CARMENA : Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma (mRCC) - Results of a phase III non-inferiority trial. (NCT00930033)


On Behalf of Carmena investigators
Background

• For the past twenty years, cytoreductive nephrectomy has been the standard of care in mRCC
  - Randomized studies have demonstrated a benefit vs cytokine therapy alone\(^1,^2\)
• Many targeted therapies have demonstrated efficacy in treating mRCC\(^3\), but there is no direct comparison with nephrectomy
• Retrospective studies and meta-analyses have suggested a benefit for nephrectomy\(^4,^5\)

mRCC, metastatic renal cell carcinoma
(IMDC) retrospective database study found better survival in patients given nephrectomy...

3245 mRCC patients

2569 (79%) patients with nephrectomy

1587 (49%) EXCLUDED with nephrectomy prior to metastases

676/1658 (41%) No nephrectomy

982/1658 (59%) Nephrectomy

FINAL NUMBERS

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma
(IMDC) retrospective database study found better survival in patients given nephrectomy...

3245 mRCC patients

- 2569 (79%) patients with nephrectomy
- 676/1658 (41%) No nephrectomy
- 982/1658 (59%) Nephrectomy

FINAL NUMBERS

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

Case 1: RCC
PS 0
Small metastatic tumor burden

Nephrectomy makes sense
Case 2: RCC
PS 2
High metastatic tumor burden

Nephrectomy does not make sense

RCC, Renal cell carcinoma PS, performance status
Case 3: RCC
PS 0 - 1
Limited metastatic tumor burden

Who knows if nephrectomy is useful?
In the era of targeted therapy, is cytoreductive nephrectomy still necessary?
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

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

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

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

Stratification
- MSKCC risk group
- Center location

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

Presented by: Arnaud Méjean
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.

Cl, confidence interval; HR, hazard ratio.
Study conduct

• From Sept. 2009 to Sept. 2017, 450 patients were enrolled
• Second interim analysis, cutoff Sept. 9, 2017: 326 events had occurred
• Median follow-up 50.9 months
• Based on overall survival results, the Steering Committee decided to stop the trial and considered this interim analysis as final
Patient disposition

450 patients randomized

Arm A: Nephrectomy + sunitinib (n=226)
- 6 inclusion criteria deviation
- 40 did not receive sunitinib
  - Safety population
    - Arm A: Nephrectomy + sunitinib (186)
      - 3 withdrawal of consent
      - 16 not operated
      - 165 deaths
      - 2 lost to follow up
- 11 did not receive sunitinib
  - Safety population
    - Arm B: Sunitinib alone (213)
      - 38 received secondary nephrectomy, including 3 not treated with sunitinib
      - 161 deaths
      - 2 lost to follow up

Arm B: Sunitinib alone (n=224)
- 8 inclusion criteria deviation

Data cutoff: September 9, 2017

ITT, intention to treat
Patient population

450 patients randomized

ITT population

Arm A: (n=226)

Nephrectomy (n=205)

Nephrectomy + sunitinib (n=176)

Arm B: (n=224)

Sunitinib (n=206)

Data cutoff: September 9, 2017

ITT, intention to treat
Patient population

450 patients randomized

PP1 population

Arm A: (n=226)

Nephrectomy (n=205)

Nephrectomy + sunitinib (n=176)

Arm B: (n=224)

Sunitinib (n=206)

Data cutoff: September 9, 2017

PP1, per protocol
Patient population

450 patients randomized

PP2 population

Arm A: (n=226)

Nephrectomy (n=205)

Nephrectomy + sunitinib (n=176)

Arm B: (n=224)

Sunitinib (n=206)

Data cutoff: September 9, 2017

PP2: per protocol
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A: Nephrectomy + sunitinib (N = 226)</th>
<th>Arm B: Sunitinib alone (N = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>63 (33-84)</td>
<td>62 (30-87)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>169 (75)</td>
<td>167 (75)</td>
</tr>
<tr>
<td>MSKCC score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>125 (56)</td>
<td>131 (59)</td>
</tr>
<tr>
<td>Poor</td>
<td>100 (44)</td>
<td>93 (41)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>130 (57)</td>
<td>122 (54)</td>
</tr>
<tr>
<td>1</td>
<td>96 (42)</td>
<td>102 (45)</td>
</tr>
</tbody>
</table>

CN, cytoreductive nephrectomy; ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan Kettering Cancer Center
### Patient characteristics (2)

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

*Assessed as a combination of primary renal tumour and metastases.

RECIST, Response Evaluation Criteria In Solid Tumors
Overall survival (ITT)

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

HR 95%CI = 0.89 (0.71-1.10)
Non inferiority study ≤1.20

Overall Survival (%) vs Months

<table>
<thead>
<tr>
<th>Numbers at risk</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>226</td>
<td>224</td>
</tr>
<tr>
<td>0 months</td>
<td>110</td>
<td>128</td>
</tr>
<tr>
<td>12 months</td>
<td>61</td>
<td>76</td>
</tr>
<tr>
<td>24 months</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>36 months</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>48 months</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>60 months</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>72 months</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>84 months</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
## Overall survival (ITT)

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

Non inferiority study ≤1.20
# Overall survival by patient population

<table>
<thead>
<tr>
<th>Population</th>
<th>Arm A (Nephrectomy + sunitinib)</th>
<th>Arm B (Sunitinib)</th>
<th>HR (95% CI), stratified by MSKCC risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Events, n (%)</td>
<td>Median (95% CI), months</td>
</tr>
<tr>
<td>ITT</td>
<td>226</td>
<td>165 (73)</td>
<td>13.9 (11.8–18.3)</td>
</tr>
<tr>
<td>PP1*</td>
<td>205</td>
<td>149 (73)</td>
<td>14.5 (11.9–20.2)</td>
</tr>
<tr>
<td>PP2#</td>
<td>176</td>
<td>122 (64)</td>
<td>18.3 (13.7–23.2)</td>
</tr>
</tbody>
</table>

*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.
Progression free survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: Nephrectomy + Sunitinib (n = 226)</th>
<th>Arm B: Sunitinib alone (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.2 (6.5-8.5)</td>
<td>8.3 (6.2-9.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.67-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

CN, cytoreductive nephrectomy; PFS, progression-free survival
## Progression free survival by patient population

<table>
<thead>
<tr>
<th>Population</th>
<th>Arm A: Nephrectomy + sunitinib</th>
<th>Arm B: Sunitinib alone</th>
<th>HR (95% CI), stratified by MSKCC risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Events, n (%)</td>
<td>Median (95% CI), months</td>
</tr>
<tr>
<td>ITT</td>
<td>226</td>
<td>194 (86)</td>
<td>7.2 (6.7-8.5)</td>
</tr>
<tr>
<td>PP1*</td>
<td>205</td>
<td>178 (87)</td>
<td>7.6 (6.8-9.4)</td>
</tr>
<tr>
<td>PP2#</td>
<td>176</td>
<td>154 (87)</td>
<td>8.7 (7.2-10.2)</td>
</tr>
</tbody>
</table>

*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.
### Response rate

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

*p=0.022

CI, confidence interval; CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease
## Mortality and morbidity post-nephrectomy (Arm A)

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

Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey


†Within 1 month of surgery

*Percentage of 82 patients with postoperative morbidity
Safety of sunitinib

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

AE, adverse event;
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

<table>
<thead>
<tr>
<th>Secondary nephrectomy, n (%)</th>
<th>Arm B: Sunitinib alone (N = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>185 (83.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (17.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>No</td>
<td>30 (81.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
</tr>
</tbody>
</table>
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

CN, cytoreductive nephrectomy; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival
Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

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 Oncologists
• DSMB members
79 Centers contributing patients to CARMENA

Hôpital Européen Georges-Pompidou / Necker - Urologie
Institut Gustave Roussy - Immunothérapie
Suresnes Foch - Oncologie
Nancy A. Vautrin - Oncologie Médicale
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Besançon Minjoz - Oncologie Médicale
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Marseille Paoli Calmettes - Oncologie Médicale
Saint-Herblain CLCC - Oncologie
Tours Bretonneau - Oncologie Médicale
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Colmar Pasteur - Oncologie
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Pointe-à-Pitre Abymes - Urologie
La Roche-sur-Yon - Onco-Hématologie
Grenoble Michallon - Urologie Transplantation
Le Mans - Cancérologie-Oncologie-Hématologie
Orléans La Source - Chirurgie Urologique et Andrologie
Nîmes - Urologie Andrologie
Mondor - Urologie
Nîmes - Hématologie clinique et oncologie médicale
Brive-la-Gaillarde - Oncologie
Urbans St. Germain - Oncologie
Saint-Brieuc-Clinique Armoricaine de Radiologie
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Lyons E. Herriot - Urologie
Avignon Ste Catherine - Oncologie Médicale
Cochin - Médecine Interne
Annecy - Oncologie
Tours Bretonneau - Urologie
Troyes - Urologie

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V. Verkarre

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F. Audenet
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