.

Most pts had intermediate or high risk disease.

Prior data regarding cytoreductive nephrectomy has all been conducted in the TKI or pre-TKI era. However, this **study provides evidence demonstrating that cytoreductive nephrectomy after IO therapy is safe, with 90-100% survival at 1 year**.







Arm	2-Year % Survival	Standard Error
Nivo	72%	8%
Nivo/Bev	60%	8%
Nivo/Ipi	56%	10%

Systematic

Review of the Role of CN in the Targeted Therapy Era and Beyond: An individualised Approach to Metastatic Renal Cell Carcinoma.

Bhindi er al. European Urology 75(2019) 111-128

- **Objective: To assess if CN versus no CN is associated with improved survival in pts treated in the TT era and beyond,** characterize the morbidity of CN, identify prognostic and predictive factors and evaluate outcomes following treatment sequencing.
- **Methods:** Medline, EMBASE and Cochrane databases were searched for Clinical trials, cohort studies and case control studies evaluating pts with MRCC who did or did not undergo CN. **Primary outcome – OS.**
- 63 reports on 56 studies: Risk of bias- moderate or serious -50 studies.
- CN-associated with improved OS among mRCC pts in 10 non randomized studies while I randomized trial (CARMENA) found OS with Sunitinib alone was noninferior to CN followed by Sunitinib.

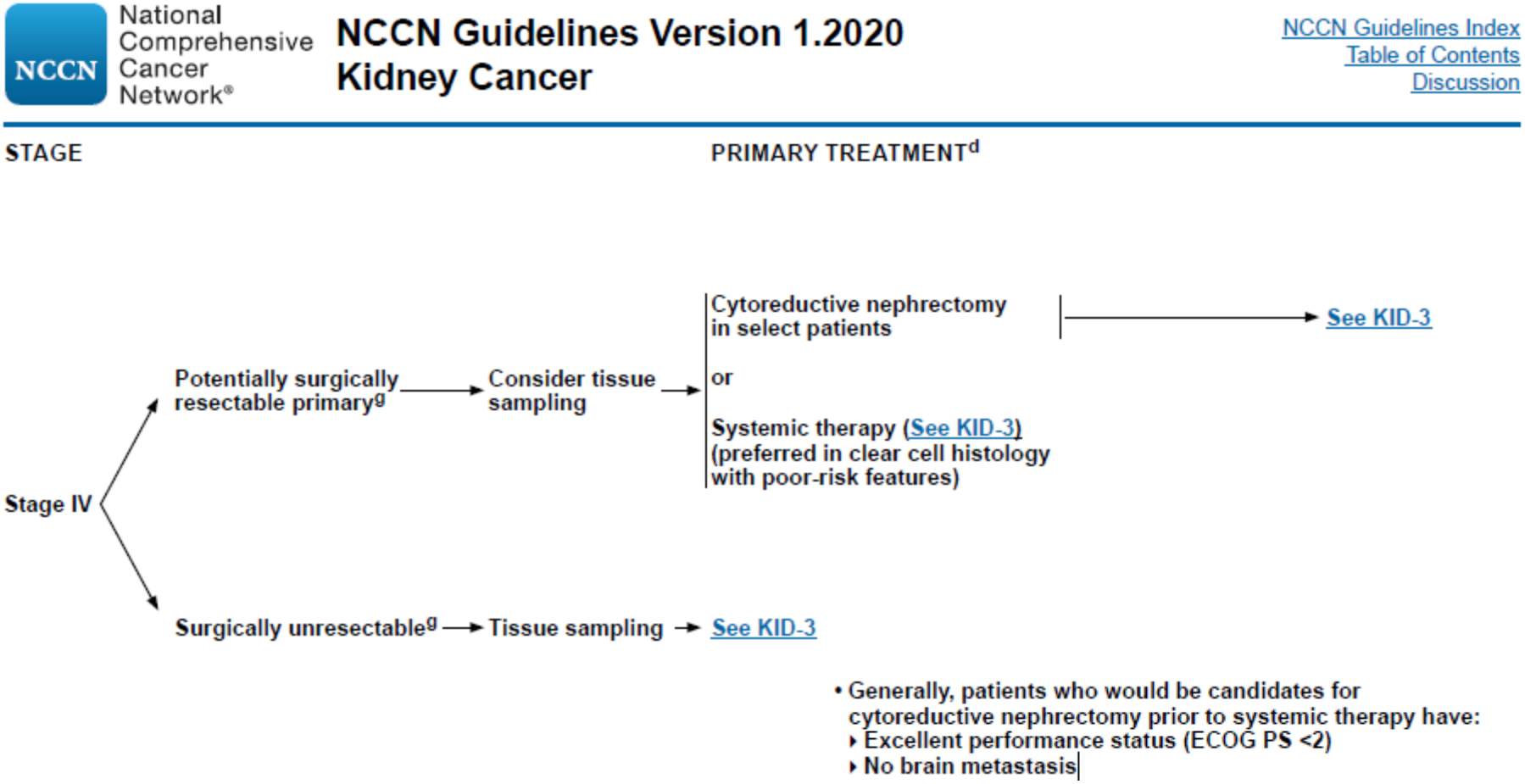
- **Risk of perioperative mortality and Clavian >3 complication** – 0-10.4 % and 3-29.4% respectively
- **No differences** between upfront or CN after presurgical Systemic Therapy.
- 12.9-30.4% did not receive Systemic therapy after CN.
- **Factors most predictive of decreased survival** – progression on presurgical Systemic therapy, high c-reactive protein, high neutrophil-lymphocyte ratio, poor IMDC/MSKCC risk classification, sarcomatoid dedifferentiation and poor performance status.
- **Good performance status and good/intermediate risk classification -**were consistently predictive of OS benefit with CN.
- Surtime-a RCT investigating the sequence of CN and ST showed an OS trend with CN after a period of ST in pts without progression vs upfront CN. **(Study underpowered and therefore findings exploratory.)**

- # Conclusions:
- In the contemporary era, receiving ST is the priority in mRCC.
- Nephrectomy remains an option in pts with limited burden of metastases, who are well selected based on established prognostic and predictive factors and Patients with a favorable response after initial systemic therapy.

Overall conclusions

- Immediate CN does not result in additional benefit in patients with intermediate/poor risk mRCC
  - May even be detrimental by limiting exposure to targeted therapies
- Delayed CN may be of some benefit to those patients who have near-complete response rates or non-progressing disease
- CN+systemic therapy w/ good risk disease still confusing

NCCN Guidelines



PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

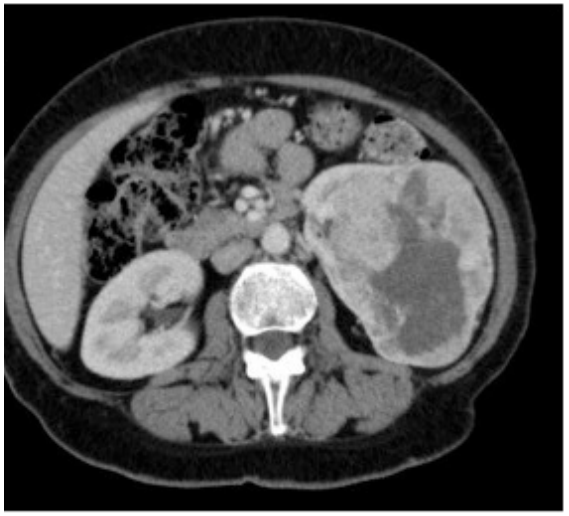
Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

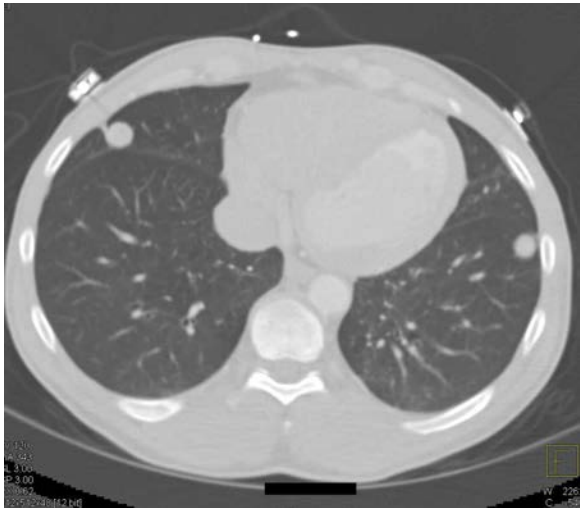
[a] See Risk Models to Direct Treatment (IMDC criteria) (KID-D).
[b] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[c] Patients with excellent performance status and normal organ function.
[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[e] Biosimilar options include: bevacizumab-awwb.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Case 1

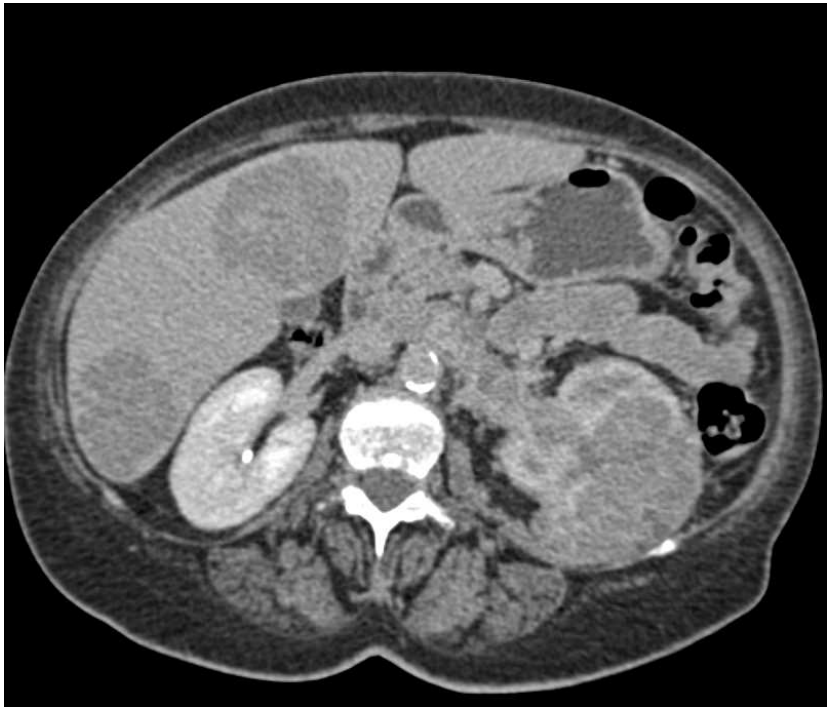
- 62yM w/ PMH of HTN, HLD who presents with several month history of hematuria
  - Labs: Hgb 7.2; all other labs unremarkable
  - Exam: unremarkable, thin
  - Imaging- CTAP w/ large left renal mass
    - Staging imaging revealing pulmonary mets
  - Bx of node confirms ccRCC
  - ECOG 0





Case 2

- 62yM w/ PMH of DM2, CAD s/p MI presenting with 50lb weight loss, fatigue
  - Labs: Hgb 8, Ca 11.5
  - Exam: unremarkable, thin
  - Imaging: CTAP w/ large left right renal mass, 2 liver mets
    - No pulm mets on staging imaging
  - Bx confirms ccRCC
  - ECOG 2



Back to the cases

- Case 1- good/intermediate risk disease
  - CN
  - Suntinib
  - Some sort of combination?

- Case 2- poor risk disease
  - Everolimus
  - Checkpoint inhibitor
  - No evidence for early CN
  - Emerging evidence for IO (immuno oncology) +CN

Questions?