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Cytoreductive nephrectomy: is it worth doing it?

Role of Nephrectomy in mRCC

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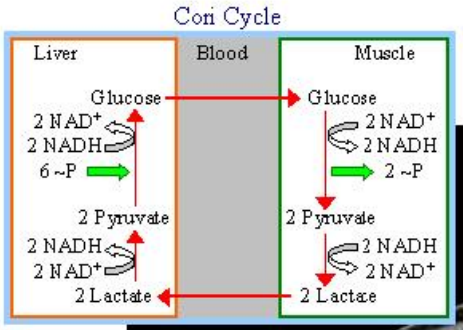
- Curative (Nephrectomy + metastasectomy)

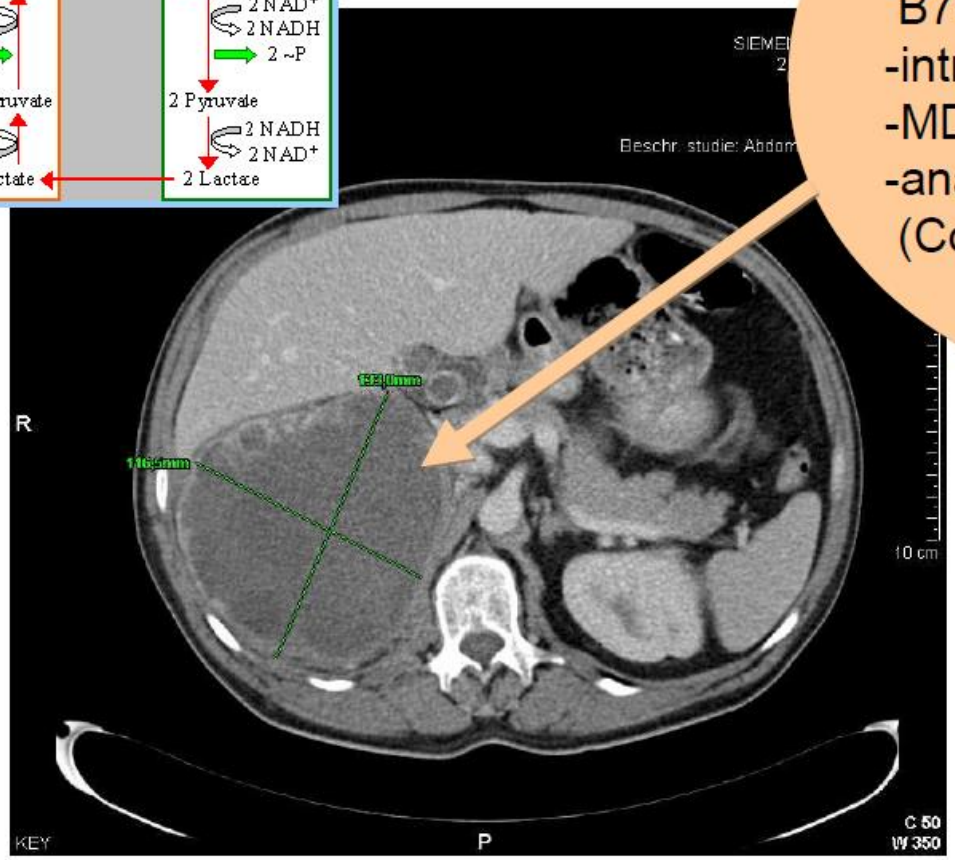
- Palliative (To improve symptoms)
  - pain related to the kidney mass
  - intractable hematuria
  - paraneoplastic syndrome

- Cytoreductive (To resect primary tumor in the prior to the initiation of systemic therapy for unresectable metastases)

Why should there be a survival benefit by removal of the primary tumor ?

The influence of microenvironment



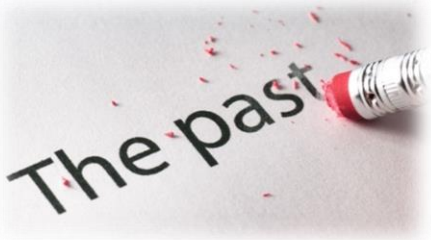


-VEGF, PDGF, FGF, TGF-β
-Inhibitory molecules CTLA-4, B7-H1 (PD-L1),B7-H3, B7-H4
-intratumoral regulatory T-cells
-MDSC, STAT 3 and 5 crosstalk
-anaerobic metabolism of hypoxia (Cori-cycle) and cachexia

Gajewski et al., Immunol Rev 213:131-145, 2006
Thompson et al., Cancer Res 66:3381-85, 2006
Krambeck et al., PNAS 103:10391-96, 2006
Finke et al., Clin Canc Res 14:6674-82, 2008
Ko et al., Cancer Res 70:3526-36, 2010
Griffioen et al., Thromb Haemost 101:1025-31, 2009
Lindenberg et al.,
Dosquet et al., Cli
Jacobsen et al., J

Thomas Powles
Barts Cancer Institute
St Bartholomew's Hospital
London

Does **CN extend survival** in the average patient in the targeted therapy era ?



In a metanalysis of two randomized studies SWOG-8949 EORTC-30947, comparing nephrectomy combined with immunotherapy versus immunotherapy only, an increased long-term survival was found in patients subjected to tumour nephrectomy.

The New England Journal of Medicine

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VOLUME 345 DECEMBER 6, 2001

NEPHRECTOMY FOLLOWED BY INTERFERON ALFA-2b COMPARED WITH INTERFERON ALFA-2b ALONE FOR METASTATIC RENAL-CELL CANCER

Robert C. Flanigan, M.D., Sydney E. Salmon, M.D., Brent A. [illegible], Ph.D., Scott I. Bearman, M.D., Vivek Roy, M.D., Patrick C. McGrath, M.D., John R. Cassady, Jr., M.D., Nasir Munshi, M.D., and E. David Crawford, M.D.

ARTICLES

[illegible] interferon-alfa-based immunotherapy compared with interferon-alfa alone in metastatic renal-cell carcinoma: a randomised trial

G H J Mickisch, S Garin, H van Poppel, L de Prijck, R Sylvester, and members of the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group

Lancet 2001; **358:** 966–70

6.5.2 *Recommendation*

Tumour nephrectomy is recommended for metastatic RCC patients with good performance status when combined with IFN-alpha (grade A recommendation).

Does **CN extend survival** in the average patient in the targeted therapy era ?

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Basing on retrospective studies CN+ seems to reduce the risk of death in mRCC by more than 50%

Review

CrossMark

Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma Treated With Targeted Therapies: A Systematic Review With a Meta-Analysis

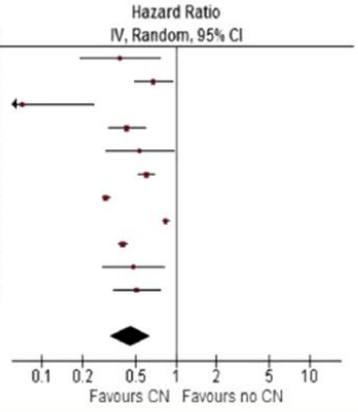
Fausto Petrelli,[1] Andrea Coinu,[1] Ivano Vavassori,[2] Mary Cabiddu,[1] Karen Borgonovo,[1] Mara Ghilardi,[1] Veronica Lonati,[1] Sandro Barni[1]

Clinical Genitourinary Cancer, Vol. 14, No. 6, 465-72 © 2016

Figure 2 Forrest Plot Assessing the Risk of Overall Mortality Following CN Plus Targeted Therapies Versus Targeted Therapies Alone

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Warren 2009	-0.9676	0.3537	7.5%	0.38 [0.19, 0.76]	2009
Choueiri 2011	-0.3857	0.1672	9.8%	0.68 [0.49, 0.94]	2011
Stroup 2013	-2.6451	0.6215	4.6%	0.07 [0.02, 0.24]	2013
Aizer 2013	-0.844	0.1669	9.8%	0.43 [0.31, 0.60]	2013
Bamias 2014	-0.6162	0.2999	8.2%	0.54 [0.30, 0.97]	2014
Heng 2014	-0.5108	0.073	10.5%	0.60 [0.52, 0.69]	2014
Vaishampayan 2014	-1.204	0.0352	10.7%	0.30 [0.28, 0.32]	2014
Conti 2014	-0.1744	0.0249	10.7%	0.84 [0.80, 0.88]	2014
Abern 2014	-0.9163	0.0398	10.6%	0.40 [0.37, 0.43]	2014
Tatsugami 2015	-0.734	0.275	8.5%	0.48 [0.28, 0.82]	2015
Mathieu 2015	-0.6733	0.2069	9.3%	0.51 [0.34, 0.77]	2015
Total (95% CI)			100.0%	0.46 [0.32, 0.64]	

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 667.29$, $df = 10$ ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.47$ ($P < 0.00001$)



EUROPEAN UROLOGY 66 (2014) 704–710

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European Association of Urology

Platinum Priority – Kidney Cancer

Editorial by Stephen H. Culp on pp. 711–712 of this issue

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng [a,,†], J. Connor Wells [a,†], Brian I. Rini [b], Benoit Beuselinck [c], Jae-Lyun Lee [d], Jennifer J. Knox [e], Georg A. Bjarnason [f], Sumanta Kumar Pal [g], Christian K. Kollmannsberger [h], Takeshi Yuasa [i], Sandy Srinivas [j], Frede Donskov [k], Aristotelis Bamias [l], Lori A. Wood [m], D. Scott Ernst [n], Neeraj Agarwal [o], Ulka N. Vaishampayan [p], Sun Young Rha [q], Jenny J. Kim [r], Toni K. Choueiri [s]*

Parameter	Parameter Estimate ± SE	Hazard Ratio	95% CI	*P*
Clinical				
KPS < 80%	0.92 ± 0.14	2.51	1.92 to 3.29	< .0001
Time from diagnosis to treatment < 1 year	0.35 ± 0.13	1.42	1.09 to 1.84	.0096
Laboratory				
Hemoglobin < LLN	0.54 ± 0.14	1.72	1.31 to 2.26	.0001
Calcium > ULN	0.59 ± 0.17	1.81	1.29 to 2.53	.0006
Neutrophil count > ULN	0.88 ± 0.17	2.42	1.72 to 3.39	< .0001
Platelet count > ULN	0.40 ± 0.16	1.49	1.09 to 2.03	.0121

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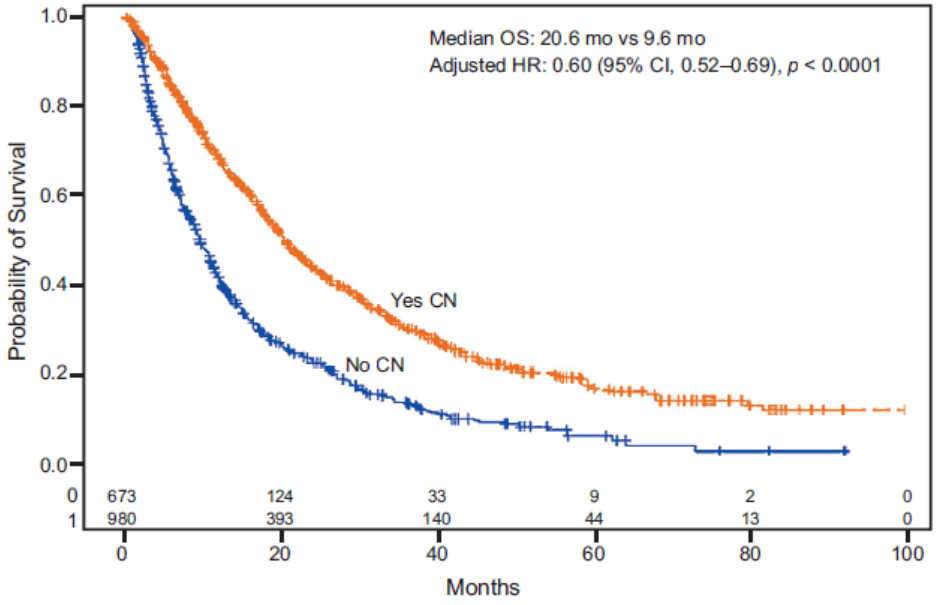

But cytoreductive nephrectomy is the ideal treatment for all patients ?

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eau European Association of Urology

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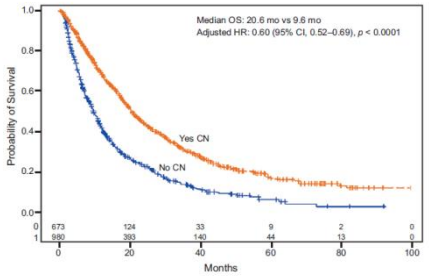

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Table 3 – Incremental overall survival benefit from cytoreductive nephrectomy separated by estimated survival times

OS, mo	No CN OS, mo	CN OS, mo	Incremental benefit, mo	*p* value	HR (95% CI) adjusted for IMDC criteria
<24	7.1 *n* = 456	12.3 *n* = 480	+5.2	<0.0001	0.72 (0.62–0.85) *p* < 0.001 *n* = 676*
<18	6.7 *n* = 430	10.0 *n* = 395	+3.3	<0.0001	0.85 (0.72–1.00) *p* = 0.05 *n* = 602*
<12	5.5 *n* = 366	7.3 *n* = 290	+2.2	<0.0001	0.97 (0.81–1.17) *p* = 0.761 *n* = 483*
<9	4.5 *n* = 303	5.5 *n* = 218	+1.0	0.0027	0.98 (0.79–1.20) *p* = 0.811 *n* = 385*
<6	3.2 *n* = 230	4.0 *n* = 151	+0.8	0.0084	1.02 (0.80–1.31) *p* = 0.856 *n* = 280*
<3	2.1 *n* = 118	2.2 *n* = 71	+0.1	0.9429	1.03 (0.72–1.46) *p* = 0.878 *n* = 146*

Table 4 – Overall survival differences in those with and without cytoreductive nephrectomy by number of International Metastatic Renal Cell Carcinoma Database Consortium criteria met

No. of IMDC criteria met	No CN OS, mo (*n*)	CN OS, mo (*n*)	*p* value
0	92% of patients (65/71) had CN, insufficient number to compare		
1	22.5 (*n* = 72)	30.4 (*n* = 178)	0.002
2	10.2 (*n* = 143)	20.2 (*n* = 253)	<0.001
3	10.0 (*n* = 113)	15.9 (*n* = 106)	<0.001
4	5.4 (*n* = 103)	6.0 (*n* = 67)	0.166
5	3.6 (*n* = 36)	2.8 (*n* = 14)	0.504
6	25% of patients (3/12) had CN, insufficient number to compare		

Overall, 1168 of 1658 subjects (70%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy.
CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.

Patients with estimated survival times < 12 mo or≥ 4 IMDC prognostic factors may not benefit from Cytoreductive Nephrectomy

Does **CN extend survival** in the average patient in the targeted therapy era ?

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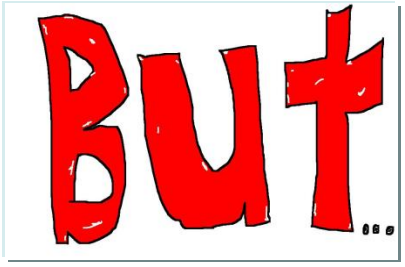
CN+ reduces the risk of death in mRCC by more than 50%



Randomized studies?

EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

EORTC
Avenue E. Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

Intergroup Study (EORTC 30073)

Randomized Phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma.

SURTIME
SURgery TIME

Coordinating Group: EORTC Genito-Urinary Cancers Group

Collaborative Groups: NCRI Renal Clinical Studies Group - Wales Cancer Trials Unit
Canadian Uro-Oncology Group (CUOG)

Study Coordinators: Axel Bex
John B.A.G. Haanen

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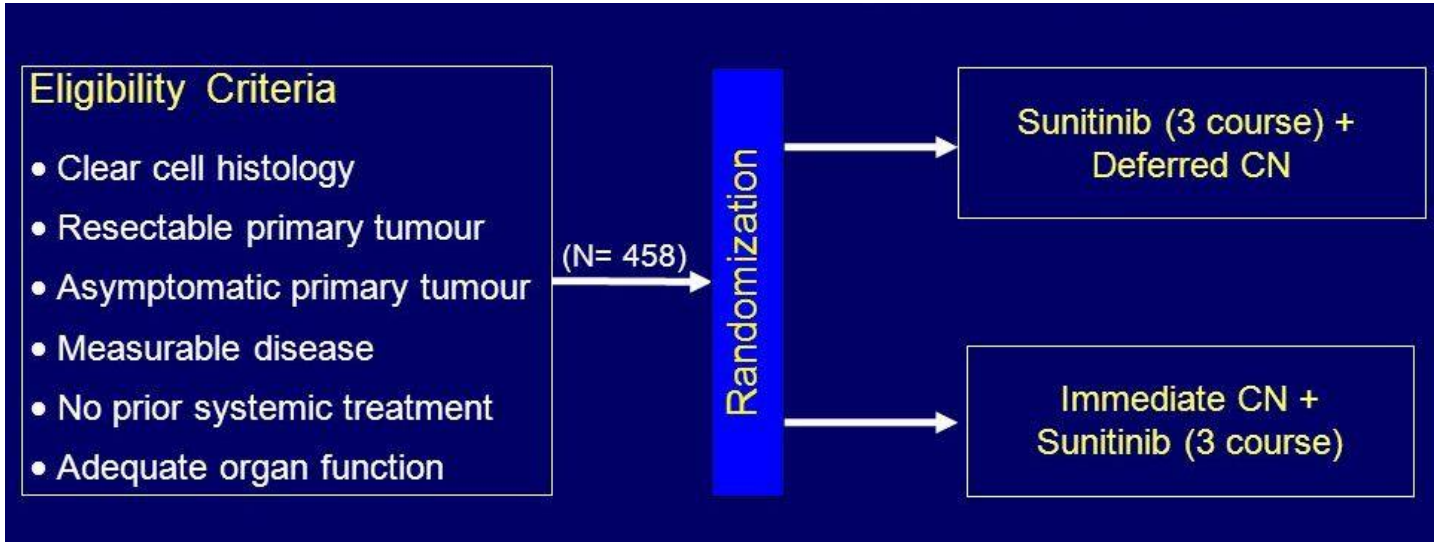
2.2 End points

The primary end-point is overall progression free survival. Progression will be defined according to the "RECIST" 1.1 criteria (Ref. 37).

Secondary end-points include

- Overall survival
- Morbidity
- Overall response to treatment in the deferred nephrectomy arm including the proportion of patients who become unresectable
- Effect of nephrectomy on early progression in both arms

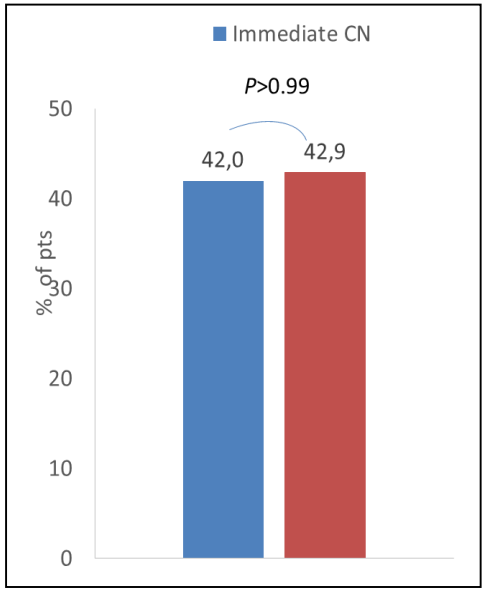


*380 events in 458 pts needed over 3 yr, but very poor accrual

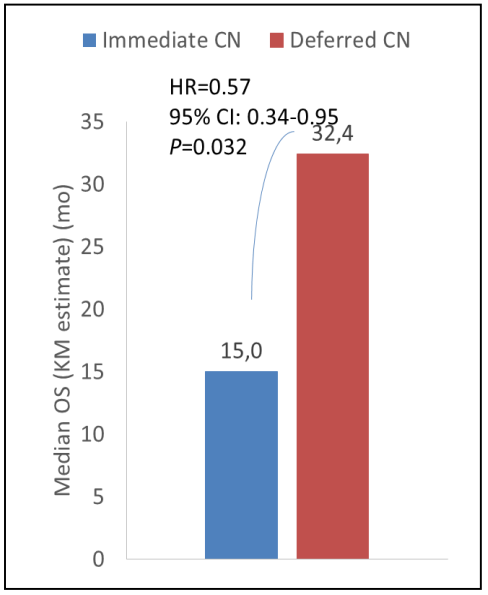
→ Amended primary endpoint: PFR at 28 wk (N=98 pts needed)

→ Study closed after 5.7 yr with 99 pts over 19 centres

PFR at 28 wk



Median OS



- **No difference in: Progression-free rate (PFR) at 28 weeks**, using RECIST v1.1
- The sample size precludes definitive conclusions from other endpoints, although an OS signal was seen for deferred CN

CARMENA Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Lebret, and B. Escudier

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

- Confirmed metastatic clear cell RCC / Biopsy
- ECOG-PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC

R 1:1

Stratification
- MSKCC risk group
- Center location

Arm A
nephrectomy → 3-6 weeks → Sunitinib 50 mg QD 4 wks on / 2 wks off

Arm B
Sunitinib 50 mg QD 4 wks on / 2 wks off

Primary endpoint: Overall survival

Secondary endpoints: Progression-free survival, objective response rate, clinical benefit, safety

LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

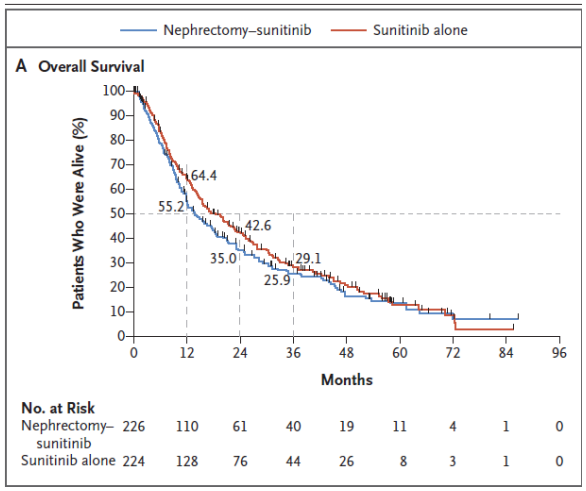
Statistical hypothesis : non inferiority design

- The study was designed to have 80% power at a 1-sided significance level of 5% (risk alpha)
- Non-inferiority margin of HR: upper 95% CI ≤1.20 for sunitinib alone
- Enrolment of 576 patients needed to observe 456 events for demonstration of non-inferiority
  - Two interim analyses were planned (after 152 and 302 events)
  - Monitored by independent DSMB

CI, confidence interval; HR, hazard ratio

Non inferiority trials are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin.

The results of such trials are not as credible as those from a superiority trial.
(Non inferiority trials -Steven M Snapinn, http://cvm.controlled-trials.com/content/1/1/019).



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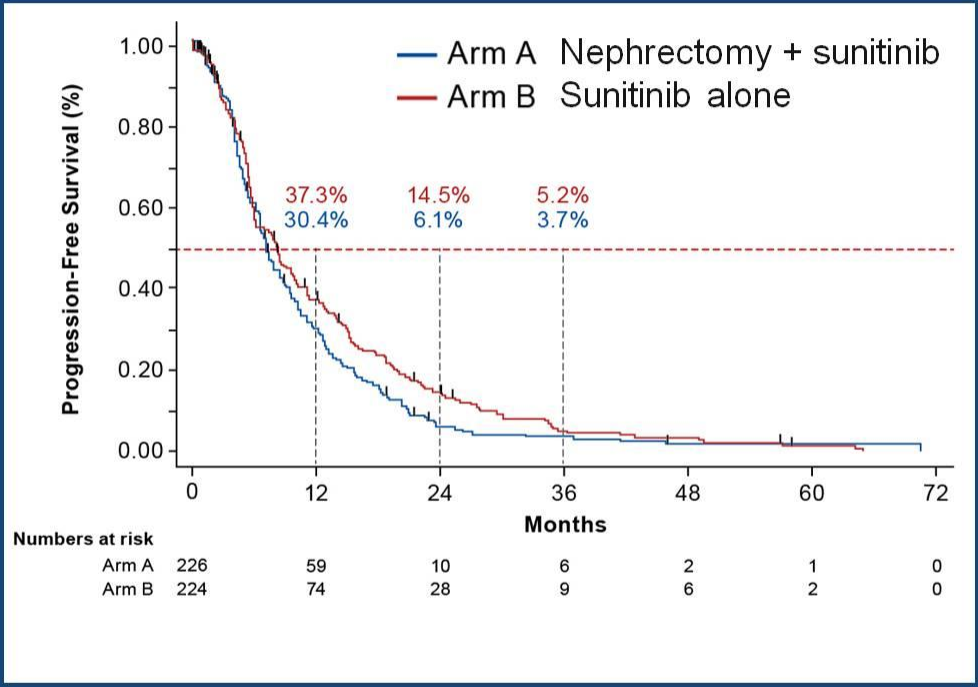
Overall survival (ITT)

Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n = 226)	Arm B: Sunitinib alone (n = 224)	HR (95% CI)
Overall	13.9 (11.8-18.3)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
MSKCC intermediate risk	19.0 (12.0-28.0)	23.4 (17.0-32.0)	0.92 (0.6-1.24)
MSKCC poor risk	10.2 (9.0-14.0)	13.3 (9.0-17.0)	0.86 (0.62-1.17)

Non inferioriy study ≤1.20

Progression free survival (ITT)



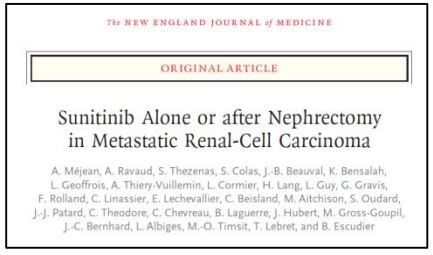
	Median PFS, months (95% CI)	HR (95% CI)
Arm A: Nephrectomy + Sunitinib (n = 226)	7.2 (6.5-8.5)	0.82 (0.67-1.00)
Arm B: Sunitinib alone (n = 224)	8.3 (6.2-9.9)	

CN, cytoreductive nephrectomy; PFS, progression-free survival

Sunitinib alone is non-inferior to nephrectomy followed by sunitinib for OS

Population	Arm A (CN + sunitinib)			Arm B (Sunitinib)			HR (95% CI), stratified by MSKCC risk group
	n	Events, n (%)	Median (95% CI), months	n	Events, n (%)	Median (95% CI), months	
ITT	226	165 (73.0)	13.9 (11.8-18.3)	224	161 (71.9)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
PP1*	205	149 (72.7)	14.5 (11.9-20.2)	206	143 (69.4)	20.5 (15.6-25.2)	0.87 (0.69-1.1)
PP2#	176	122 (69.3)	18.3 (13.7-23.2)	206	143 (69.4)	20.5 (15.6-25.2)	0.98 (0.77-1.25)

*The PP1 analysis included only patients who had CN in Arm A, and patients who receive sunitinib in Arm B
#The PP2 analysis included only patients who had CN and receive sunitinib after CN in Arm A, and patients who receive sunitinib in Arm B
CI, confidence interval; CN, cytoreductive nephrectomy; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PP, per-protocol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CONCLUSIONS

Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease. (Funded by Assistance Publique–Hôpitaux de Paris and others; CARMENA ClinicalTrials.gov number, NCT00930033.)

Population weighted toward poor outcome

Characteristic	Arm A: Nephrectomy + sunitinib (N = 226)	Arm B: Sunitinib alone (N = 224)
Median age (range), years	63 (33-84)	62 (30-87)
Male sex, n (%)	169 (75)	167 (75)
MSKCC score, n (%)		
Intermediate	125 (56)	131 (59)
Poor	100 (44)	93 (41)
Missing	1	0
ECOG PS, n (%)		
0	130 (57)	122 (54)
1	96 (42)	102 (45)

CN, cytoreductive nephrectomy; ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Cytoreductive Nephrectomy — Patient Selection Is Key

Robert J. Motzer, M.D., and Paul Russo, M.D.

The selection of patients plays a critical role in day-to-day patient care as well as in clinical trial design. We think that nephrectomy in properly chosen patients with metastatic renal-cell carcinoma remains an essential component of care. Often, for patients with limited or slow-growing metastatic disease after nephrectomy, prolonged surveillance-only periods are used until the progression of distant metastases occurs and then systemic therapy is initiated.[10] The CARMENA trial was heavily weighted toward poor-risk patients, and it is not surprising that the noninferiority end point was achieved. For practicing surgeons and medical oncologists, these data should not lead to the abandonment of nephrectomy but instead emphasize the importance of careful selection of patients undergoing nephrectomy, on the basis of published risk models.[1,6,7] The main focus is on pretreatment

Is cytoreductive nephrectomy still necessary in the era of targeted tx?

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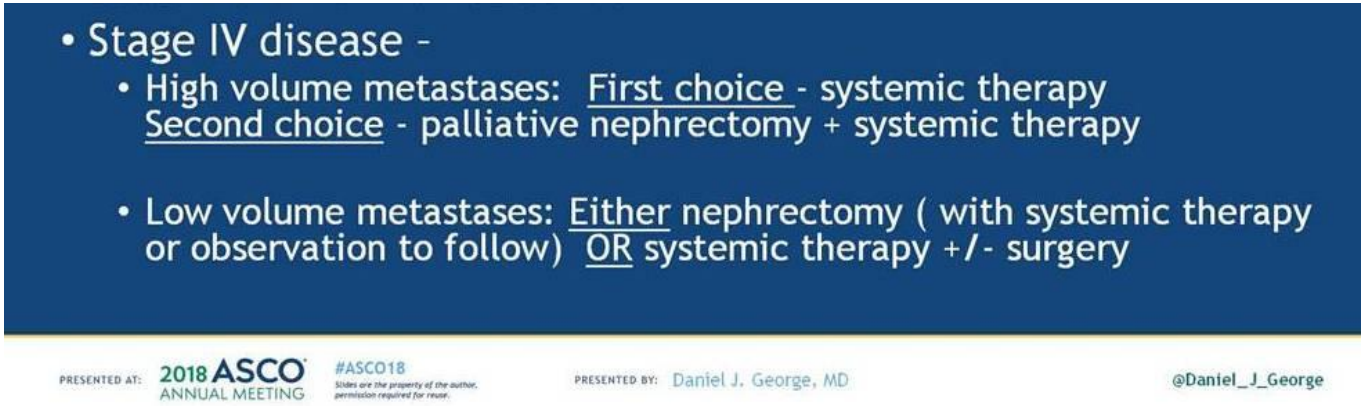
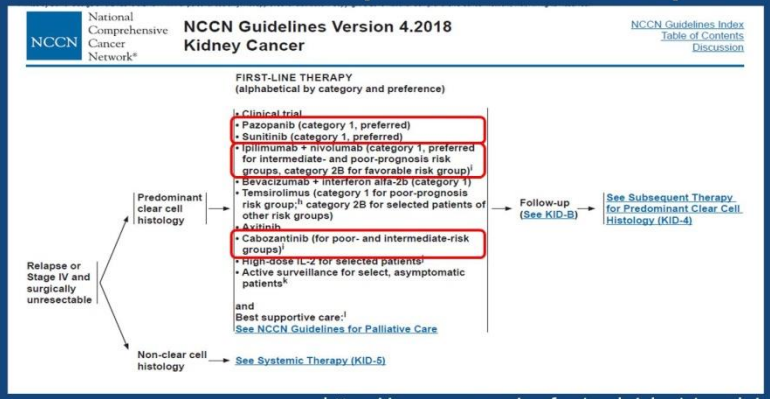
Pts with intermediate- or poor-risk metastatic ccRCC should initially not undergo nephrectomy. If needed, nephrectomy can be performed after systemic tx.



Patients with a short life expectancy or **IMDC/MSKCC poor risk** disease are unlikely to benefit from CN.

Additional treatment options for mRCC patients



https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

Survival benefit seen with nivolumab and ipilimumab with or without nephrectomy

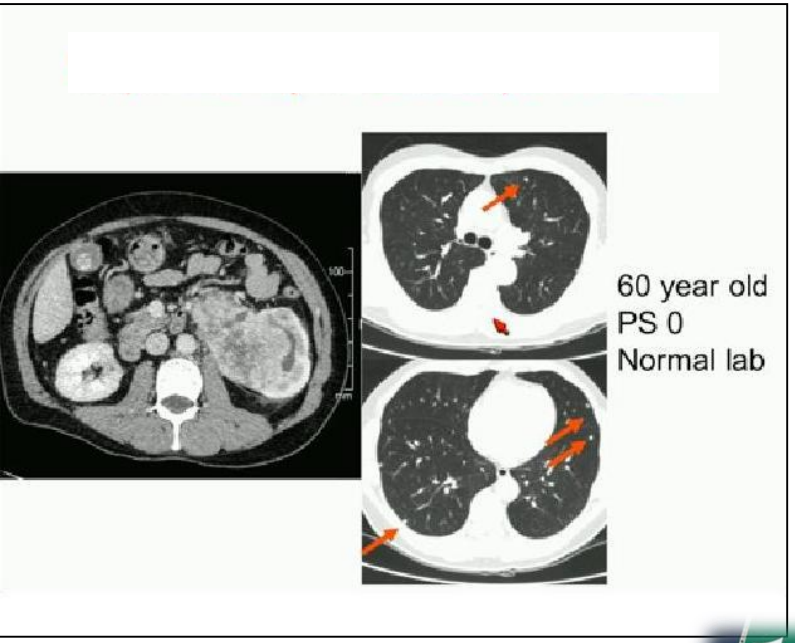
Subgroup	Nivolumab +Ipilimumab	Sunitinib	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of patients		
Overall	140/425	188/422	0.66 (0.53–0.82)
Age			
<65 yr	77/265	118/259	0.53 (0.40–0.71)
≥65 and <75 yr	46/125	55/133	0.86 (0.58–1.27)
≥75 yr	17/35	15/30	0.97 (0.48–1.95)
Sex			
Male	104/314	130/301	0.71 (0.55–0.92)
Female	36/111	58/121	0.52 (0.34–0.78)
Region			
United States	33/112	43/110	0.64 (0.40–1.00)
Canada and Europe	51/148	68/147	0.70 (0.49–1.01)
Rest of the world	56/165	77/165	0.63 (0.45–0.89)
Baseline IMDC prognostic risk			
Intermediate	87/314	121/317	0.66 (0.50–0.87)
Poor	52/102	66/97	0.57 (0.39–0.82)
Previous nephrectomy			
Yes	103/341	127/319	0.69 (0.53–0.89)
No	37/84	61/103	0.63 (0.42–0.94)

Motzer RJ, et al. NEJM 2018 Apr 5;378(14):1277-90

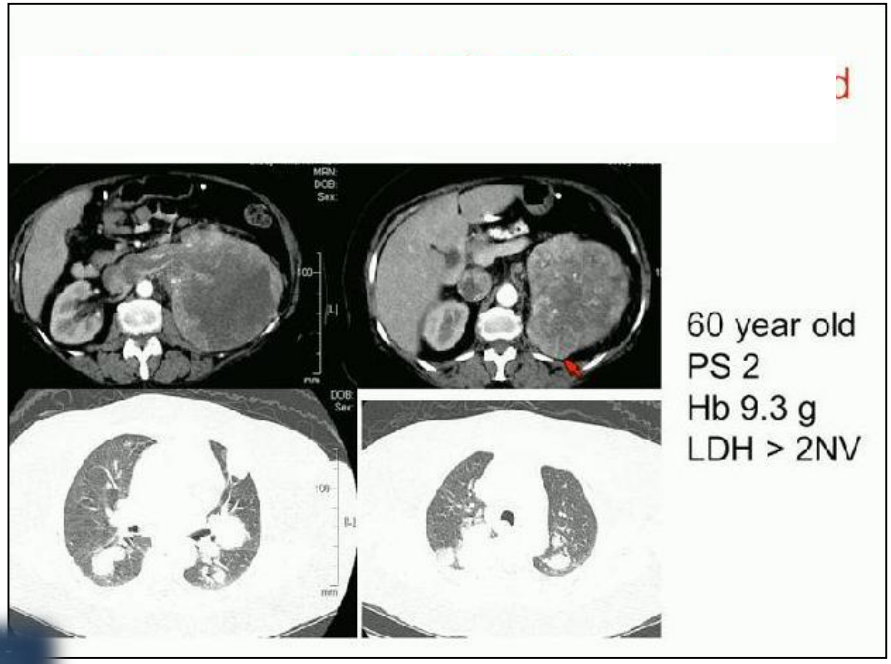
Two additional hypotheses for starting with systemic therapy

- Primary in place: abundant source of neoantigens for cross-priming with immunotherapy
  - Rationale for the EA8143 (PROSPER RCC) perioperative nivolumab
- Post-operative wound-healing and inflammatory response to surgery promotes tumor growth
  - Preclinical studies suggestive of a detrimental clinical effect in the setting of unresected metastases

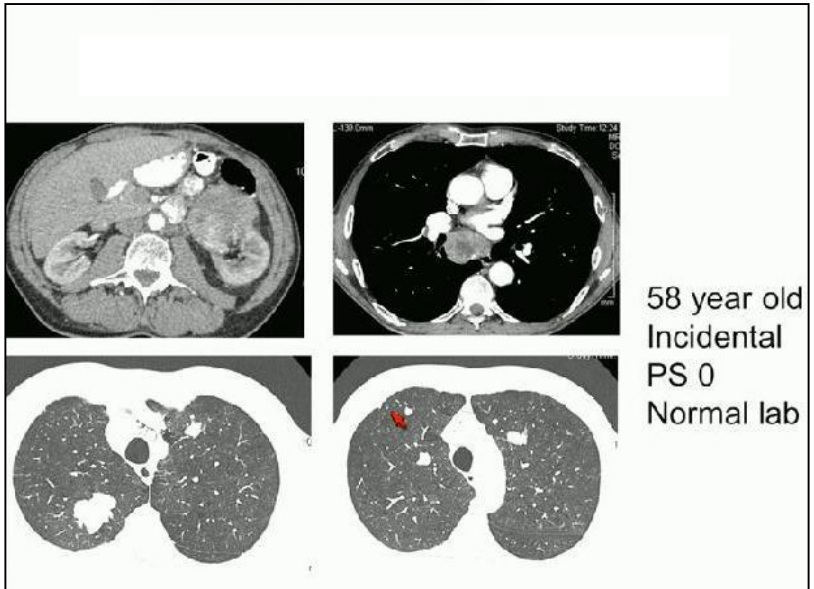
Liu J et al. Cancer Discov; 6(12); 1-18
Krall J, et al Sci Trans Med 2018



60 year old
PS 0
Normal lab



60 year old
PS 2
Hb 9.3 g
LDH > 2NV



58 year old
Incidental
PS 0
Normal lab