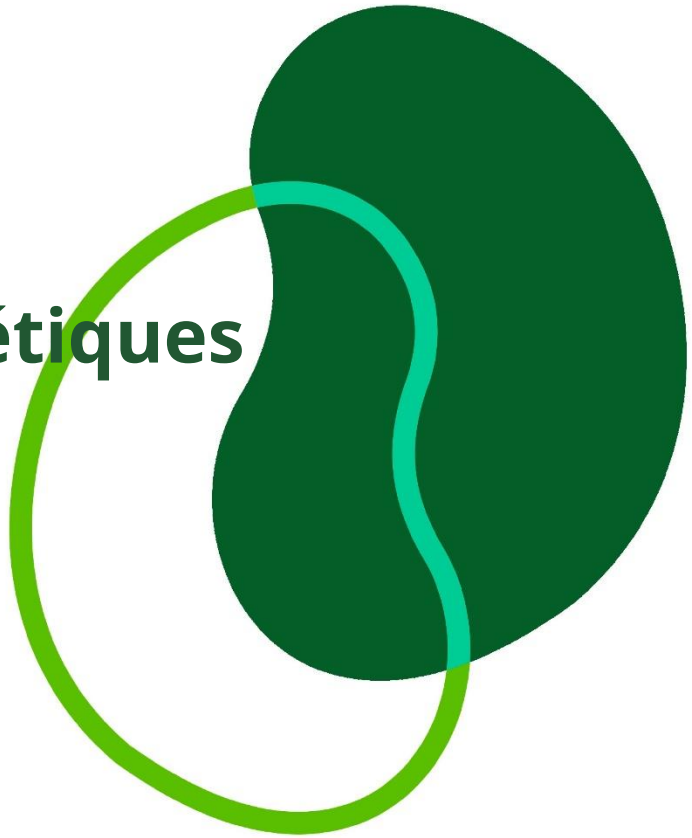
13ème Rencontre Patients de l'Association A.R.Tu.R.

Vendredi 12 avril 2019
à l'Institut des Maladies Génétiques IMAGINE



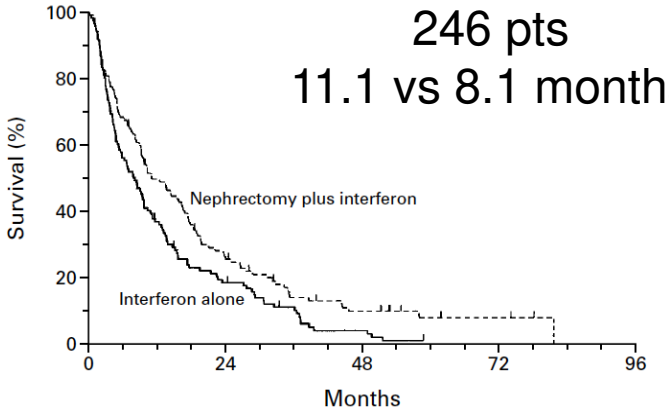
Place de la néphrectomie chez les patients d'emblée métastatiques

Arnaud Méjean

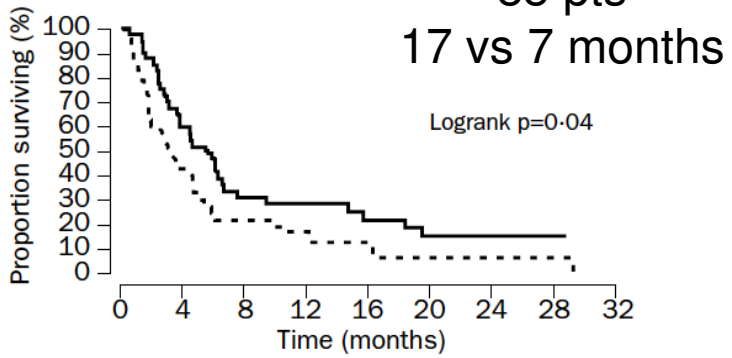
Service d'Urologie
et Transplantation Rénale

CN (Cytoreductive nephrectomy) est définie comme une resection chirurgicale de la tumeur primaire avant l'initiation d'une thérapie systémique.

Historique



Flanigan et al SWOG, 2001



Mickisch et al EORTC, 2001

Seulement pour patients 0-1 ECOG PS

mRCC, metastatic renal cell carcinoma

1. Flanigan R, et al. *N Engl J Med* 2001;345:1655. 2. Mickish G, et al. *Lancet* 2001;358:966.

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Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) Score for Metastatic Renal Cell Carcinoma (RCC)	IMDC/Heng Score for Metastatic Renal Cell Carcinoma (RCC) Prognosis
Time from diagnosis to systemic treatment <1 year	Time of diagnosis to systemic therapy < 1 year
Performance status <80% (Karnofsky)	Performance status <80% (Karnofsky)
Hemoglobin < lower limit of Normal	Hemoglobin < lower limit of Normal
Calcium >10mg/dL (>2.5 mmol/L)	Calcium > upper limit of normal
LDH > 1.5x Upper Limit of Normal	Neutrophil > upper limit of normal
	Platelets > upper limit of normal

0 point : favorable OS = 20 months
1 or 2 points = intermediate OS = 10 months
> 2 points = high risk OS = 4 months

0 point : favorable OS = 43,2 months
1 or 2 points : intermediate OS = 21,5 months
> 2 points : poor OS = 7,8 months

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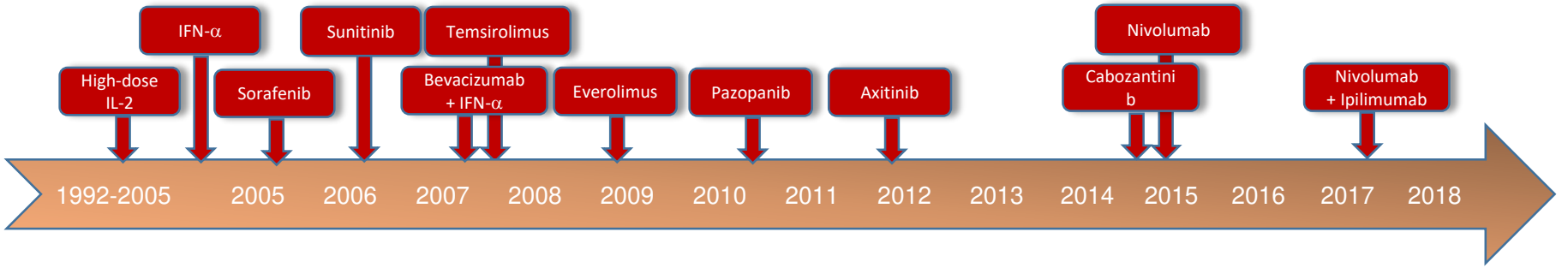

ORR
PFS
OS
Tolerance

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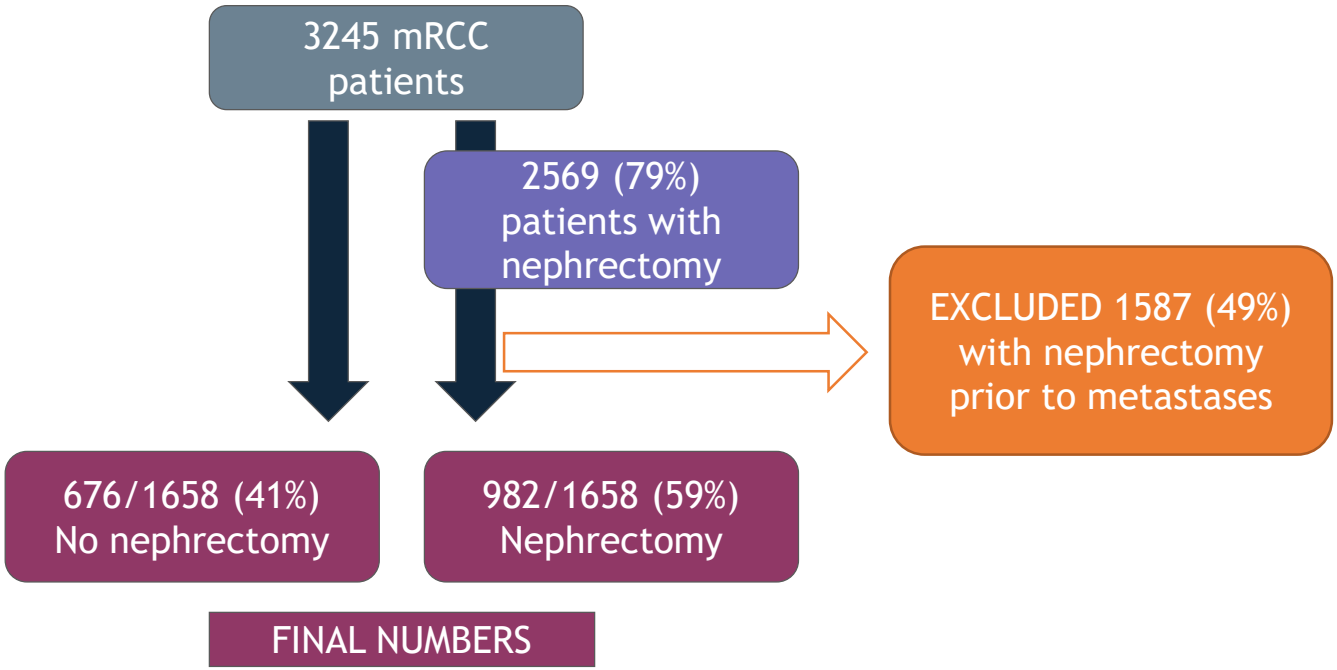
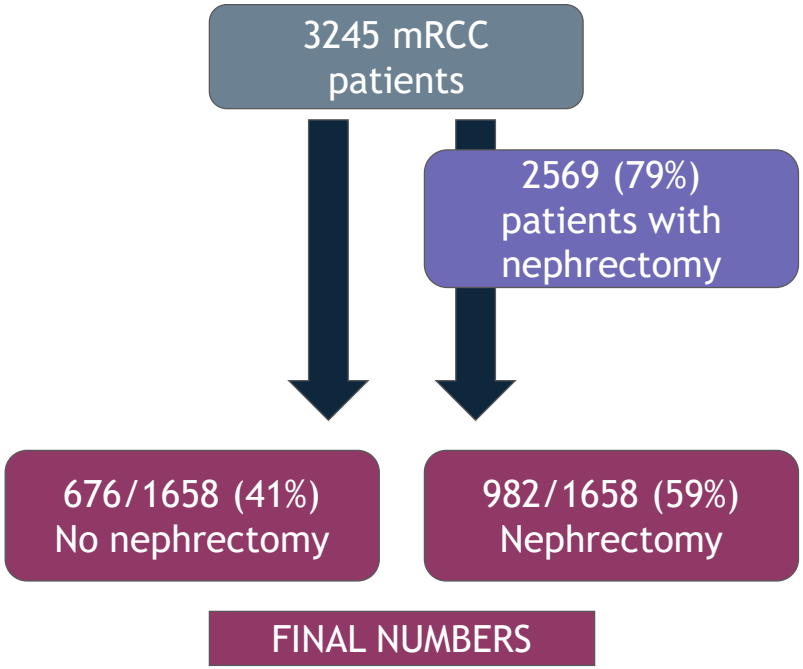
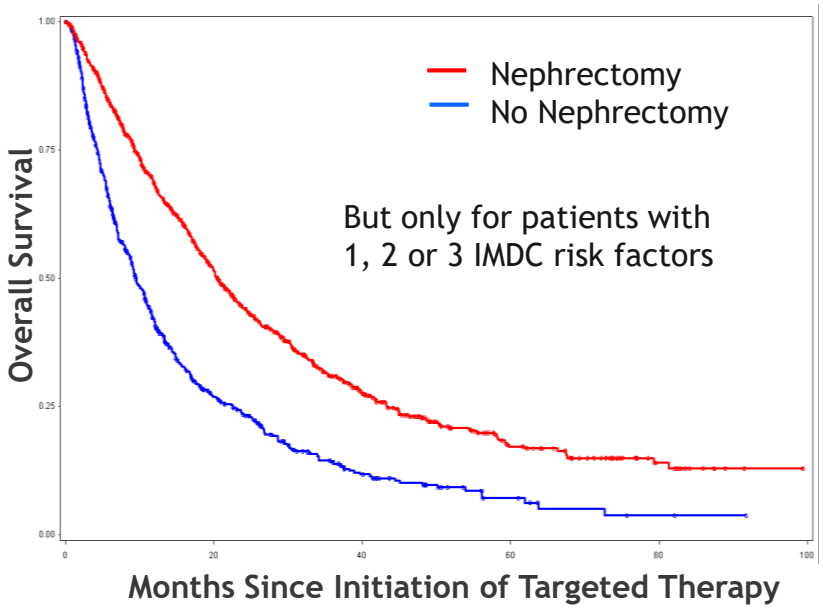
IMDC retrospective database study



IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma
Heng D, et al, *Eur Urol* 2014;66:704.

IMDC retrospective database study





IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma
Heng D, et al, *Eur Urol* 2014;66:704.

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Table 2 – Subgroup analysis of patients receiving and not receiving cytoreductive nephrectomy

Subgroup analysis	Median OS, mo		Hazard ratio (95% CI)	*p* value
	Without CN	With CN		
Risk				
Favorable*	41.0	37.0	–	–
Intermediate	13.3	23.0	0.58 (0.47–0.71)	<0.001
Poor	6.0	9.5	0.64 (0.52–0.78)	<0.001
KPS				
>80	12.2	23.4	0.53 (0.45–0.62)	<0.001
<80	5.3	8.6	0.70 (0.56–0.88)	0.002
Age at TKI, yr				
<75	9.6	20.8	0.52 (0.46–0.59)	<0.001
>75	8.6	16.7	0.66 (0.44–0.98)	0.038
No. of metastases				
1	15.0	38.6	0.50 (0.38–0.66)	<0.001
>1	8.9	17.7	0.55 (0.48–0.63)	<0.001
Brain metastases				
No	9.5	21.9	0.51 (0.45–0.58)	<0.001
Yes	6.9	12.5	0.57 (0.39–0.83)	0.003
Liver metastases				
No	10.7	21.5	0.53 (0.46–0.61)	<0.001
Yes	6.6	10.6	0.65 (0.51–0.84)	0.001
Bone metastases				
No	9.5	24.3	0.48 (0.40–0.56)	<0.001
Yes	9.3	14.9	0.65 (0.54–0.77)	<0.001
Sarcomatoid				
No	10.9	22.3	0.51 (0.44–0.59)	<0.001
Yes	5.5	10.2	0.56 (0.36–0.86)	0.009
Non–clear cell				
No	10.9	21.4	0.52 (0.45–0.59)	<0.001
Yes	8.0	15.3	0.61 (0.43–0.87)	0.006

CI = confidence interval; CN = cytoreductive nephrectomy; KPS = Karnofsky Performance Score; OS = overall survival; TKI = tyrosine kinase inhibitor.
* Numbers too small.

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A l'ère des TKI, la CN est-elle encore nécessaire ?

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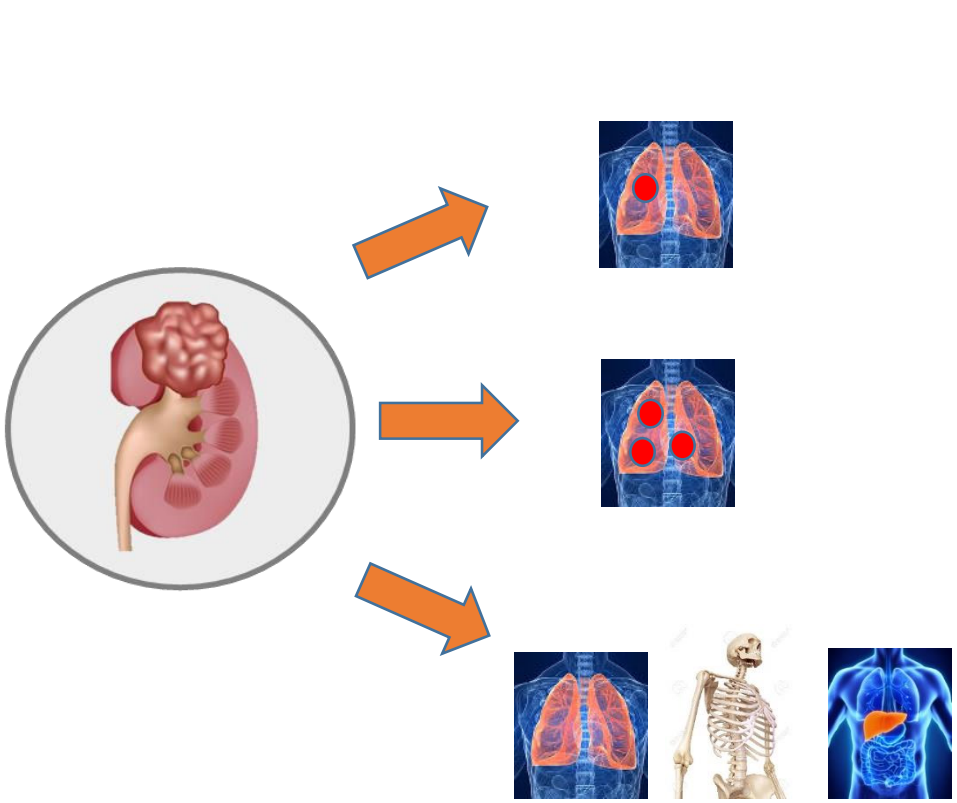

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Comment mieux sélectionner les patients ?

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Quels critères ?

- ECOG PS : 0-1 ?
- IMDC : Intermediate risk factors
- Volume tumoral ?
- Nombre de sites métastatiques ?
- Résécabilité des métastases ?
- Délai pour initier un traitement systémique ?
- Réponse à une première ligne ?

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

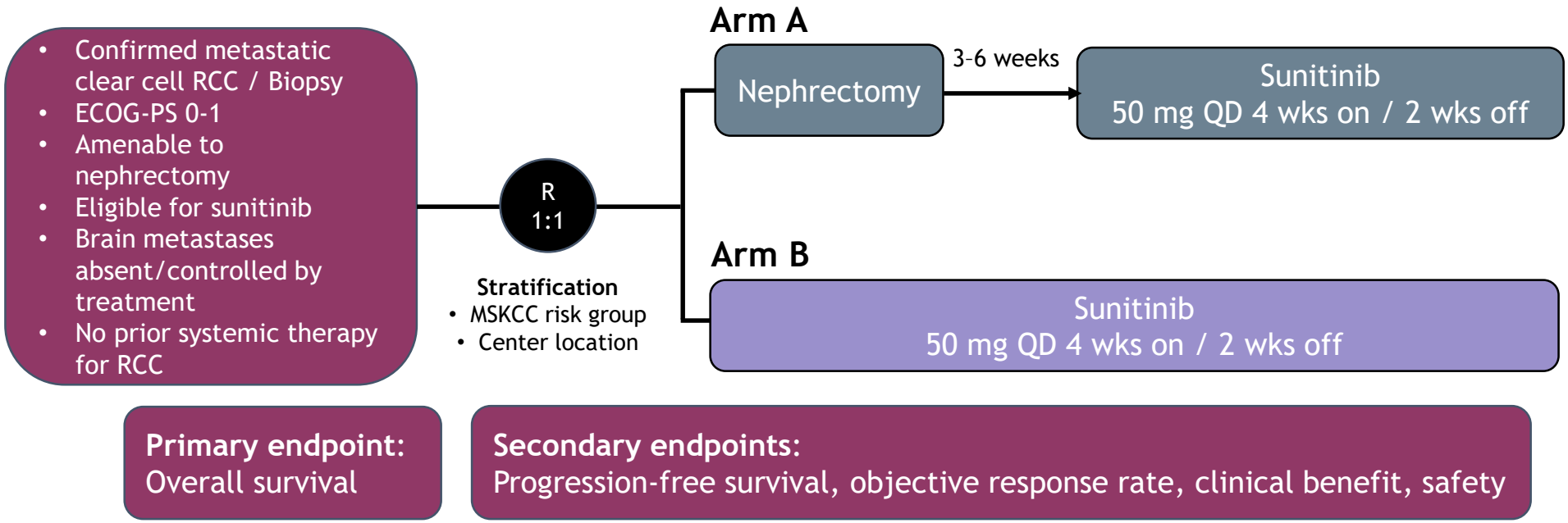
Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

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

A. Méjean, A. Ravaud, S. Thezenas, et al Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma N Engl J Med 2018;379:417-27

CARMENA: Prospective, multicentrique, randomisée, phase 3, Etude de non-infériorité



Primary endpoint: Overall survival

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

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

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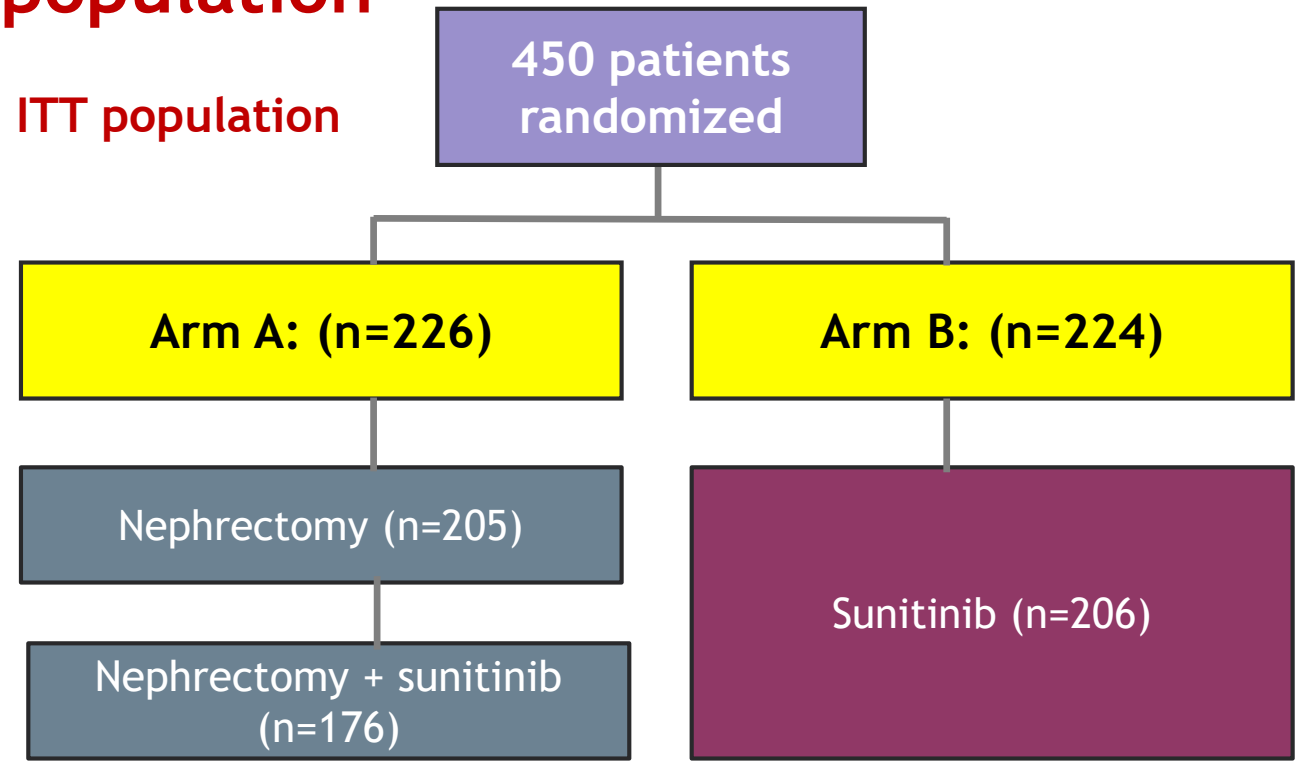
Patient population

ITT population



ITT, intention to treat

Data cutoff : September 9, 2017

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Patient characteristics (1)

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)**

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

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Patient characteristics (2)

Characteristic	Arm A: Nephrectomy + sunitinib (N = 226)	Arm B: Sunitinib alone (N = 224)
Median size of primary tumor, mm (range)	88 (6–200)	86 (12–190)
Median number of metastatic sites, n (range)	2 (1–5)	2 (1–5)
Tumor burden* by RECIST v1.1, mm (range)	140 (23–399)	144 (39–313)
Location of metastases, n (%)		
Lung	172 (79)	161 (73)
Bone	78 (36)	82 (37)
Lymph nodes	76 (35)	86 (39)
Other	78 (36)	90 (40)

*Assessed as a combination of primary renal tumour and metastases. RECIST, Response Evaluation Criteria In Solid Tumors

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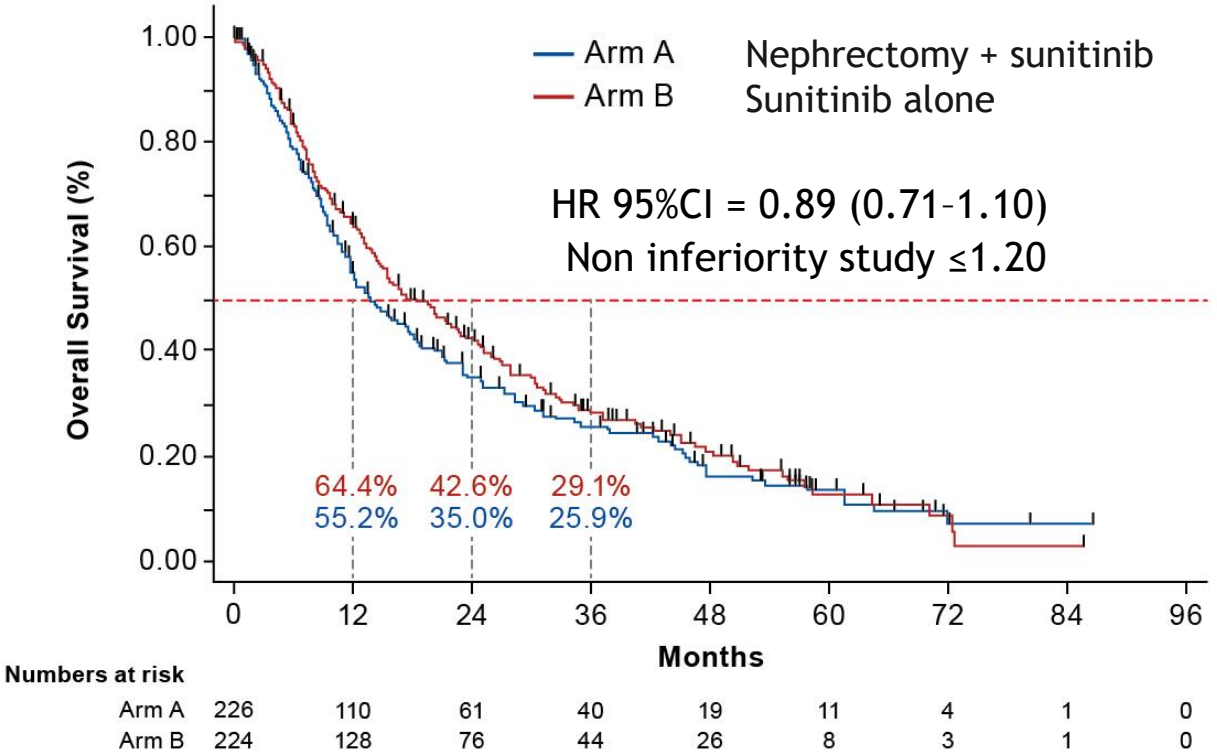
Overall survival (ITT)



Median follow-up was 50.9 months (range 0.0-86.6)

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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 inferiority study ≤1.20

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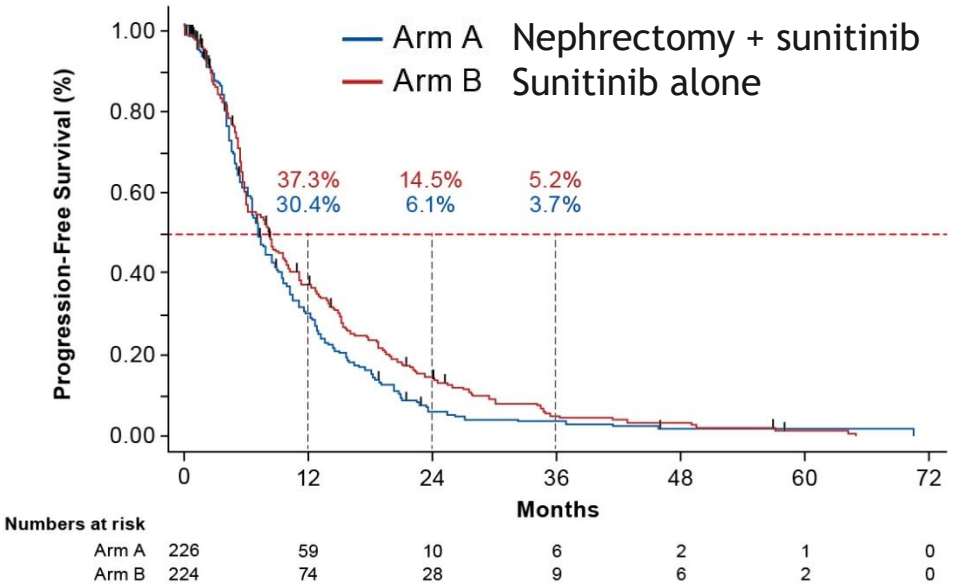
Progression free survival (ITT)



	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)	

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CN, cytoreductive nephrectomy; PFS, progression-free survival

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Response rate

Best overall response, n (%)	Arm A: Nephrectomy + sunitinib (N = 186)	Arm B: Sunitinib alone (N = 213)
CR	1 (0.6)	0 (0)
PR	50 (28)	62 (30)
SD	64 (36)	97 (47)
PD	49 (27)	40 (19)
Not evaluable	14 (8)	9 (4)
Missing	8	5
Objective response rate (CR + PR), % (95% CI)	27.4 (21-34)	29.1 (23-36)
Disease control rate (CR + PR + SD), % (95% CI)	61.8 (54-69)	74.6 (68-80)
Clinical benefit, % (disease control beyond 12 wks)	36.6	47.9*

***p=0.022**

CI, confidence interval; CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease[2]

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Mortality and morbidity post-nephrectomy (Arm A)

	Arm A: Nephrectomy + sunitinib (N = 210)
Total nephrectomy performed	199 (95)
Open surgery	114 (58)
Postoperative mortality†	4 (2)
Postoperative morbidity, n (%)	82 (39)
Clavien-Dindo Grade I	45 (55*)
Clavien-Dindo Grade II	24 (29*)
Clavien-Dindo Grade III	9 (11*)
Clavien-Dindo Grade >III	4 (5*)

Classification of Surgical Complications A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey
Dindo D, et al, *Ann Surg* 2004;240(2):205.
†Within 1 month of surgery
*Percentage of 82 patients with postoperative morbidity

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Safety of sunitinib

	Arm A: Nephrectomy + Sunitinib (N = 186)	Arm B: Sunitinib alone (N = 213)
Median treatment duration, months (range)	6.7 (1.4–67.2)	8.5 (0.9–63.7)
Dose reductions, n (%)	57 (31)	65 (30)
Severe (grade 3–4) AE, n (%)	61 (33)	91 (43)*
Asthenia, n (%)	16 (9)	21 (10)
Hand/foot syndrome, n (%)	8 (4)	12 (6)
Anemia, n (%)	5 (3)	11 (5)
Neutropenia, n (%)	5 (3)	10 (5)
Kidney or urinary tract disorder, n (%)	1 (0)	9 (4)

*p=0.04

AE, adverse event;

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Secondary nephrectomy in Arm B (sunitinib alone)

- 38 patients required secondary nephrectomy
  - For emergency treatment of the primary tumor
  - For CR or near CR in metastatic sites (> 6 months)
- Median 11.1 months (range 0.7–85.4) from randomisation to surgery
- 31.3% of patients with secondary nephrectomy restarted sunitinib

	Arm B: Sunitinib alone (N = 224)
Secondary nephrectomy, n (%)	
No	185 (83.0)
Yes	38 (17.0)
Missing	1
Emergency	
Yes	7 (18.9)
No	30 (81.1)
Missing	1

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Conclusion de Carmena

- La néphrectomie cytoreductive ne devrait plus être considérée comme le traitement standard du cancer du rein métastatique, au moins lorsqu'un traitement medical est nécessaire

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Acknowledgments

- Patients, families and friends
- Assistance Publique – Hôpitaux de Paris (Clinical Research and Innovation Delegation)
- URC-CIC Paris Descartes Necker-Cochin (S. Colas and S. Thezenas)
- The research was funded by a grant from Programme Hospitalier de Recherche Clinique Cancer – PHRC-K 2007 (Ministère de la Santé) and realized with the financial support of Pfizer
- Urologists and Medical Oncologist
- DSMB members



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79 Centers contributing patients to CARMENA




- Hôpital Européen Georges-Pompidou / Necker - Urologie
- Institut Gustave Roussy - Immunothérapie
- Suresnes Foch - Oncologie
- Nancy A. Vautrin - Oncologie Médicale
- Bordeaux St André - Oncologie Médicale et Radiothérapie
- Rennes Pontchaillou - Urologie
- Toulouse Rangueil - Urologie-Andrologie
- Besançon Minjoz - Oncologie Médicale
- Strasbourg Civil - Chirurgie Urologique
- Clermont G. Monpied - Urologie
- Dijon Bocage - Chir. Urologique-Andrologie
- Marseille Paoli Calmettes - Oncologie Médicale
- Saint-Herblain CLCC - Oncologie
- Tours Bretonneau - Oncologie Médicale
- Marseille Timone Adultes - Oncologie Médicale
- Toulouse Regaud - Oncologie Médicale
- Montpellier - Saint Eloi - Oncologie
- La Roche-sur-Yon - Chir. Uro.
- Mondor - Oncologie Médicale
- Angers P. Papin - Urologie
- Lille O. Lambret - Cancérologie Urologique et Digestive
- Grenoble Michallon - Oncologie Médicale
- Poitiers Milétrie - Oncologie Médicale
- Nantes - Catherine de Sienne - Oncologie
- Cabestany - Polyclinique Médipôle - Urologie
- Lyon Sud - Oncologie Médicale
- Limoges - Oncologie
- Nîmes Valdegour - Oncologie Médicale
- Rouen C. Nicolle - Urologie
- Caen F. Baclesse - Oncologie Médicale
- Pitié - Oncologie Médicale
- Orléans La Source - Oncologie Médicale et Hématologie Clinique
- Hyères - Clinique Sainte Marguerite - Oncologie
- Saint-Brieuc-Clinique Armoricaine de Radiologie
- St-Priest ICL - Oncologie Médicale Adulte
- Montpellier Clémentville - Cancérologie
- Bichat - Urologie
- Versailles A. Mignot - Oncologie
- Poitiers Milétrie - Urologie Néphrologie
- Lyon Bérard - Cancérologie Médicale
- Lyon E. Herriot - Urologie
- Colmar Pasteur - Oncologie
- Reims J. Godinot - Radiothérapie Curiethérapie
- Pointe-à-Pitre Abymes - Urologie
- La Roche-sur-Yon - Onco-Hématologie
- Grenoble Michallon - Urologie Transplantation
- Le Mans - Cancérologie-Oncologie-Hématologie
- Colmar Pasteur - Urologie
- Orléans La Source - Chirurgie Urologique et Andrologie
- Nîmes - Urologie Andrologie
- Mondor - Urologie
- Nîmes - Hématologie clinique et oncologie médicale
- Brive-la-Gaillarde - Oncologie
- Reims R. Debré - Urologie
- Lyon Sud - Urologie
- Avignon Ste Catherine - Oncologie Médicale
- Cochin - Médecine Interne
- Annecy - Oncologie
- Tours Bretonneau - Urologie
- Troyes - Urologie
- Pontoise R. Dubos - Chirurgie Urologique
- Suresnes Foch - Urologie
- Nice Pasteur - Urologie
- Troyes - Oncologie
- Auxerre - Oncologie
- Toulouse - Clinique Saint-Jean Languedoc - Oncologie
- Bergen Haukeland University Hospital - Urology
- Oslo Universitetssykehus - Aker - Urology
- East Kent Hospital - Urology
- Leicester Royal Infirmary - Oncology
- Royal Devon & Exeter Hospital - Oncology
- Darent Valley Hospital - Urology
- Lincoln County Hospital - Clinical Oncology
- Manchester - The Christie Hospital - Oncology
- Cheltenham General Hospital - Oncology
- London - Royal Free Hospital - Oncology
- Birmingham - Heartlands Hospital - Oncology
- Beatson West of Scotland Cancer Centre - Urology Day Surgery Unit
- Lund - Skane University Hospital - Oncology

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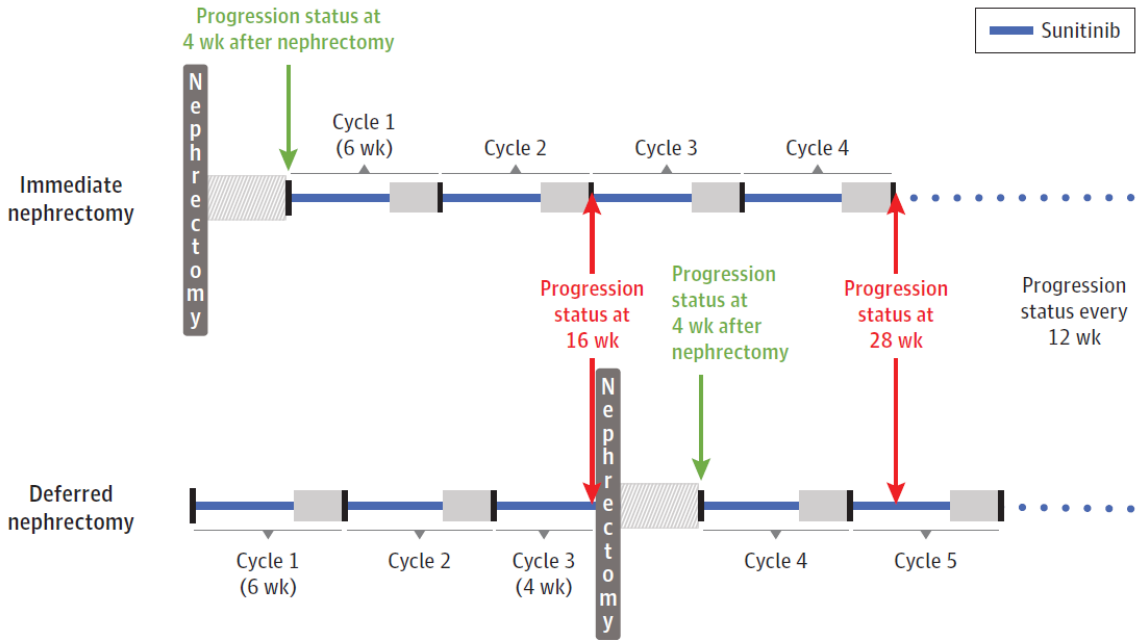
JAMA Oncology | Original Investigation

Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib

The SURTIME Randomized Clinical Trial

Axel Bex, MD, PhD; Peter Mulders, MD, PhD; Michael Jewett, MD; John Wagstaff, MD; Johannes V. van Thienen, MD, PhD; Christian U. Blank, MD, PhD; Roland van Velthoven, MD, PhD; Maria del Pilar Laguna, MD, PhD; Lori Wood, MD, PhD; Harm H. E. van Melick, MD, PhD; Maureen J. Aarts, MD, PhD; J. B. Lattouf, MD; Thomas Powles, MD; Igle Jan de Jong, MD, PhD; Sylvie Rottey, MD, PhD; Bertrand Tombal, MD, PhD; Sandrine Marreaud, MD; Sandra Collette, MSC; Laurence Collette, PhD; John Haanen, MD

Figure 1. Trial Design



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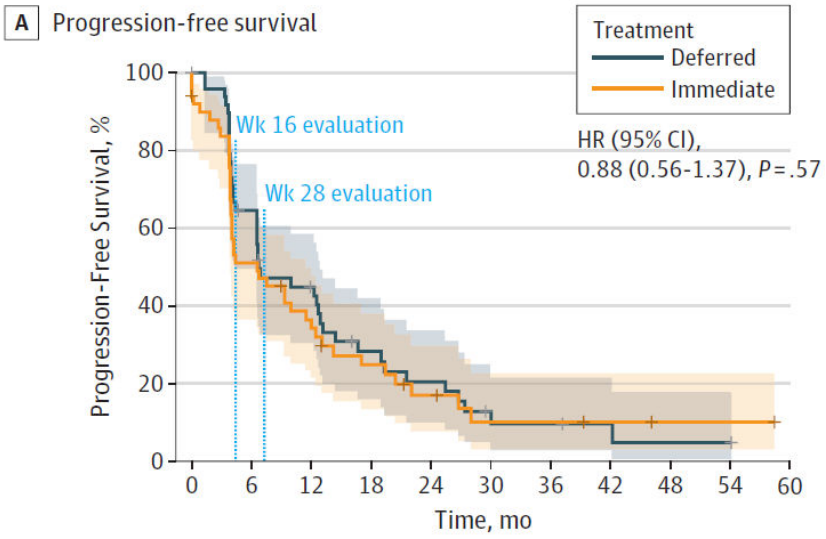

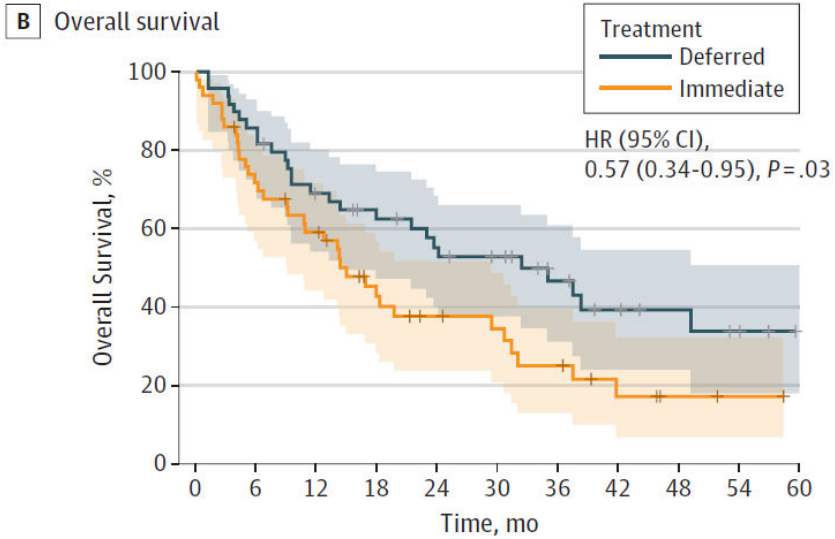

Key Points

Findings In this randomized clinical trial of 99 patients, the progression-free rate at 28 weeks did not improve when patients began sunitinib therapy before planned cytoreductive nephrectomy; however, more patients received systemic therapy, and cytoreductive nephrectomy could be avoided in those with progressive disease.

Meaning Pretreatment with sunitinib may identify patients with inherent resistance to systemic therapy before planned cytoreductive nephrectomy without inferior outcome.

Median OS deferred CN : 32.4 months (95%CI, 14.5-65.3 months)

Median OS immediate CN : 15.0 months (95%CI, 9.5-29.5 months)

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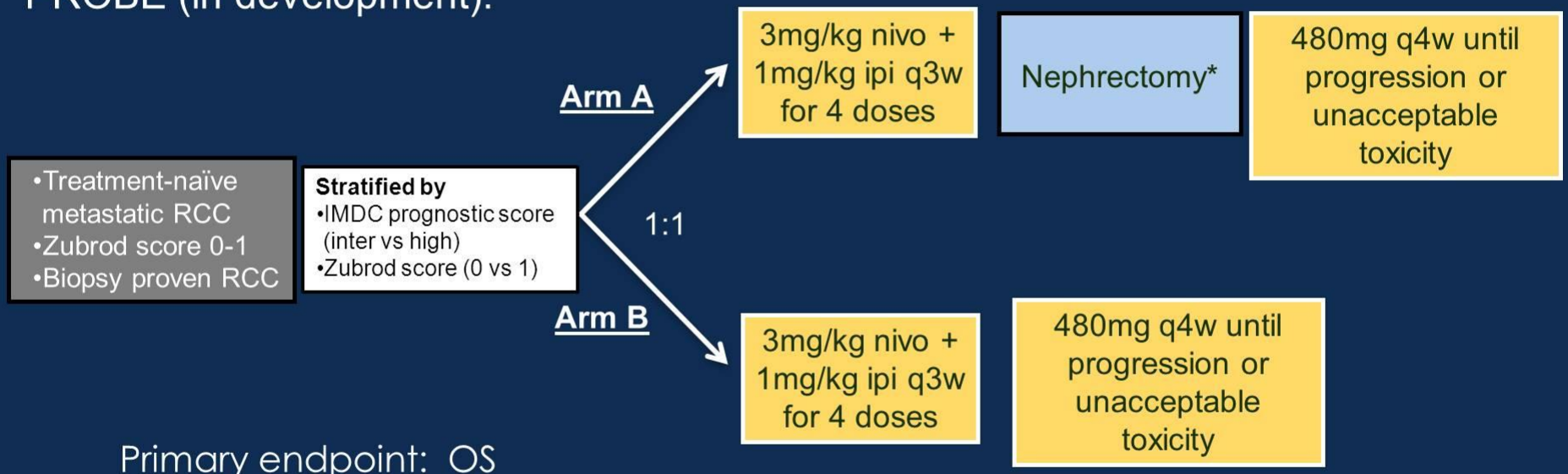
Peut-on extrapoler les résultats de Carmena à l'aire de l'immunothérapie ?

CPI +/- Cytoreductive Nephrectomy in the IO era (PROBE)

PROBE (in development):



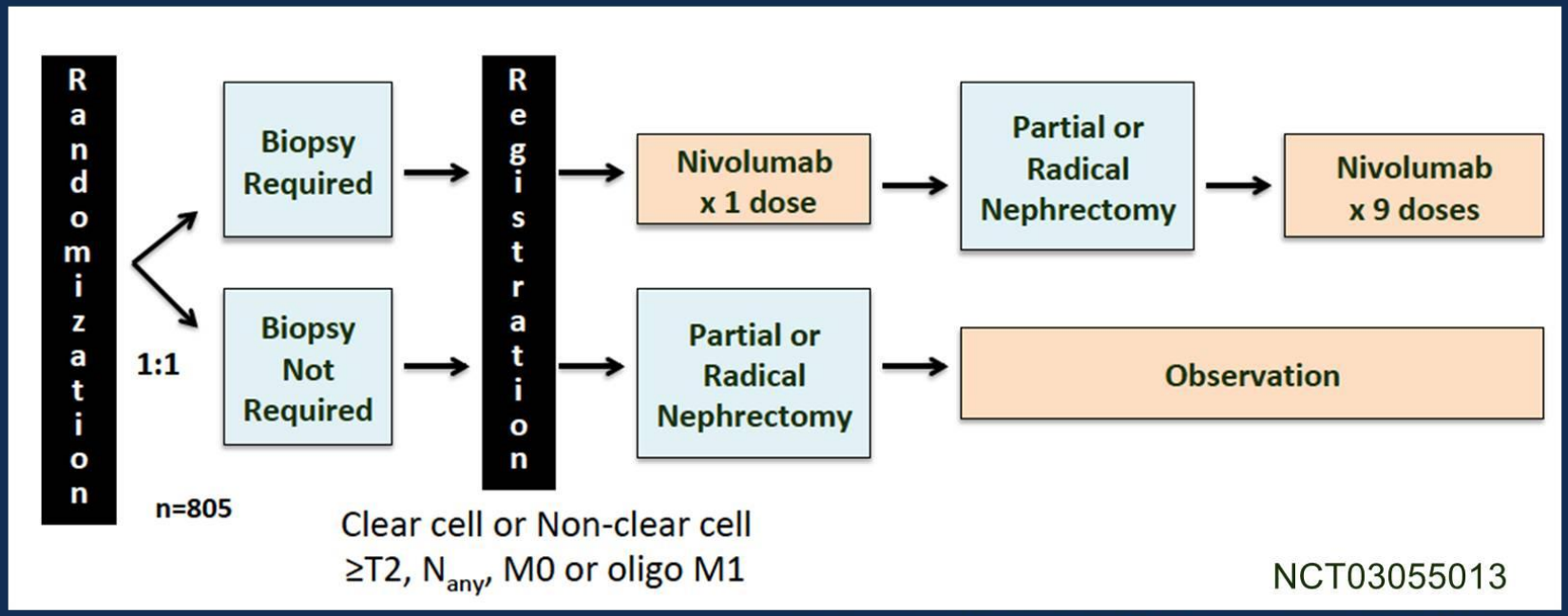
Primary endpoint: OS

PIs: Hyung Kim, Ulka Vaishampayan

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: L. Harshman MD

PROSPER RCC (EA8143): OligoMetastatic Subset

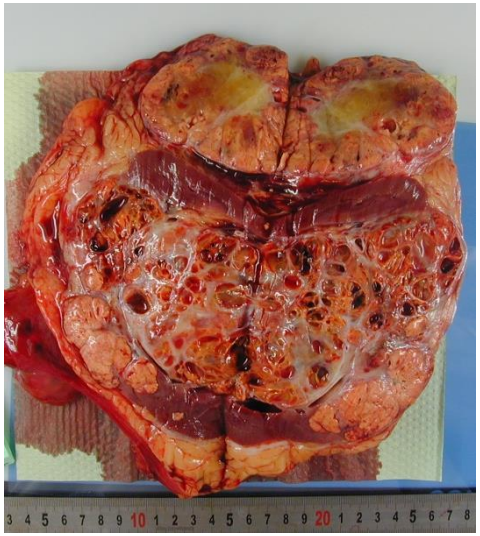


Urology chair: M Allaf, Co PIs: L Harshman, D McDermott

- Need the trifecta: presurgical priming with PD-1 blockade necessary to enhance efficacy
- Future Questions if +: selection of who benefits from the CN and optimal timing

Conclusions

- mRCC : maladie caractérisée par une histoire naturelle variable
- Pas de situation unique
- Nephrectomie / mRCC PS 0-1 pourrait être indiquée :
  - Petites mets pulmonaires
  - Met unique
  - Initiation retardée du ttt systémique
  - Symptômes sévères liés à la tumeur primaire



- Paradigme a changé eu égard à Carmena et Surtime
- Post-hoc analysis en cours…. (ASCO 2019 ?)
- D'autres Carmena / IO ?
- Rôle de la néphrectomie différée/secondaire ? (Surtime/Carmena)

→ Sélection des bons répondeurs

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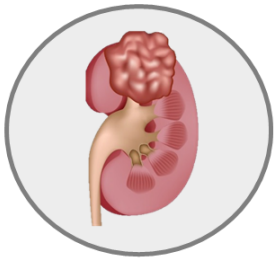
13ème Rencontre Patients de l'Association A.R.Tu.R.



Oligometastatic

CytoR Nephrectomy
+/- local ttt of mets
+/- delayed systemic therapy

Non oligometastatic

Intermediate risk | Poor risk

Better selection of patients

?

CytoR Nephrectomy

1L Systemic therapy

PR or CR | PD or SD

2L Systemic therapy

CytoR : cytoreductive, ttt : treatment
PR : Partial Response, CR : Complete Response
PD : Progessive Disease, SD : Stable Disease
1L : first line, 2L : second line

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