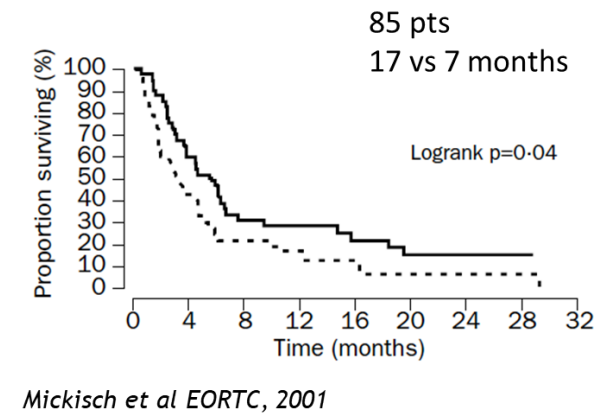
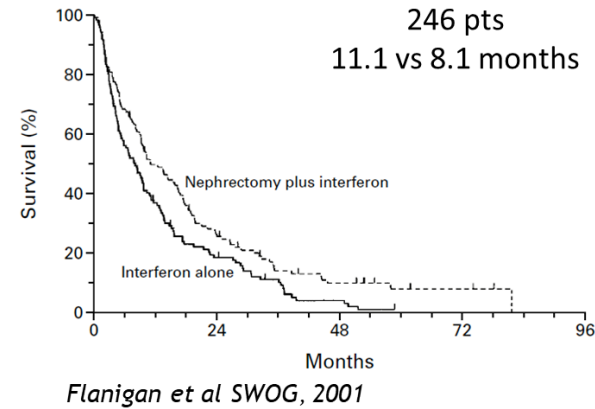


CARMENA & the Role of Cytoreductive Nephrectomy in 2019

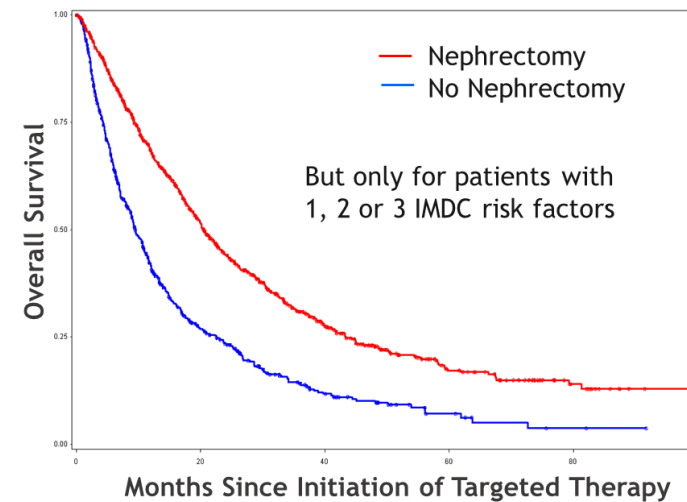
Laurence Albiges
Gustave Roussy Institute

CKCF19, Toronto April 11th

2001, 2 randomized studies



Retrospective studies Meta-analysis 2014, IMDC database analysis



CN : Cyto-reductive nephrectomy

SOC : Standard of Care

mRCC, metastatic renal cell carcinoma

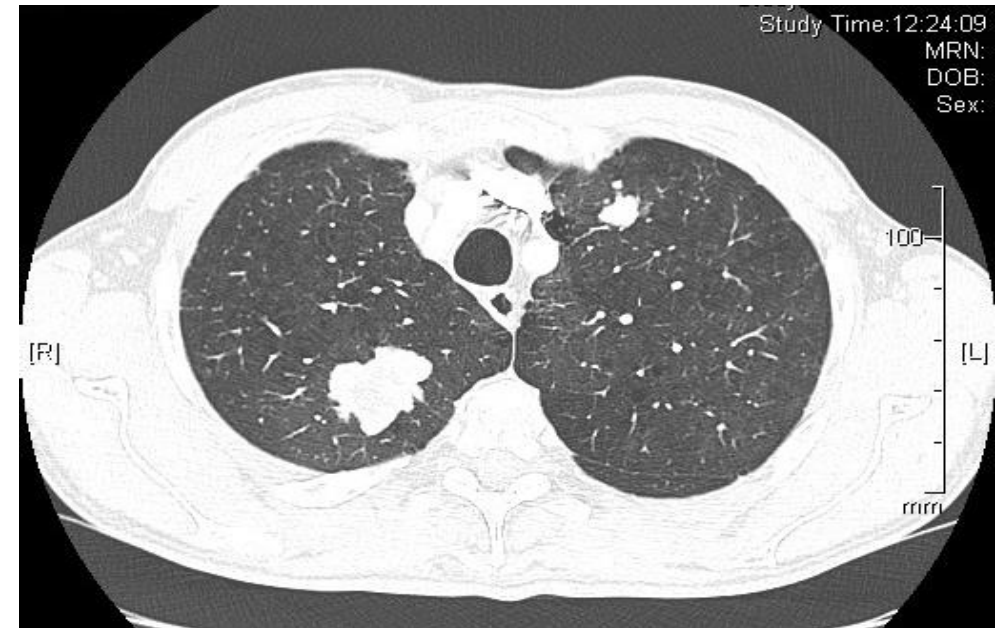
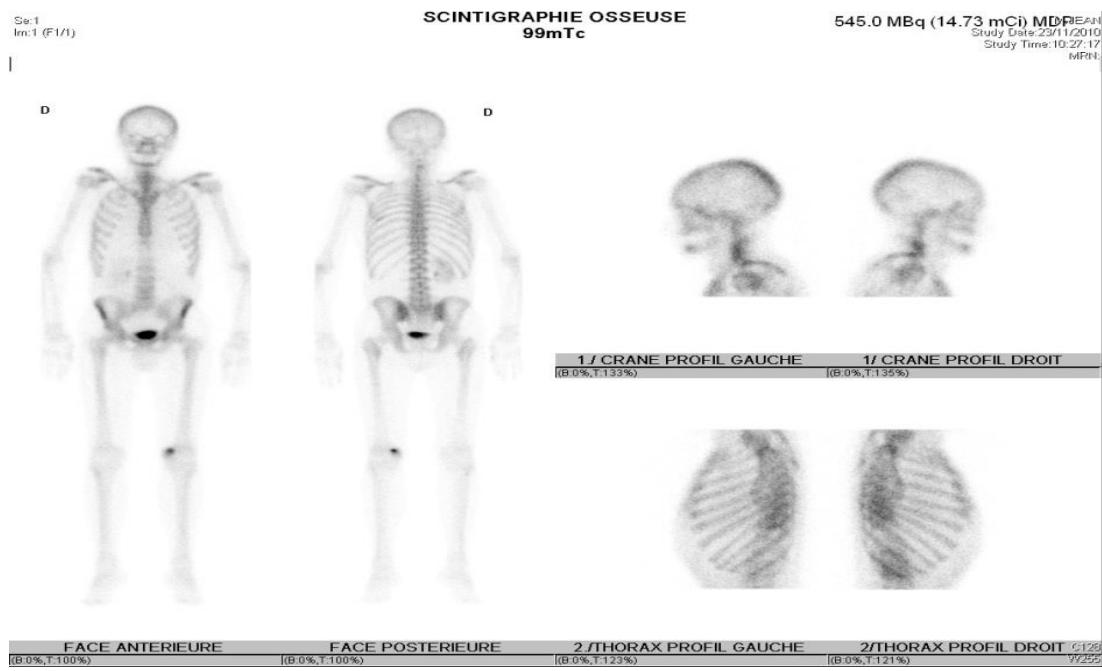
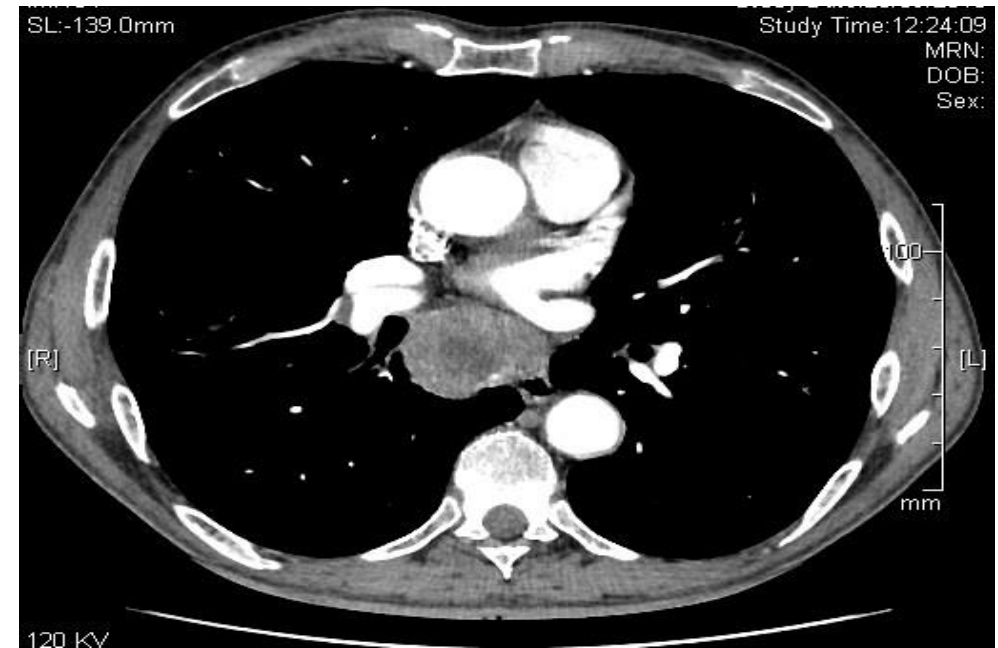
1. Flanigan R, et al. *N Engl J Med* 2001;345:1655. 2. Mickish G, et al. *Lancet* 2001;358:966.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma

Heng D, et al, *Eur Urol* 2014;66:704.

A Carmena Case

- 63 year old male
- Past medical history: tobacco (40 pxyear)
- Presentation:
 - Hematuria
 - Asthenia grade 1 + weight loss (7%)
- CT scans and staging:

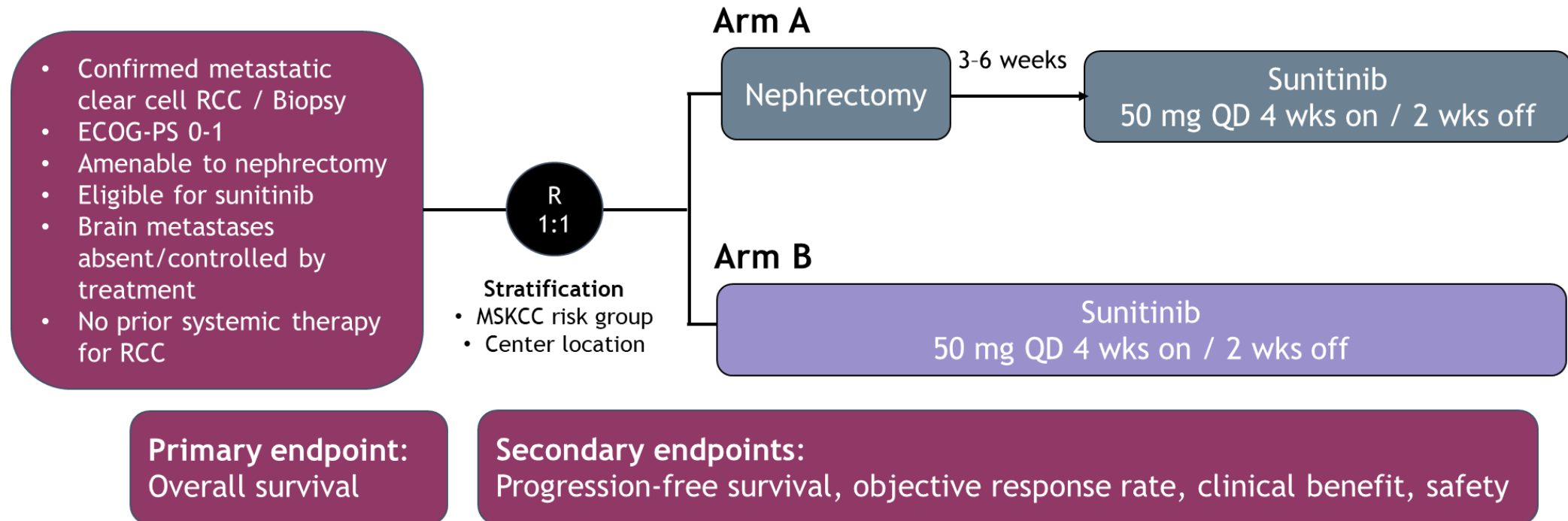


A Carmena Case

- 63 year old male
- Past medical history: tobacco (40 pxyyear)
- Presentation:
 - Hematuria
 - Asthenia grade 1 + weight loss (7%)
- Initial evaluation:
 - PS 1 (IK 80%)
 - Normal lab values

CARMENA

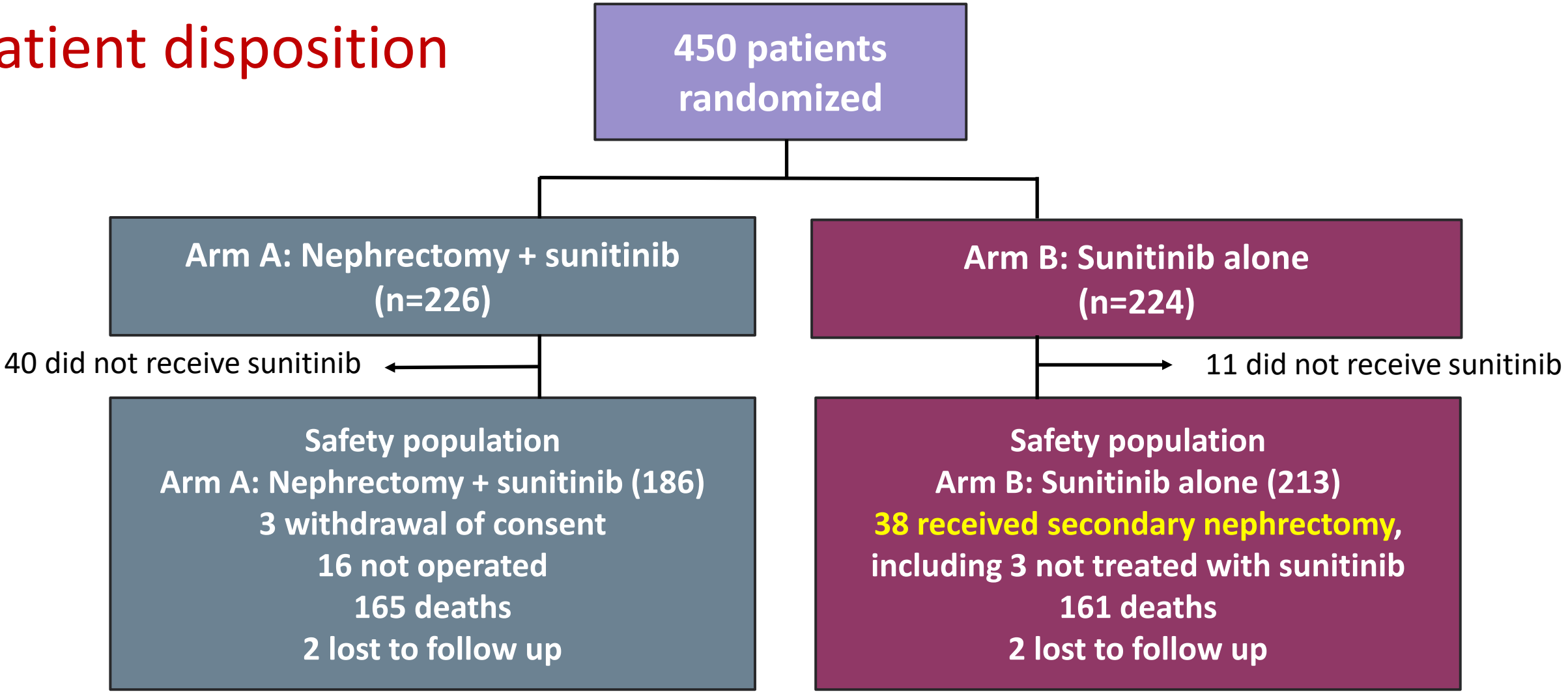
Prospective, multicenter, academic, randomized, phase 3 non-inferiority study



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

A. Méjean et al, *N Engl J Med* 2018;379:417-27

Patient disposition



ITT, intention to treat

Data cutoff : September 9, 2017

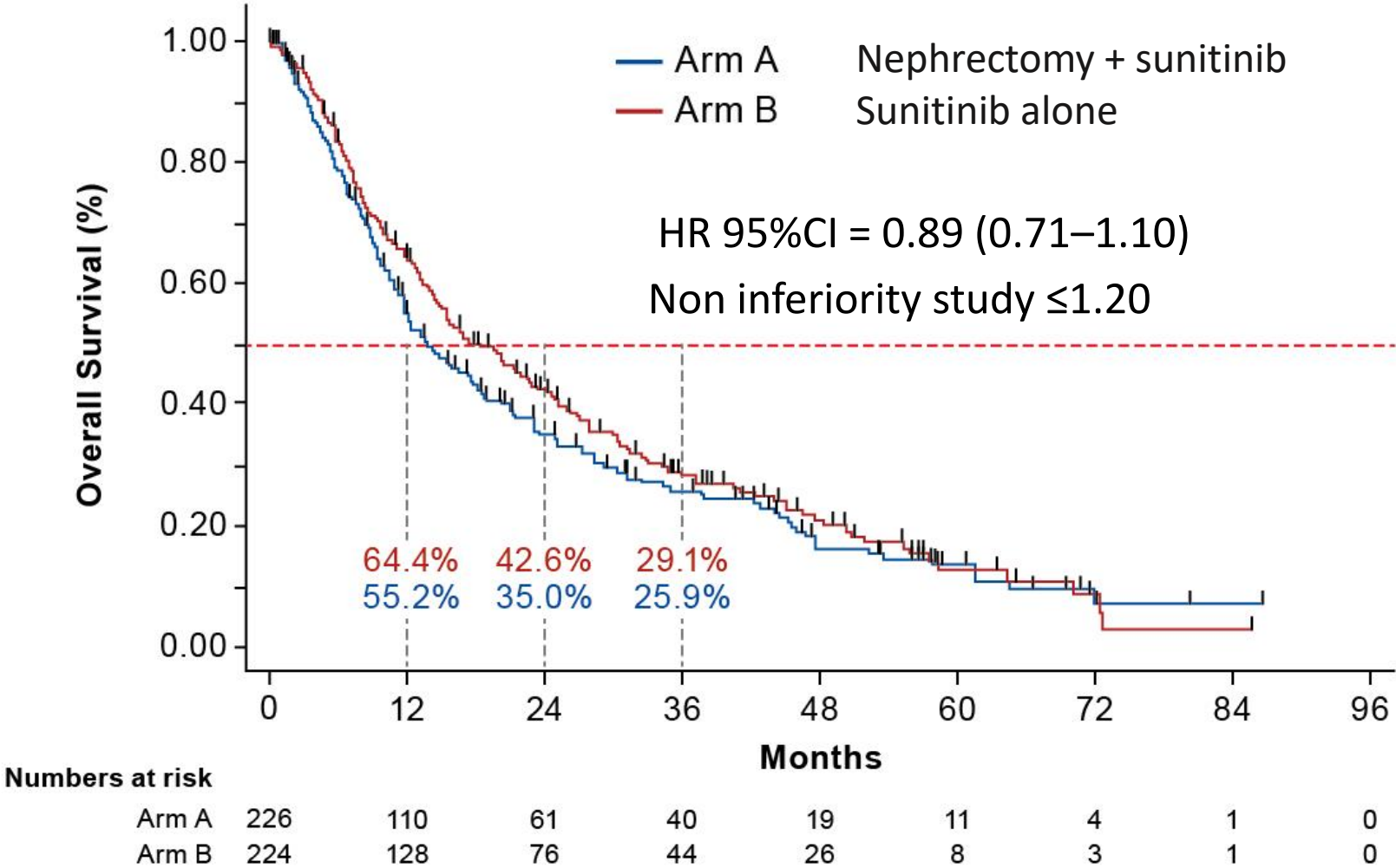
Patient characteristics

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

A. Méjean et al, *N Engl J Med* 2018;379:417-27

Overall survival (ITT)



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

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

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 disease²

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

Conclusions

- Sunitinib alone is non-inferior to cytoreductive nephrectomy followed by sunitinib for OS, both in intermediate- and poor-risk patients with mRCC
- Clinical benefit was significantly higher in sunitinib alone arm
- Cytoreductive nephrectomy should no longer be considered the standard of care in mRCC, at least when medical treatment is required



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. Lebrete, and B. Escudier

Guidelines have changed after CARMENA report

- **CARMENA demonstrated that upfront CN should no longer be considered the standard of care** in MSKCC intermediate- and poor-risk patients with asymptomatic primary tumours when medical treatment is required [I, A].
- Results of these trials **should not be used to abandon CN in patients with low volume metastatic disease, a good PS and favourable and intermediate risk, who are candidates for initial observation.**

Yes – CARMENA is changing our SOC

CARMENA SCRUTINIZED

- **Why to choose a non-inferiority design?**

- At the start of the trial, the standard of care was CN followed with sunitinib
- Based on retrospective data in TKI era (and prospective cytokine era) suggested that CN + sunit was better than sunit alone
- **the non-inferiority trial design was justifiable, ethical and pragmatic**
 - If met : avoid the risk/delay/pain/cost associated to surgery
- Upper limit of non-inferiority of 1.20 was selected a priori, and is commonly used in non inferiority trials

CARMENA SCRUTINIZED

- **Enrolment was slow ...**
- Underline the **challenge of surgical trial** and medical **community belief** of one assumption
- 13 centers included ≥ 10 pts for a total of 247 pts (55%)

CARMENA SCRUTINIZED

- **Study did not meet planned accrual...**
- Study was discontinued after 2nd planned interim analysis
- By sponsor upon IDMC recommendation
- based on the fact that **complete enrollment could not change the outcome of the reported results**

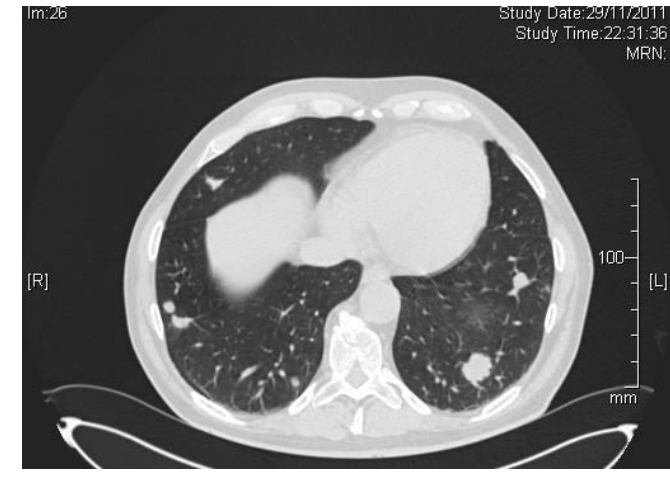
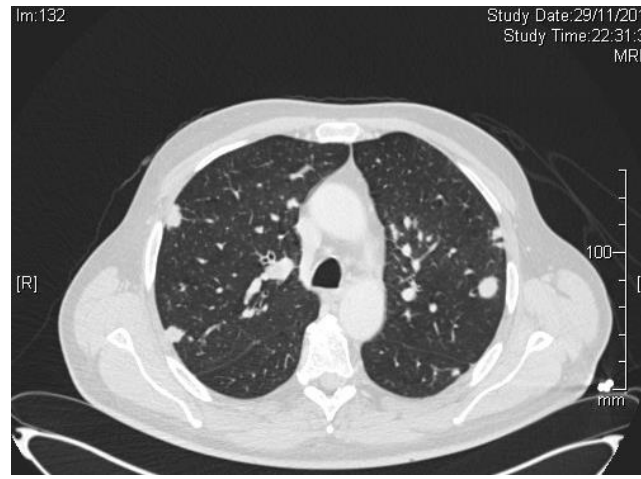
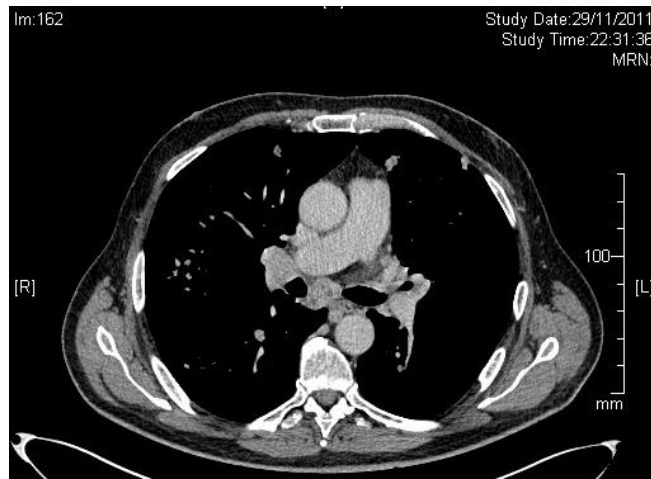
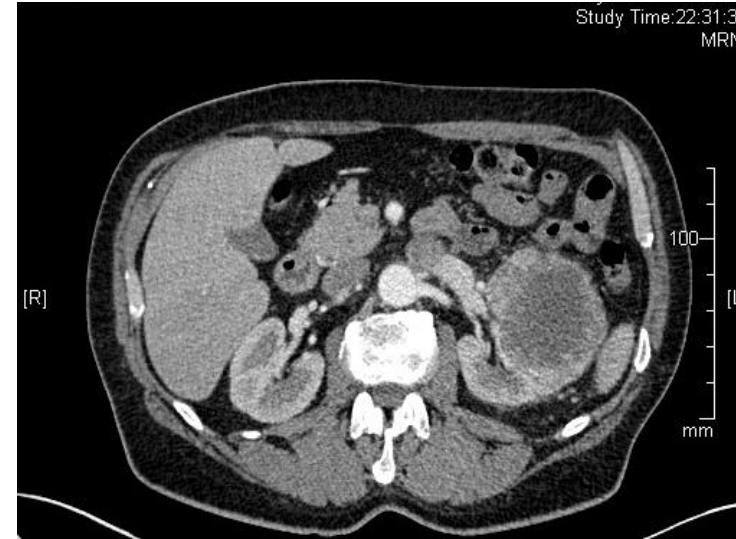
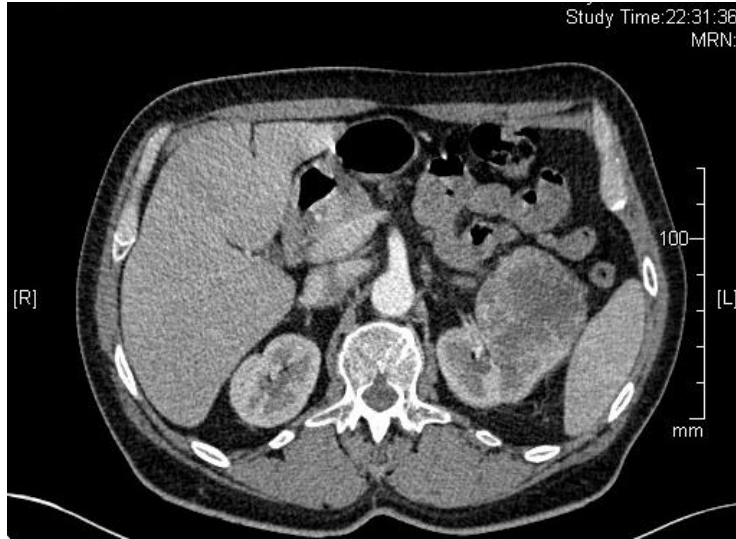
CARMENA SCRUTINIZED

- **42% of patients were poor risk...**
- CARMENA inclusion criteria **included PS 0,1** and eligible both for surgery and systemic therapy
- Therefore capture a **clinically fit** population

Case 2

- 66 year old male
- No past history
- Hematuria and weight loss 3 kgs

Case 3 staging



Case 3

- 66 year old male
- No past history
- Hematuria and weight loss 3 kgs
- PS 0
- Hemoglobin 10,8 g
- Platelets 520 000
- Neutrophils, calcemia, LDH normal

CN?

CARMENA IN CONTEXT

- **How SURTIME adds to CAMENA understanding?**

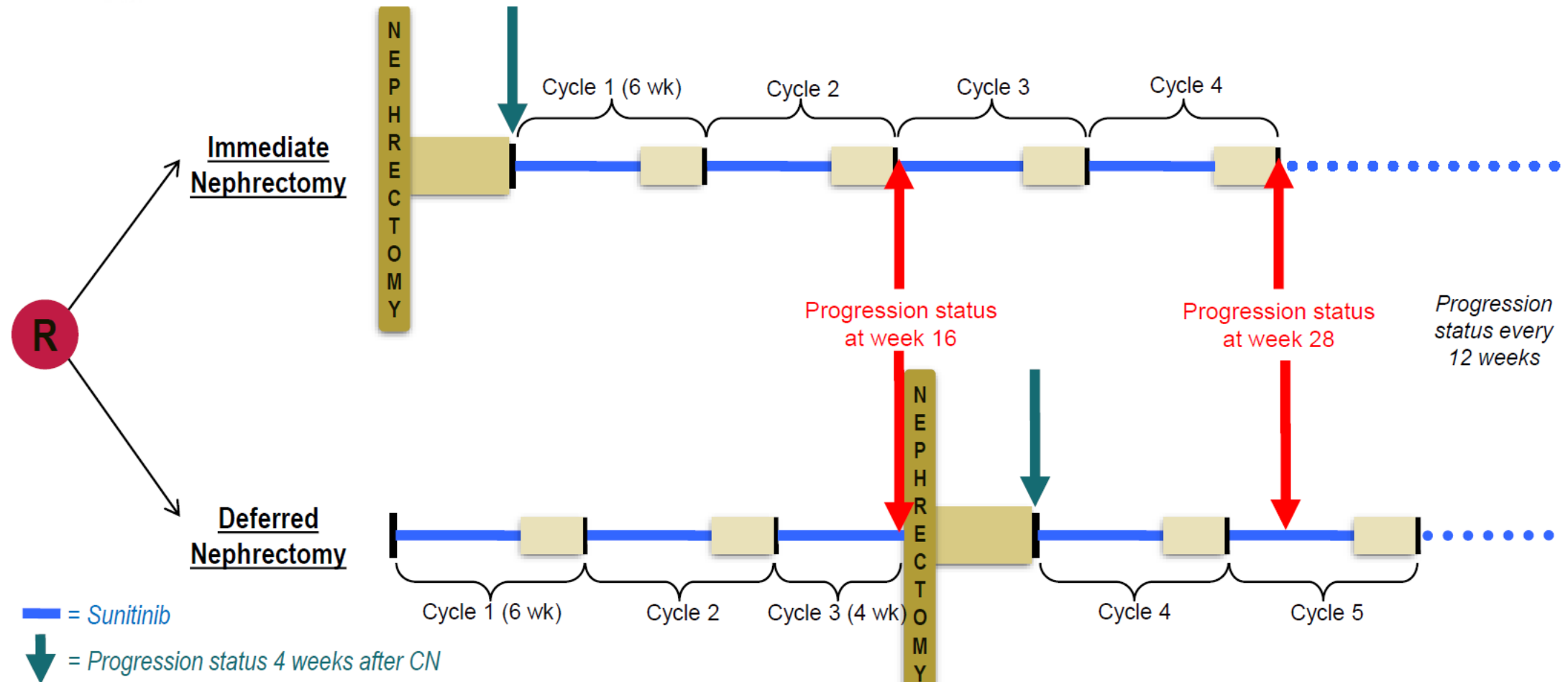
SURTIME INSIGHT: SEQUENCE TRIAL



- Due to **poor accrual (64 patients after 3 years recruitment)**, a revised statistical design had been submitted before the end of accrual to the Independent Data Monitoring Committee (IDMC) and approved the following changes:

- Primary endpoint:** Progression-free rate (PFR) at 28 weeks, using RECIST v1.1

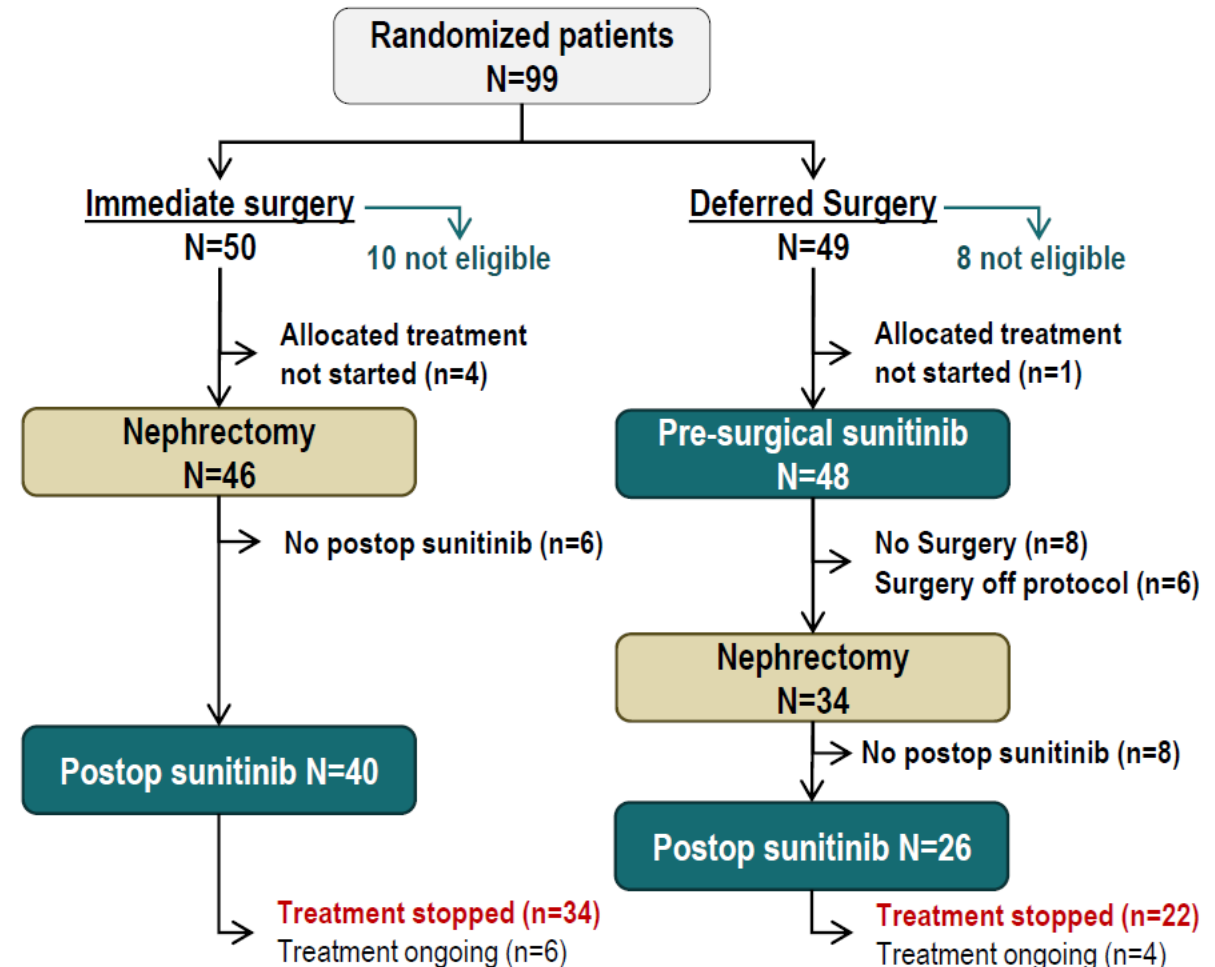
- Sample size:** Based on the PFR at 7 months (28 weeks) in the sunitinib arm in the pivotal trial comparing sunitinib and interferon-alpha, in which 90% of the patients had a nephrectomy¹, a PFR at 28 weeks of 70% was assumed for the immediate arm in trial 30073. To show an increase in the PFR at 28 weeks from 70% in the immediate arm to 90% in the deferred arm (H0: no difference versus H1: increase of 20% in the PFR), based on a one sided Fisher Exact test at 5% with 80% power in the intention-to-treat population, **98 patients were needed**.



SURTIME INSIGHTS

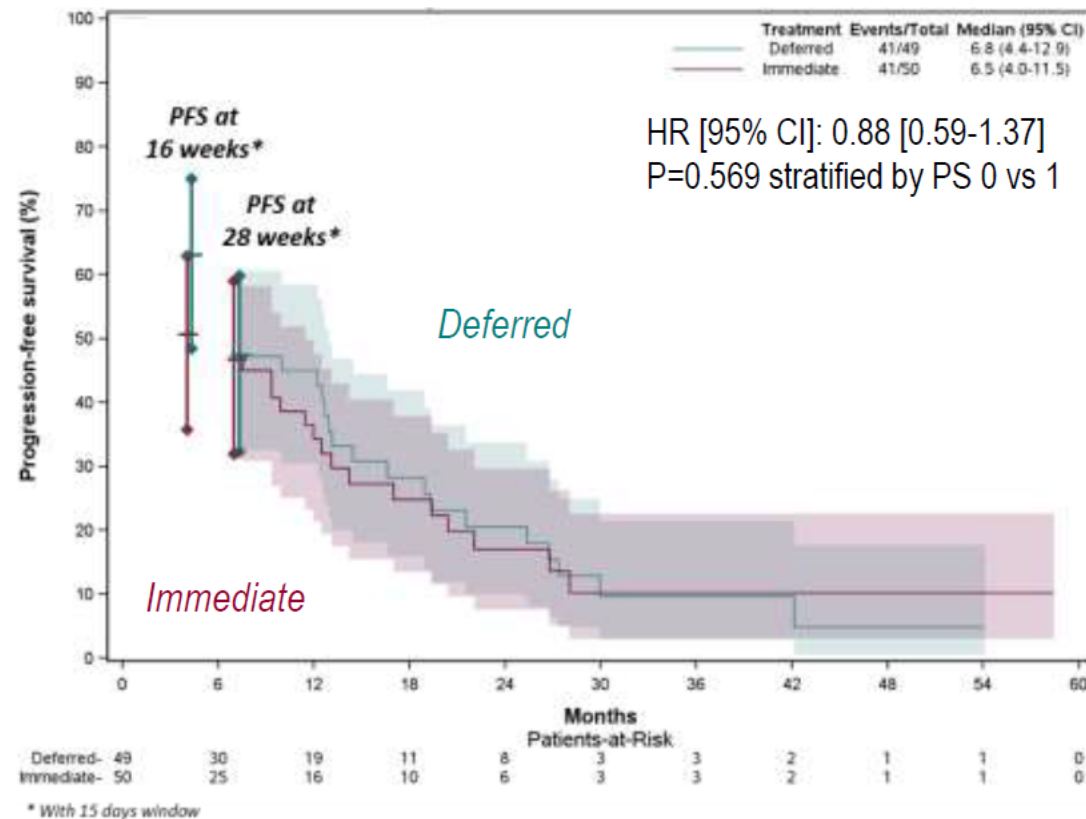
RECRUITMENT

- From 14/07/2010 to 24/03/2016 (ie 5.7 years):
 - 99 patients randomized
 - by 19 institutions
 - from 4 countries (the Netherlands, Canada, United Kingdom, Belgium).
- As of May 5, 2017, median follow-up is 3.3 years (95% CI: 2.8, 3.8).



SURTIME INSIGHTS

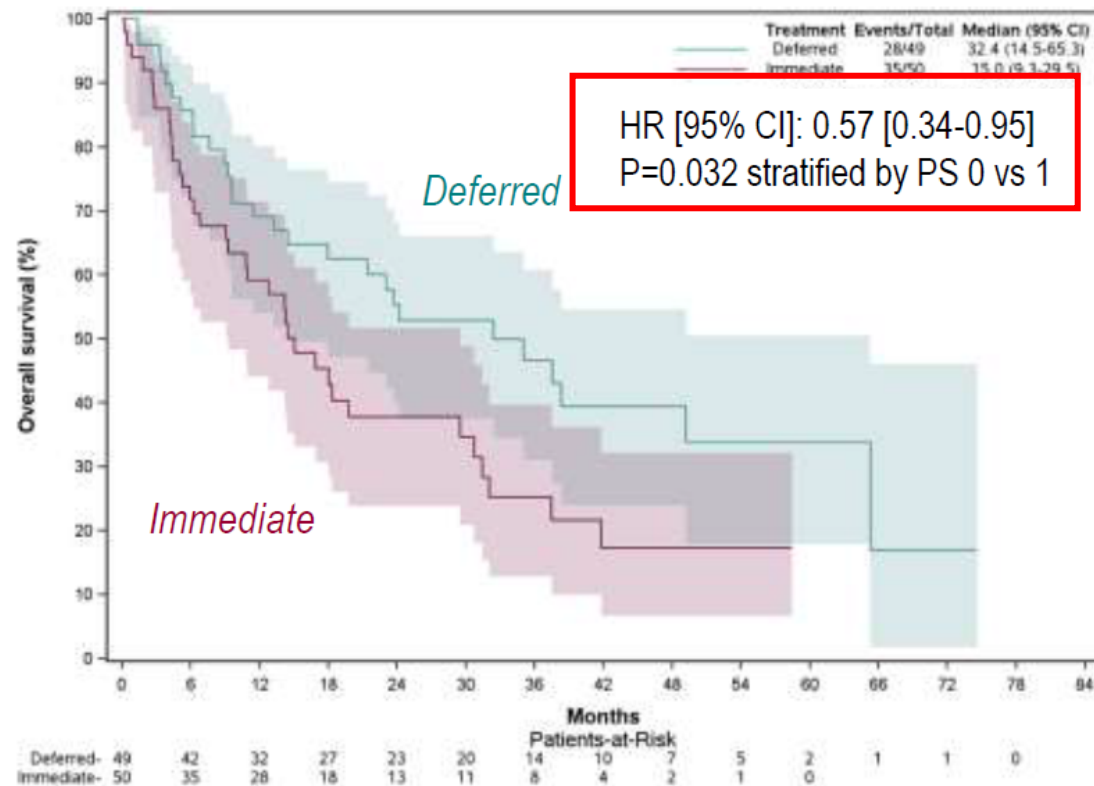
PROGRESSION-FREE SURVIVAL - INTENTION TO TREAT -



Progression-free status at w 28 (±15 days)	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Progression-free at week 28	21 (42.0%)	21 (42.9%)
[95% CI]	[28.2% – 56.8%]	[28.8% – 57.8%]
p-value (Fisher exact test)	>0.99	
Progression before or at week 28, or treatment failure	25 (50.0%)	24 (49.0%)
Not assessable	4 (8.0%)	4 (8.2%)

SURTIME INSIGHTS

OVERALL SURVIVAL - INTENTION TO TREAT -



	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Survival status		
Dead	35 (70.0)	28 (57.1)
Reason of death		
Progression	30	25
Surgery related toxicity	1	0
Progression and surgery related toxicity	1	0
Cardiovascular disease (not due to toxicity or progression)	1	0
Other (not due to toxicity or progression)	1	0
Unknown	1	3

SURTIME KEY MESSAGES

- Study accrued poorly and closed after 5.7 years

(strict eligibility criteria to include best surgical candidates based on 7 preoperative factors predicting outcome after CN)

- Deferred versus immediate CN

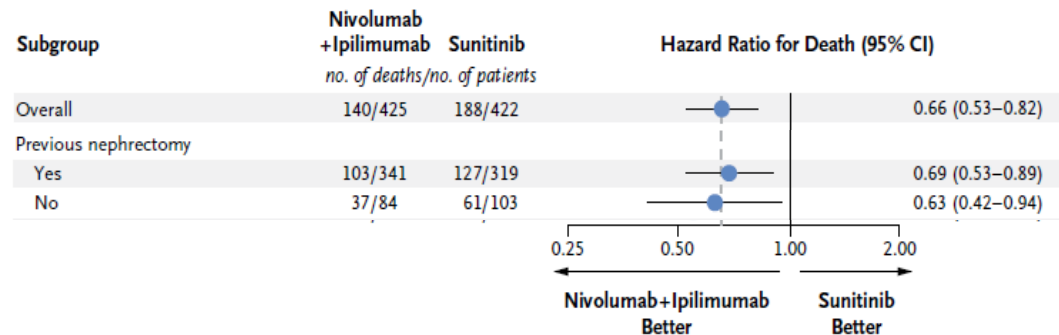
- OS in ITT(secondary endpoint) **HR 0.57** (95% CI: 0.34–0.95, p=0.032)
- median OS 32.4 (95%CI: 14.5-65.3) vs 15.0 months (95% CI: 9.3–29.5)

- **These data support the hypothesis that delaying systemic therapy to perform immediate CN may result in a detrimental effect**

CARMENA in an IO era?

- **Are these data relevant in the IO era...**

- Checkmate 214 suggest **similar activity of nivo+ipi in patients with/without CN**
- CARMENA questions a **general strategy of systemic therapy upfront**, it is anticipated to remain valid in the IO era
- New IO combos have demonstrated **superiority over sunitinib**-> **increased activity of our systemic therapies**
- Could the primary exposure to IO 'enhance' the immune response?



CARMENA Taken altogether

- Best prospective data available for CN
 - Demonstrate feasibility of surgical trial
 - Long Follow up
 - Hard endpoint
 - Homogenous results in all subgroups and endpoints (OS/PFS)
 - In line with SURETIME RCC trial
- Answer a clinically meaning full question
- PRACTICE CHANGING TRIAL

Acknowledgement

Arnaud Mejean

Bernard Escudier

Gustave Roussy GU Group
laurence.albiges@igr.fr



Even more

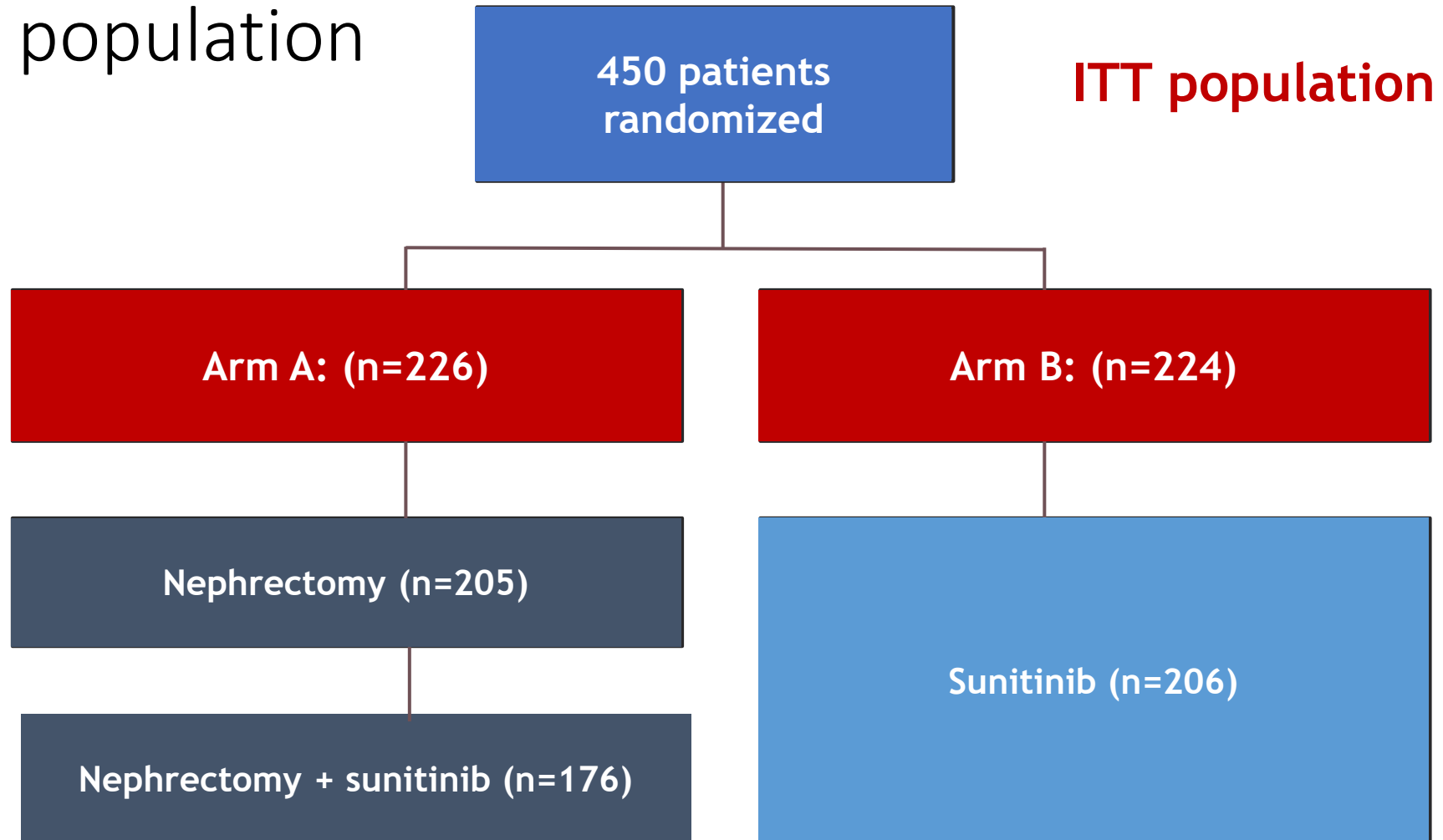
Not in the scope of CARMENA

- Does not answer the questions of
 - What to do in small metastatic burden where **CN+ surveillance** is the standard (good risk patients that don't require upfront systemic therapy)
 - When (nor even if needed!) to operate on great responders to Systemic therapy

CARMENA REVOLUTION

- **But all previous study said right the opposite...**
- RCT in cytokines era:
 - Flanigan study, only PS 0 with lung mets benefited.... These are the one likely to be under delay strategy
- Retrospective (even large) data are biased especially in surgery, IMDC factors don't capture the reason why the patient was taken to surgery (mets size, mets kinetics physiological status...)

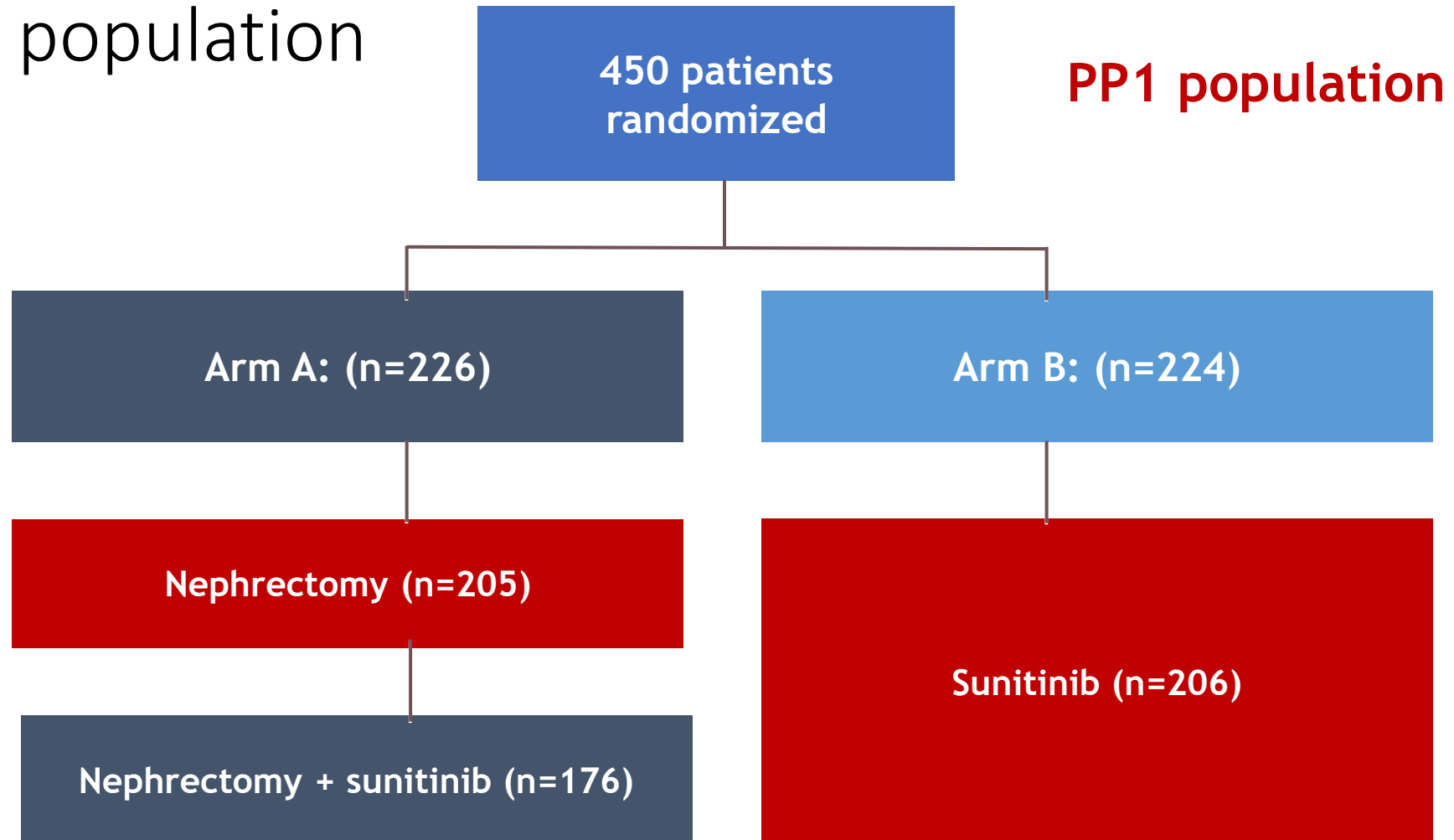
Patient population



ITT, intention to treat

Data cutoff : September 9, 2017

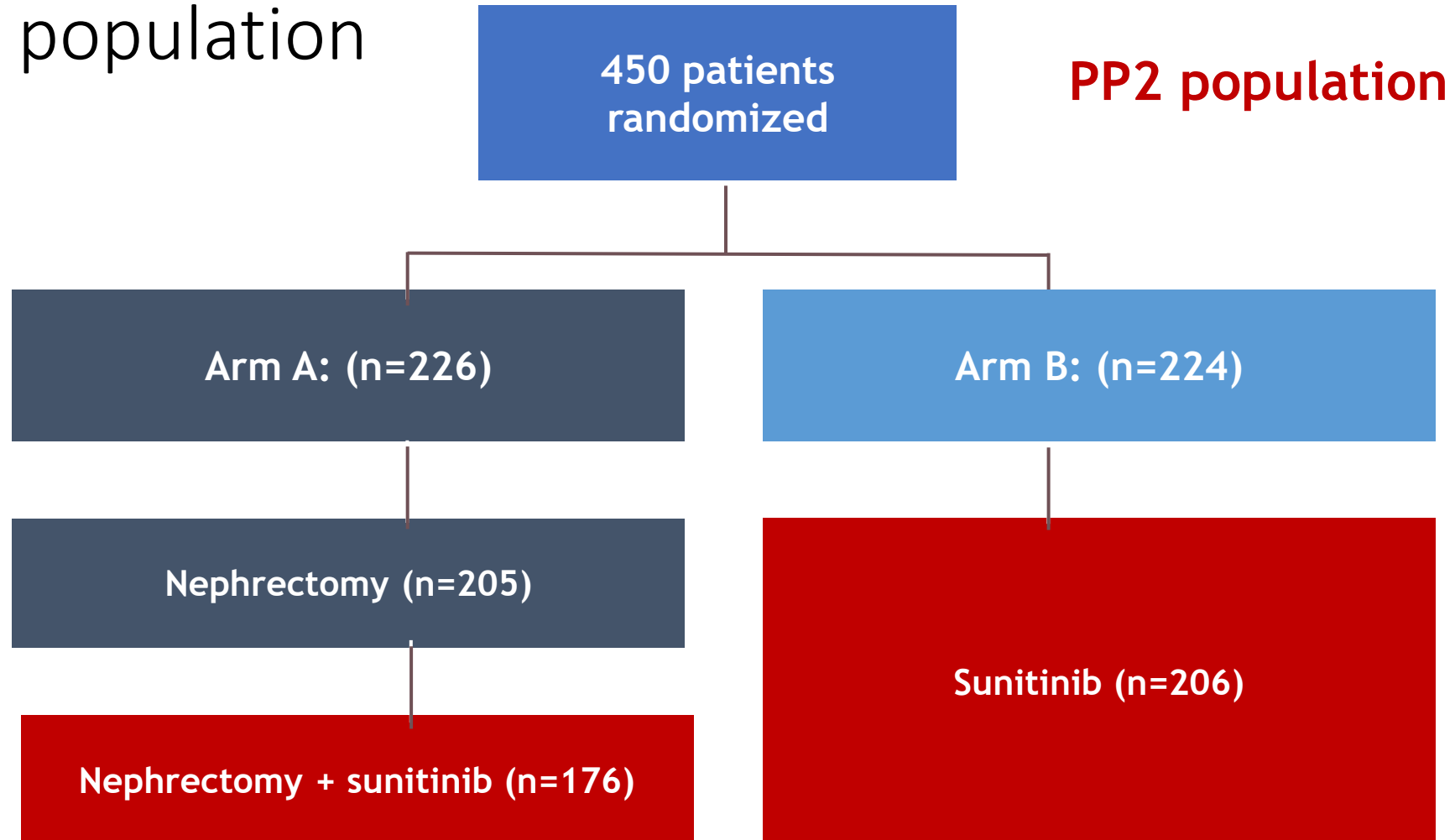
Patient population



PP1, per protocol

Data cutoff : September 9, 2017

Patient population



PP2 population

PP2 : per protocol

Data cutoff : September 9, 2017

Overall survival by patient population

Population	Arm A (Nephrectomy + 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)	13.9 (11.8–18.3)	224	161 (72)	18.4 (14.7–23.0)	0.89 (0.71–1.10)
PP1*	205	149 (73)	14.5 (11.9–20.2)	206	143 (69)	20.5 (15.6–25.2)	0.87 (0.69–1.1)
PP2#	176	122 (64)	18.3 (13.7–23.2)	206	143 (69)	20.5 (15.6–25.2)	0.98 (0.77–1.25)

*The PP1 analysis included only patients who had nephrectomy in Arm A, and patients who receive sunitinib in Arm B.

#The PP2 analysis included only patients who had nephrectomy and receive sunitinib after nephrectomy in Arm A, and patients who receive sunitinib in Arm B.

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PP, per-protocol.

YES CARMENA HAS CAVEATS

- **Patient carried large metastatic burden ...**
- Patients **requiring systemic therapy** are the focus of CARMENA trial
- Patients considered for observation only or multimodal (oligometastatic disease) were not the focus

YES CARMENA HAS CAVEATS

- **CI cross the 1.2 boundary in the intermediate risk group...**
- **All HR are consistent (below<1)**
- trial was not powered to address this subgroup analysis

YES CARMENA HAS CAVEATS

- **PP2 CI did not meet HR<1.2 boundary...**
- CARMENA addresses the question of **sequence** and therefore **ITT** is the relevant population
- You don't know ahead if a patient will go through the full sequence

CARMENA SCRUTINIZED

- **Where patients from the CN + sunitinib arm under treated with systemic therapy?**
- CN potentially delays TKI treatment: 29 patients never received sunitinib after CN
- Proper exposure :
 - no difference in toxicity rate under sunitinib
 - No difference in subsequent lines rate

	Arm A: Nephrectomy + Sunitinib (N = 186)	Arm B: Sunitinib alone (N = 213)
Dose reductions, n (%)	57 (31)	65 (30)
Severe (grade 3-4) AE, n (%)	61 (33)	91 (43)

CARMENA SCRUTINIZED

- **Does CARMENA say CN is detrimental?**
- CN does result in some complications (Clavien Grade ≥ 3 : 16%)
- 205 – 176 = **29 patients never started systemic therapy**
 - Mostly for disease progression/death
- CN +sunitinib is associated with worse OS (by 11%) and PFS (by 18%) for all subgroups, but particularly for poor-risk disease. Median were longer for OS and PFS

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